Smooth muscle

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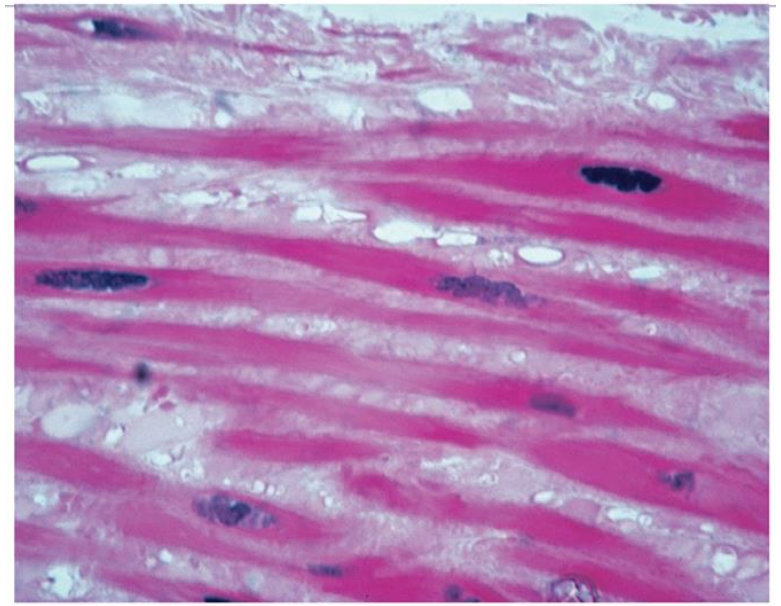
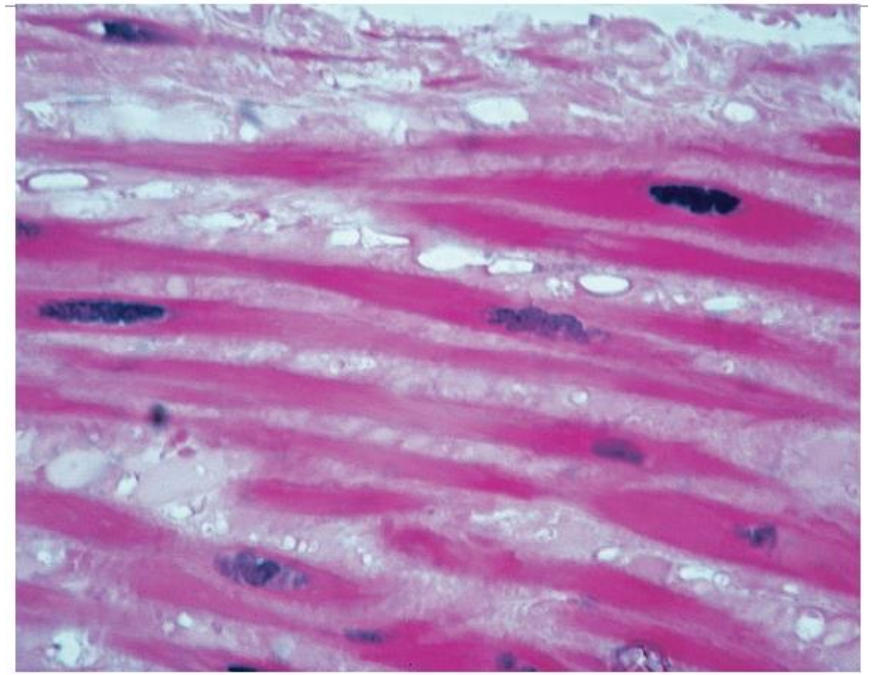
Smooth Muscle

- Lack the cross-striated banding pattern “smooth”
- The nerves to them are part of the autonomic division of the nervous system rather than the somatic division
  - Not under direct voluntary control
- Uses cross-bridge movements between actin and myosin filaments to generate force, and calcium ions to control cross-bridge activity
  - organization of the contractile filaments are different



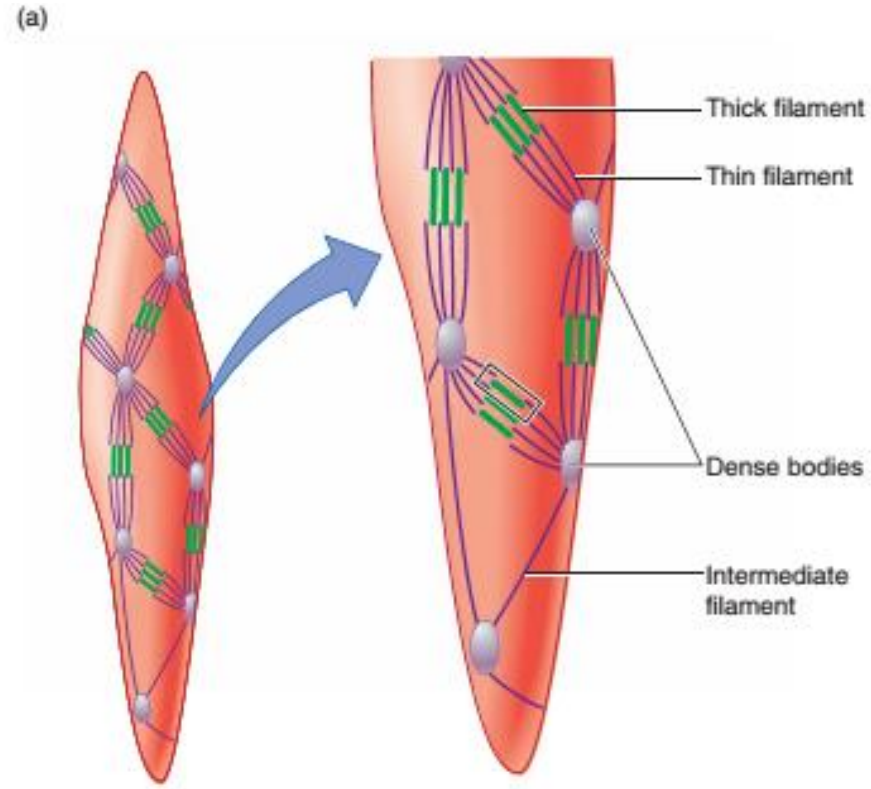
Smooth Muscle Cell

- Spindle shaped
- Single nucleus, capacity to divide
- Diameter between 2 and 10 µm (skeletal muscle 10-100 µm)
- Length 50 to 400 µm (skeletal muscle tens of centimeters)
- Sheet like layers



Smooth Muscle Cell

- No sarcomeres
- Thin:Thick filaments 16:1
- Actin-containing filaments
  - Tropomyosin (unknown function)
  - Troponin absent
  - Caldesmon
    - in some types
    - regulating contraction



Sources of Cytosolic Ca^{2+}

1. Sarcoplasmic reticulum

- Smaller in smooth muscle
- No T-tubules
  - Small cell diameter and slow rate of contraction

a. Attached membrane at some sites (action potentials are coupled to Ca^{2+} release)

b. Second messanger related Ca^{2+} release (coupled to extracellular signals)

2. Extracellular Ca^{2+} entering the cell through plasma membrane Ca^{2+} channels

- Voltage-sensitive and ligand gated Ca^{2+} channels in the plasma membranes of smooth muscle cells
  - Increased flow into the cell

Ca^{2+} Removal

- Active transport of Ca^{2+} back into the sarcoplasmic reticulum and out of the cell (slower removal → longer contraction)

- Only a portion of the cross-bridges are activated in a smooth muscle fiber in response to most stimuli
  - *Graded* tension

- Smooth muscle tone
  - the cytosolic Ca^{2+} concentration is sufficient to maintain a low level of basal cross-bridge activity in the absence of external stimuli

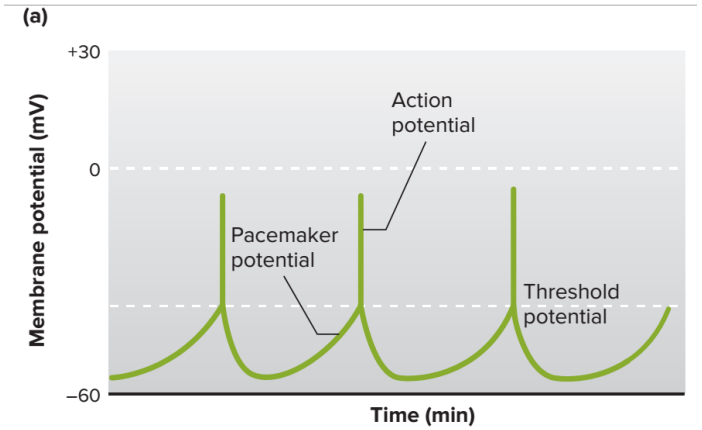
Membrane Activation

- Receives multiple inputs, with the contractile state of the muscle dependent on the relative intensity of the various inhibitory and excitatory stimuli
- All changes Ca^{2+} concentration
- Ca^{2+} mediated action potentials (not Na+)
- Graded depolarizations in membrane potential,
  - number of open Ca^{2+} channels

TABLE 9.5	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	

Spontaneous Electrical Activity

- Spontaneous action potential generator cells
  - plasma membranes do not maintain a constant resting potential
  - gradually depolarize until they reach the threshold potential and produce an action potential
  - Following repolarization, the membrane again begins to depolarize
  - Rhytmic state of contractile activity
  - pacemaker potential: membrane potential change occurring during the spontaneous depolarization to threshold

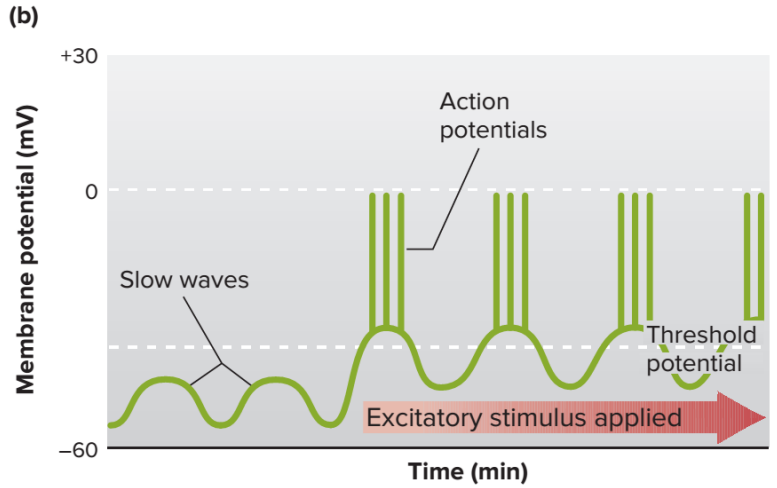


Spontaneous Electrical Activity

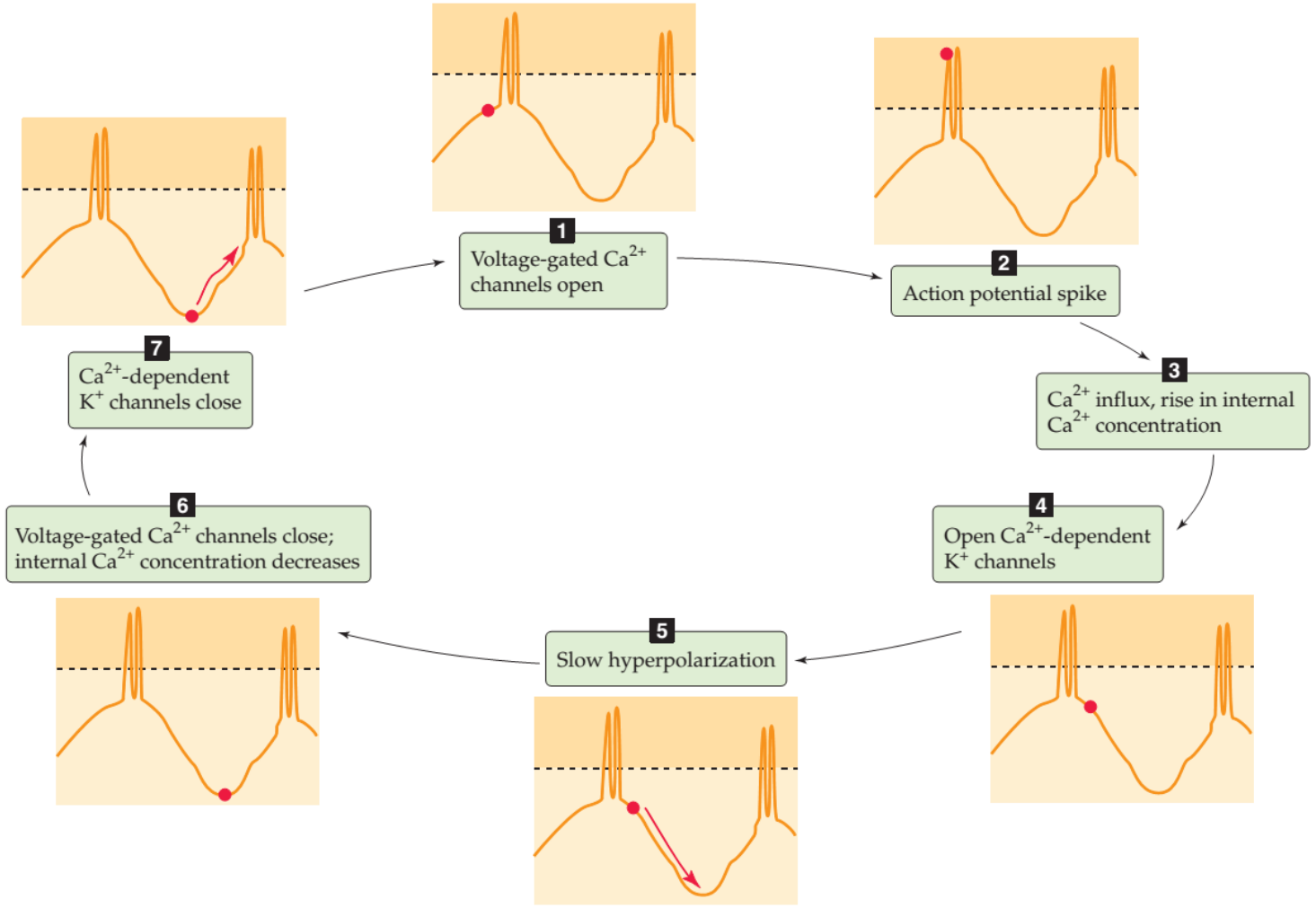
- Slow waves: The membrane potential drifts up and down due to regular variation in ion flux across the membrane

- excitatory input is superimposed, slow waves are depolarized above threshold, and action potentials lead to smooth muscle contraction

- Pacemaker cells are found throughout the gastrointestinal tract; rhythmical contraction even in the absence of neural input.

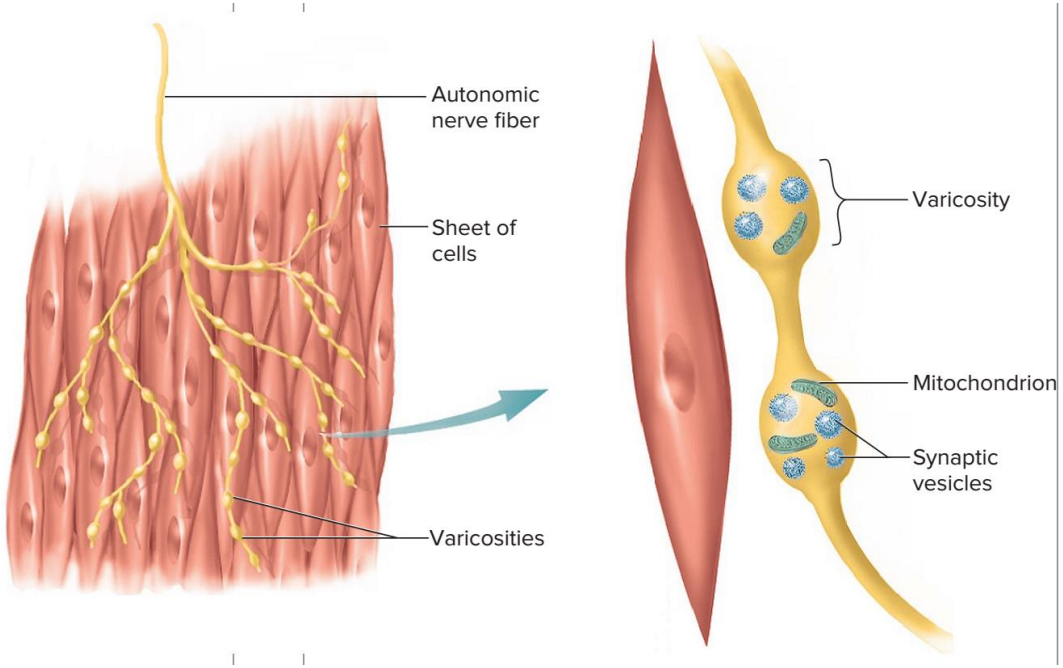


Generation of Slow Waves



Nerves and Hormones

- No specialized motor end-plate region, entire surface covered with receptors
- Varicosites: postganglionic autonomic neuron branches
  - Filled with neurotransmitter
  - Released when an action potential passes the varicosity
- Some neurotransmitters enhance contractile activity, others decrease
  - Skleletal muscles only excitation
- Receptors for hormones
  - Changes in contraction
- Local factors



Autonomic Innervation of Smooth Muscles

- Sympathetic and parasympathetic axons
  - Sympathetic → norepinephrine
  - Parasympathetic → acetylcholine

- Synapses en passant (*synapses in passing*)

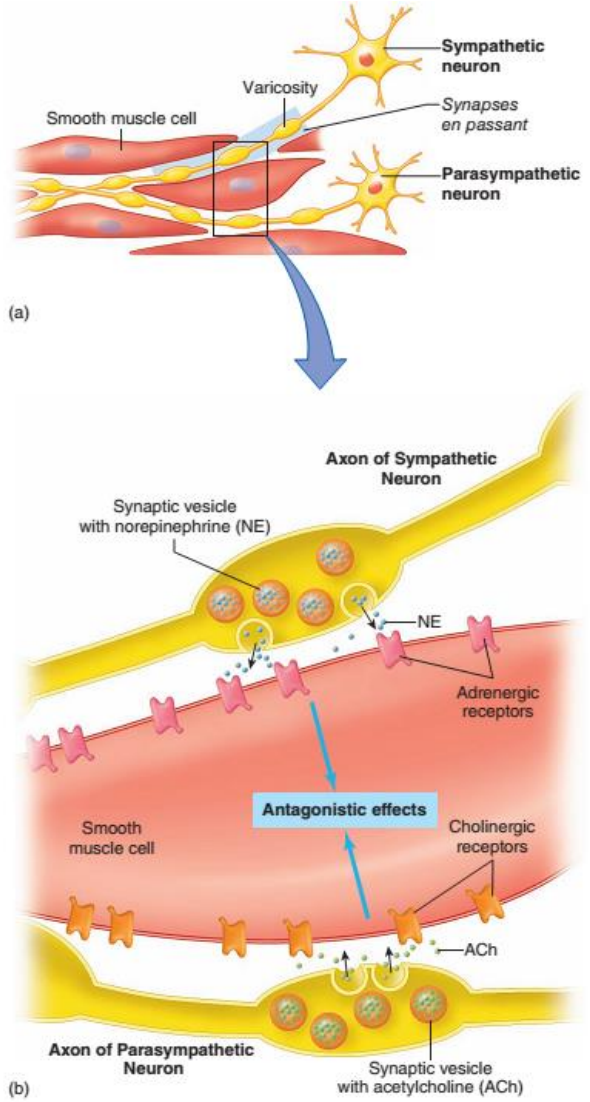


Table 9.6 | Cholinergic Receptors and Responses to Acetylcholine

Receptor	Tissue	Response	Mechanisms
Nicotinic	Skeletal muscle	Depolarization, producing action potentials and muscle contraction	ACh opens cation channel in receptor
Nicotinic	Autonomic ganglia	Depolarization, causing activation of postganglionic neurons	ACh opens cation channel in receptor
Muscarinic (M_3, M_5)	Smooth muscle, glands	Depolarization and contraction of smooth muscle, secretion of glands	ACh activates G-protein coupled receptor, opening Ca^{2+} channels and increasing cytosolic Ca^{2+}
Muscarinic (M_2)	Heart	Hyperpolarization, slowing rate of spontaneous depolarization	ACh activates G-protein coupled receptor, opening channels for K^+

Source: Simplified from table 6-2, p. 119, of Goodman and Gilman's *The Pharmacological Basis of Therapeutics.* Ninth edition. J.E. Hardman et al., eds. 1996 and table 6-3, p. 156, of the Eleventh edition, 2006. McGraw-Hill.

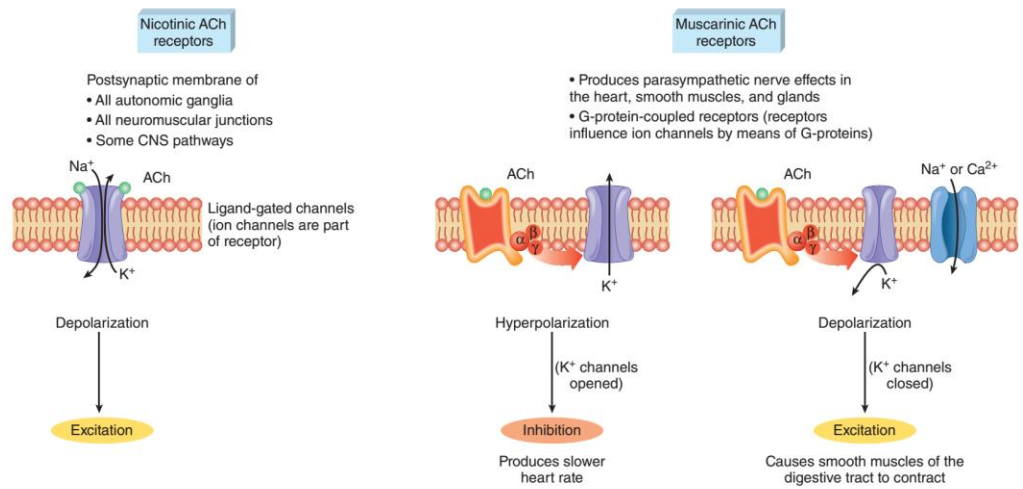
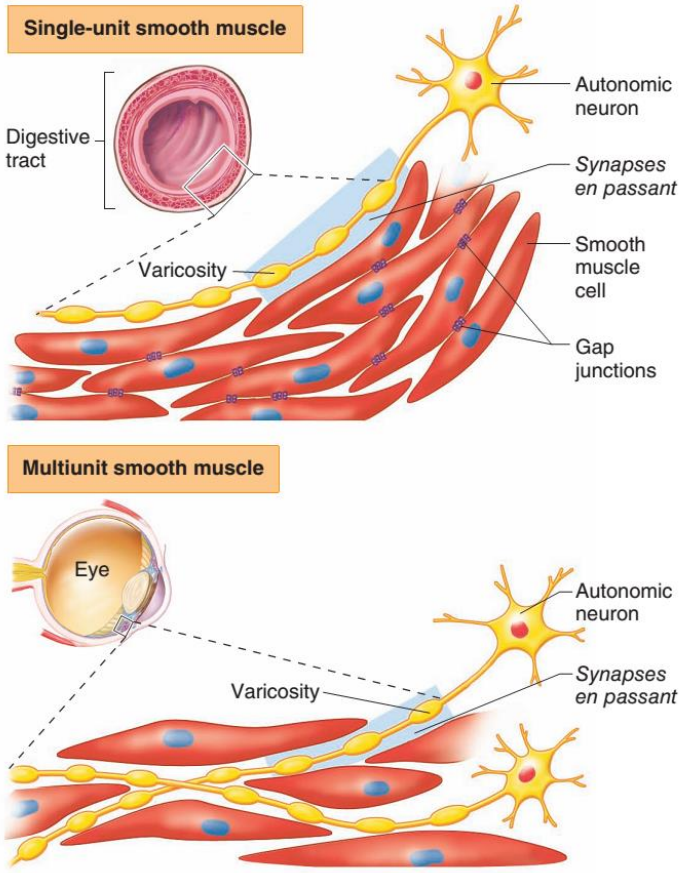


Figure 9.11 **Comparison of nicotinic and muscarinic acetylcholine receptors.** Nicotinic receptors are ligand-gated, meaning that the ion channel (which runs through the receptor) is opened by binding to the neurotransmitter molecule (the ligand). The muscarinic ACh receptors are G-protein-coupled receptors, meaning that the binding of ACh to its receptor indirectly opens or closes ion channels through the action of G-proteins. AP|R

Single Unit Smooth Muscles

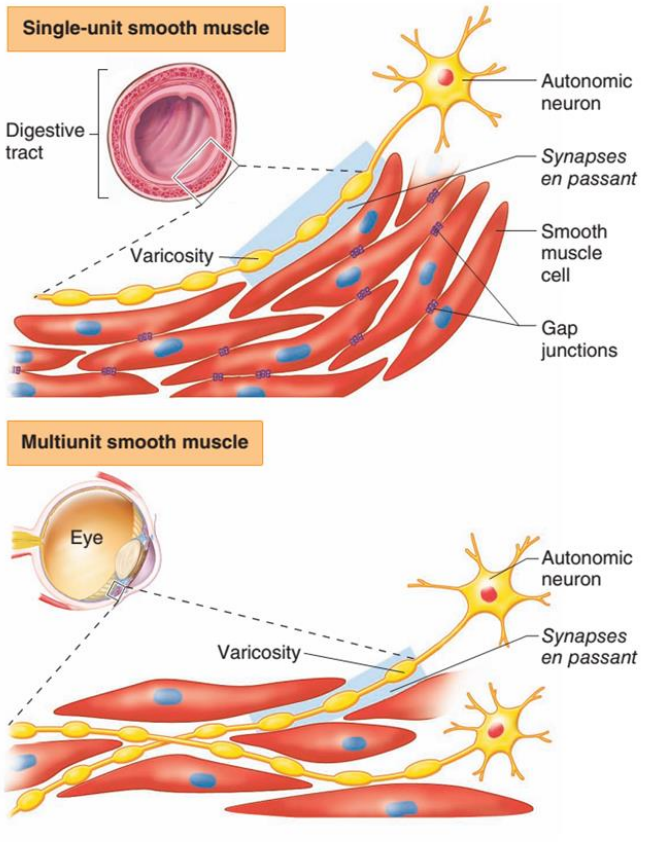
- Synchronous activity; the whole muscle tissue responds to stimulation as a single unit
  - Gap junctions
  - Pacemaker cells

- The axon terminals are often restricted to the regions of the muscle tissue that contain pacemaker cells.
- The activity of the entire muscle tissue can be controlled by regulating the frequency of the pacemaker cells' action potentials
- Activation by stretch
- Intestinal tract, uterus, and small-diameter blood vessels

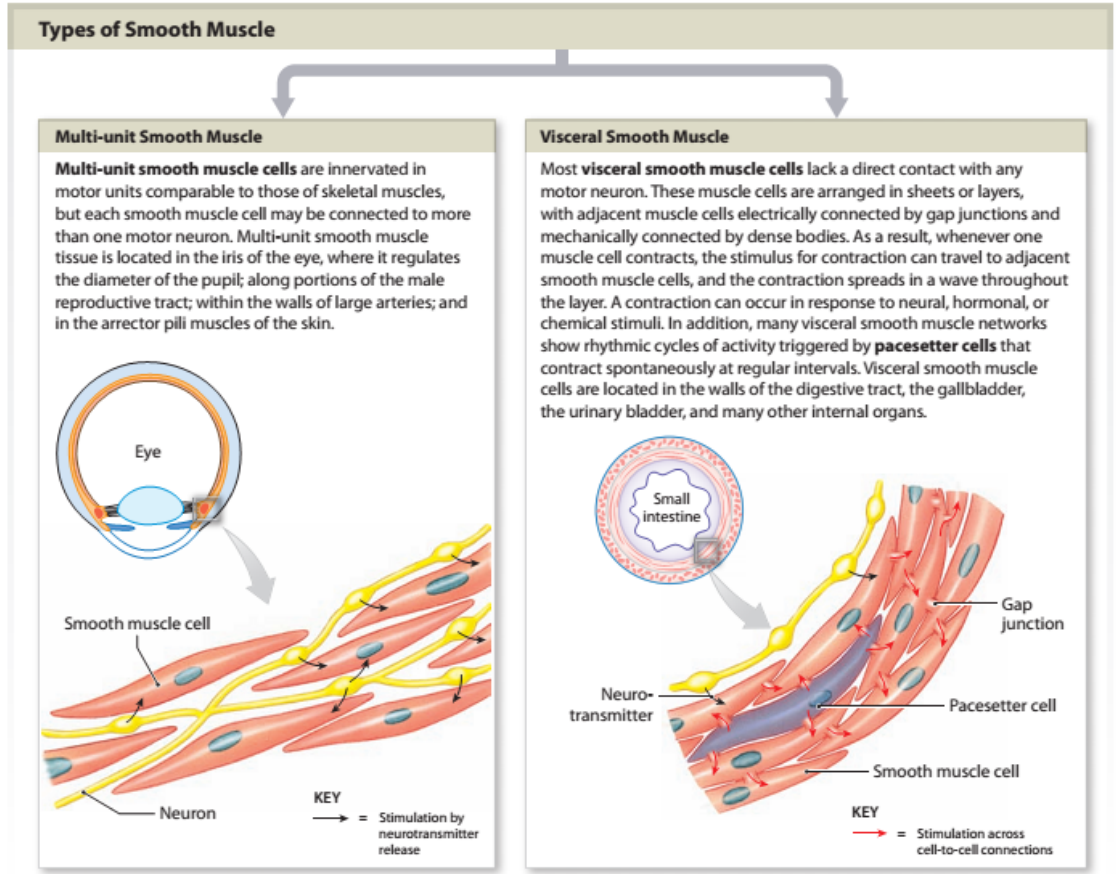


Multi Unit Smooth Muscles

- No or few gap junctions
- Each cell responds independently, and the muscle tissue behaves as multiple units
- Richly innervated
- The contractile response of the entire muscle tissue depends on the number of muscle cells that are activated and on the frequency of nerve stimulation
- The smooth muscles in the large airways to the lungs, in large arteries, and attached to the hairs in the skin



3 Smooth muscle tissue can be divided into two subtypes based on distinctively different methods of innervation and control.



Because the thick and thin filaments of smooth muscle are scattered and are not organized into sarcomeres, tension development and resting length are not directly related. A stretched smooth muscle soon adapts to its new length and retains the ability to contract on demand. This ability to function over a wide range of lengths is called **plasticity**. Smooth muscle can contract over a range of lengths four times greater than that of skeletal muscle. This is extremely important in organs like the stomach, the intestines, the urinary bladder, or the uterus, which must undergo major changes in size and shape. These smooth muscle tissues have a normal background level of activity known as **smooth muscle tone**. Neural, hormonal, or local chemical factors can increase or decrease smooth muscle tone and alter the degree of tension in the wall of a muscular organ.

LO **22.3** Describe the structural and functional features of smooth muscle tissue.

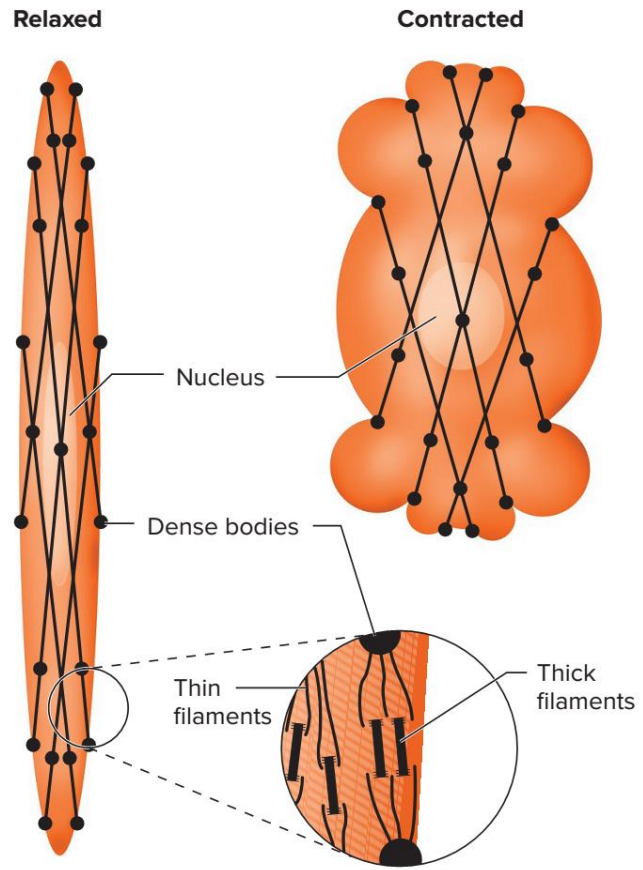
Table 12.8 | Comparison of Skeletal, Cardiac, and Smooth Muscle

Skeletal Muscle	Cardiac Muscle	Smooth Muscle
Striated; actin and myosin arranged in sarcomeres	Striated; actin and myosin arranged in sarcomeres	Not striated; more actin than myosin; actin inserts into dense bodies and cell membrane
Well-developed sarcoplasmic reticulum and transverse tubules	Moderately developed sarcoplasmic reticulum and transverse tubules	Poorly developed sarcoplasmic reticulum; no transverse tubules
Contains troponin in the thin filaments	Contains troponin in the thin filaments	Contains calmodulin, a protein that, when bound to Ca^{2+}, activates the enzyme myosin light-chain kinase
Ca^{2+} released into cytoplasm from sarcoplasmic reticulum	Ca^{2+} enters cytoplasm from sarcoplasmic reticulum and extracellular fluid	Ca^{2+} enters cytoplasm from extracellular fluid, sarcoplasmic reticulum, and perhaps mitochondria
Cannot contract without nerve stimulation; denervation results in muscle atrophy	Can contract without nerve stimulation; action potentials originate in pacemaker cells of heart	Maintains tone in absence of nerve stimulation; visceral smooth muscle produces pacemaker potentials; denervation results in hypersensitivity to stimulation
Muscle fibers stimulated independently; no gap junctions	Gap junctions present as intercalated discs	Gap junctions present in most smooth muscles

Smooth Muscle Contraction

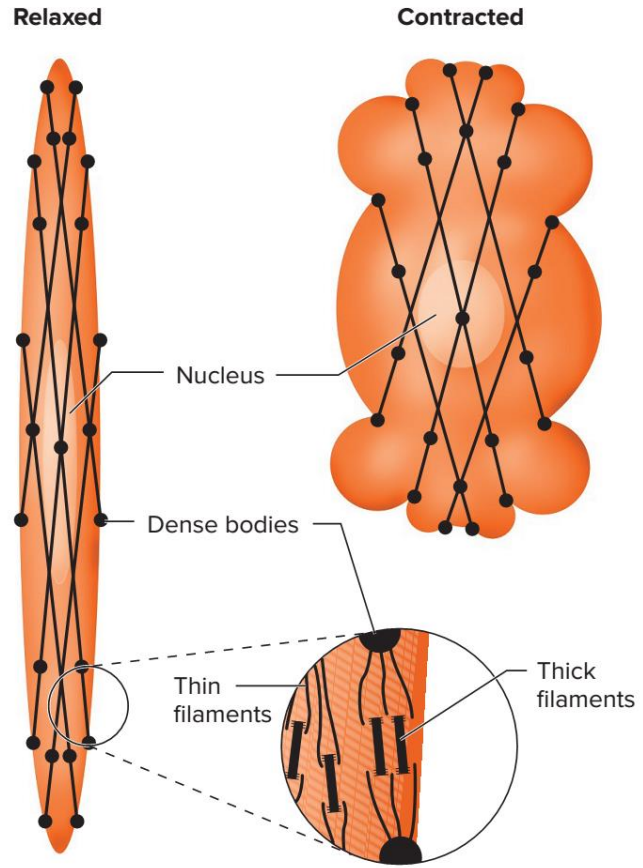
- Thin filaments are attached to plasma membrane or dense bodies (analogous to Z line)

- Filaments are oriented diagonally to the long axis of the cell
  - During shortening plasma membrane regions between attachment points balloon out



Smooth Muscle Contraction

- Sliding-filament mechanism
  - Less myosin, more actin
  - No regular alignment
  - Maximal tension developed by smooth muscles is similar to that of skeletal muscle
- The isometric tension produced by smooth muscle fibers varies with fiber length
  - tension development is highest at intermediate lengths and lower at shorter or longer lengths
  - significant force is generated over a relatively broad range of muscle lengths compared to that of skeletal muscle



Excitation-Contraction Coupling in Smooth Muscles

- The contraction of smooth muscles is triggered by a sharp rise in the Ca^{2+} concentration within the cytoplasm
  - calcium-induced calcium release
    - Sustained smooth muscle contraction
  - inositol triphosphate (IP3) produced at the plasma membrane due to stimulation by a hormone

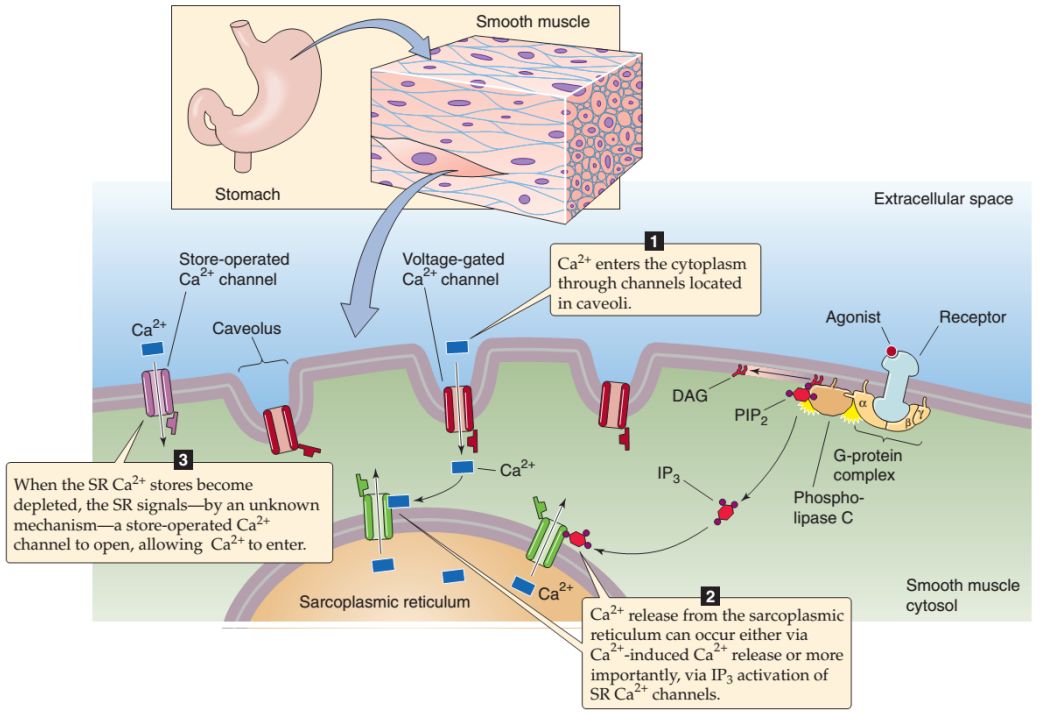
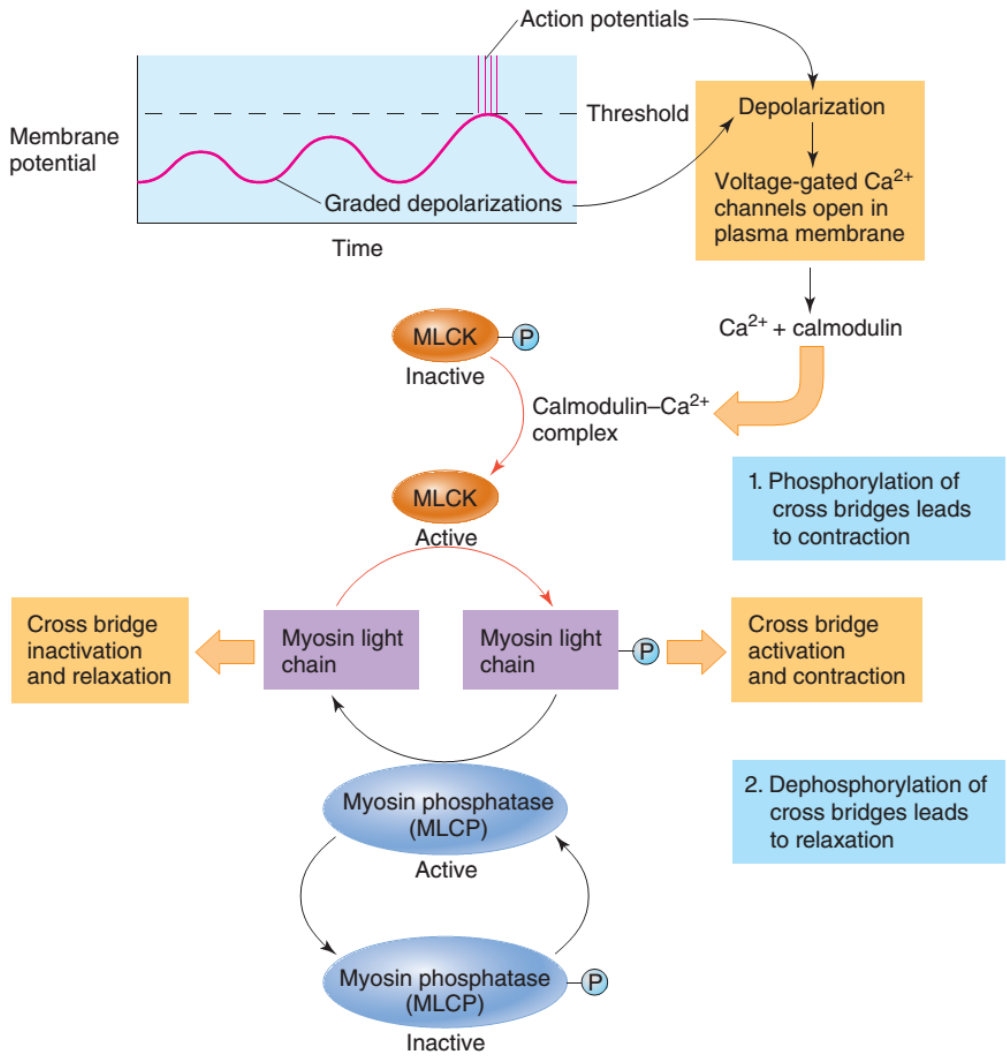
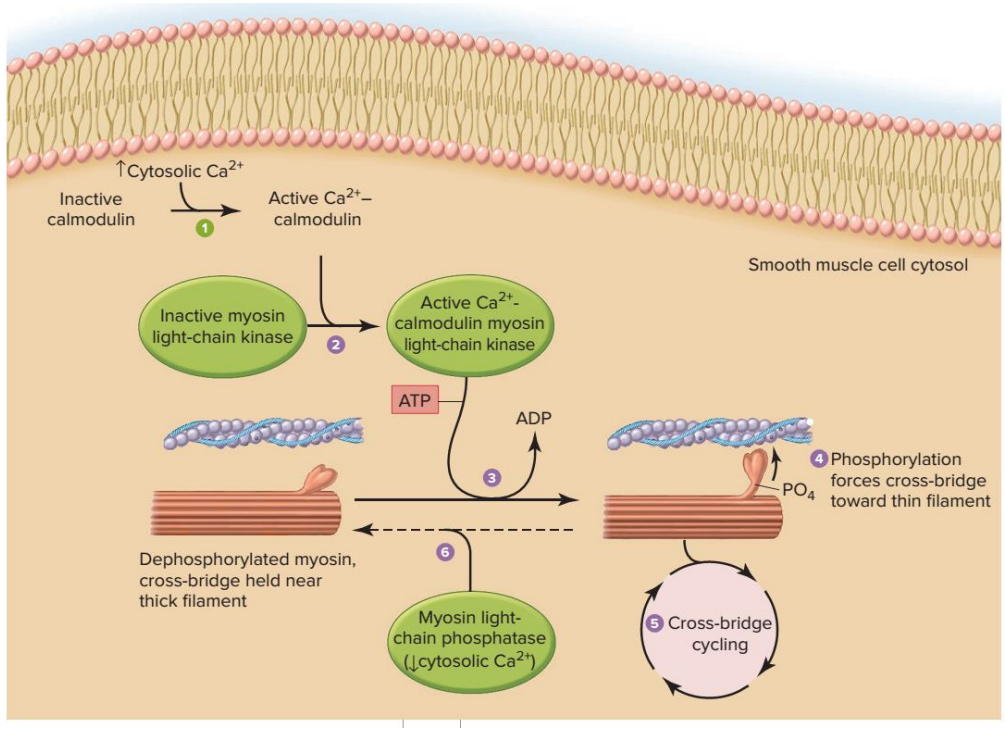


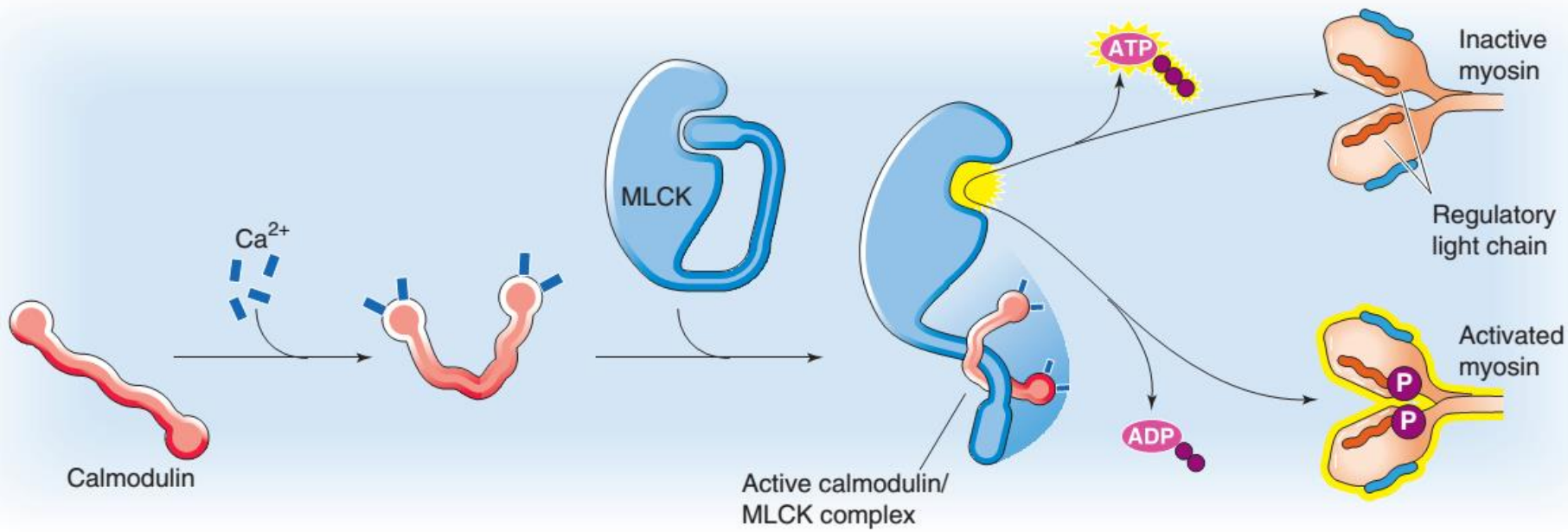
Figure 12.37 **Excitation-contraction coupling in smooth muscle.** When Ca^{2+} passes through voltage-gated channels in the plasma membrane it enters the cytoplasm and binds to calmodulin. The calmodulin-Ca^{2+} complex then activates myosin light-chain kinase (MLCK) by removing a phosphate group. The activated MLCK, in turn, phosphorylates the myosin light chains, thereby activating the cross bridges to cause contraction. Contraction is ended when myosin light-chain phosphatase (MLCP) becomes activated. Upon its activation, MLCP removes the phosphates from the myosin light chains and thereby inactivates the cross bridges.



Smooth Muscle Contraction

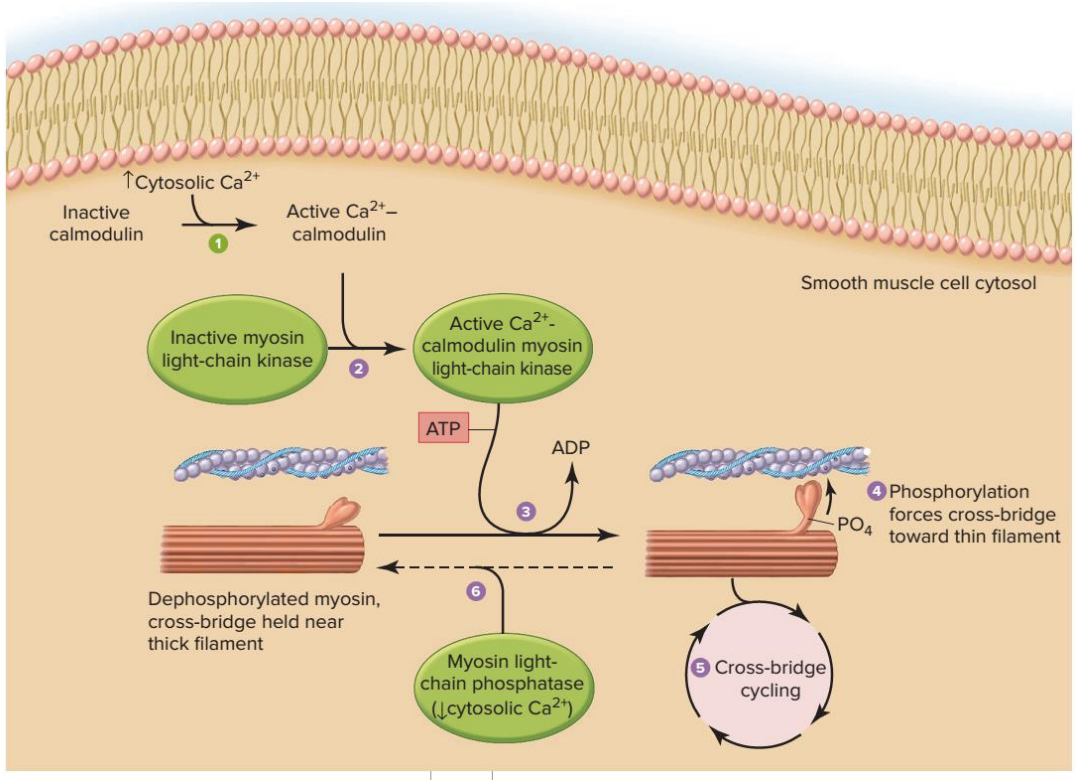
- Changes in cytosolic Ca^{2+} concentration
- Cross-bridge cycling in smooth muscle is controlled by a Ca^{2+} -regulated enzyme that phosphorylates myosin
  - Ca^{2+} -calmodulin myosin light chain kinase
- Only the phosphorylated form of smooth muscle myosin can bind to actin and undergo cross-bridge cycling



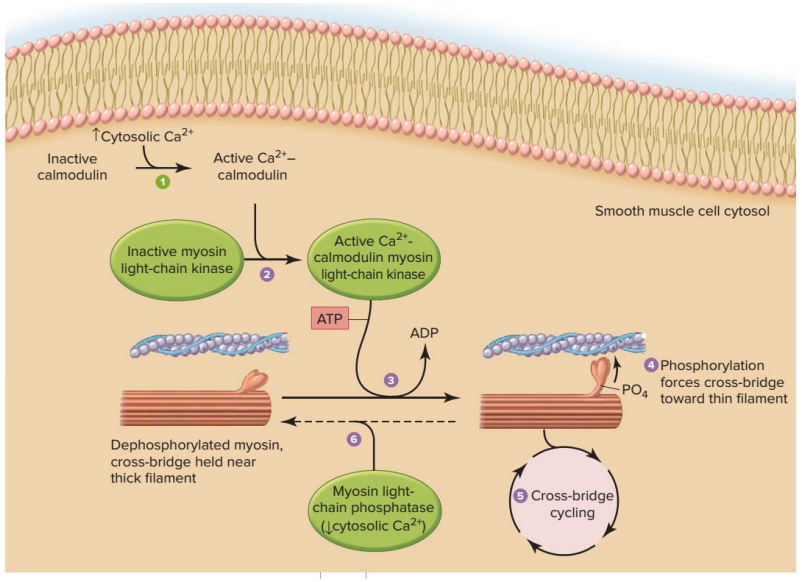

Ca2+
MLCK
ATP
Inactive
myosin
Regulatory
light chain
Activated
myosin
P
P
ADP
Calmodulin
Active calmodulin/
MLCK complex

Sliding Filaments Mechanism

1. Ca^{2+} binds to calmodulin
2. The Ca^{2+}–calmodulin complex binds to myosin light-chain kinase (MLCK), activates 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

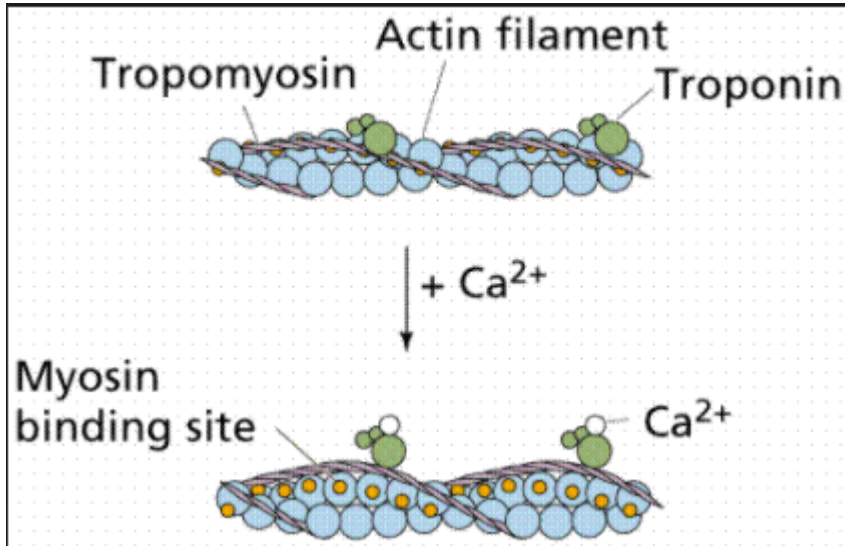


Smooth Muscle



Effect on myosin
Phosphorylation

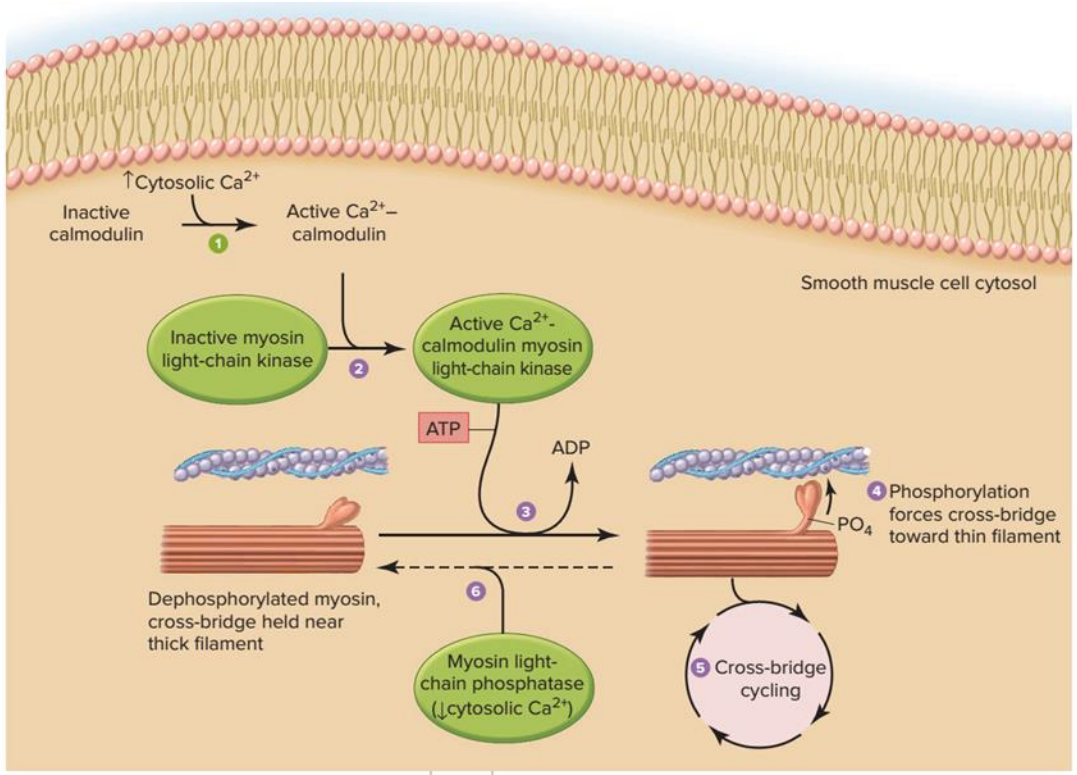
Striated Muscle



Effect on actin
Binding sites

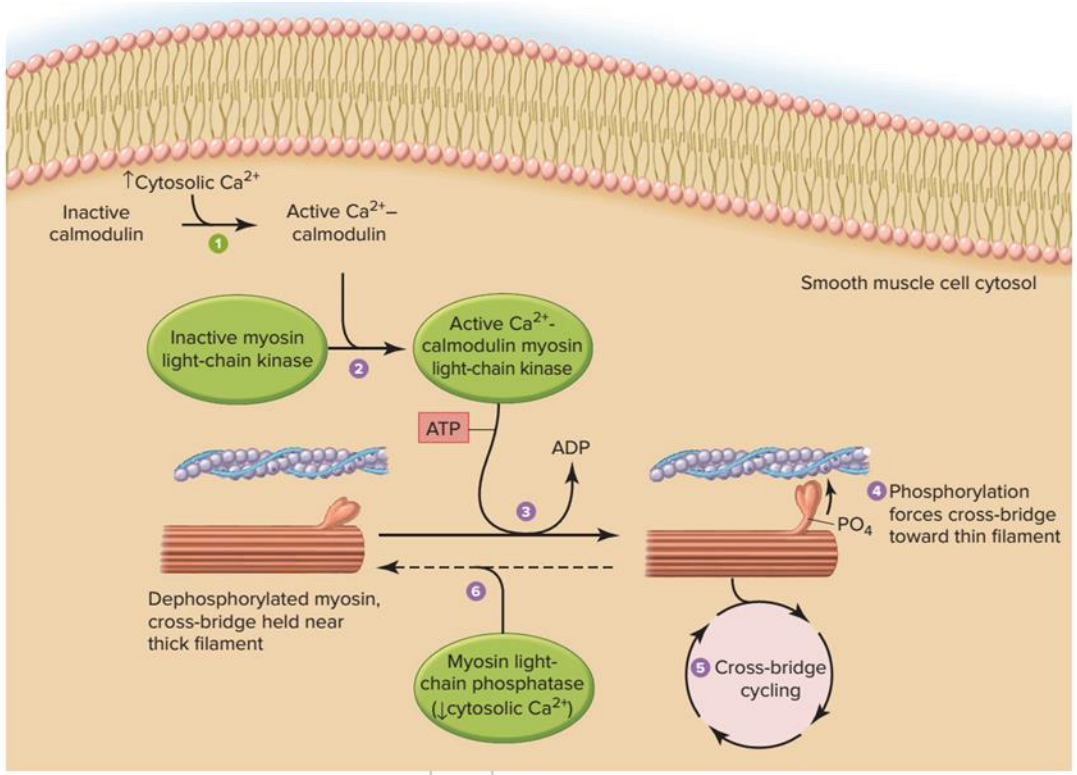
Smooth Muscle Contraction

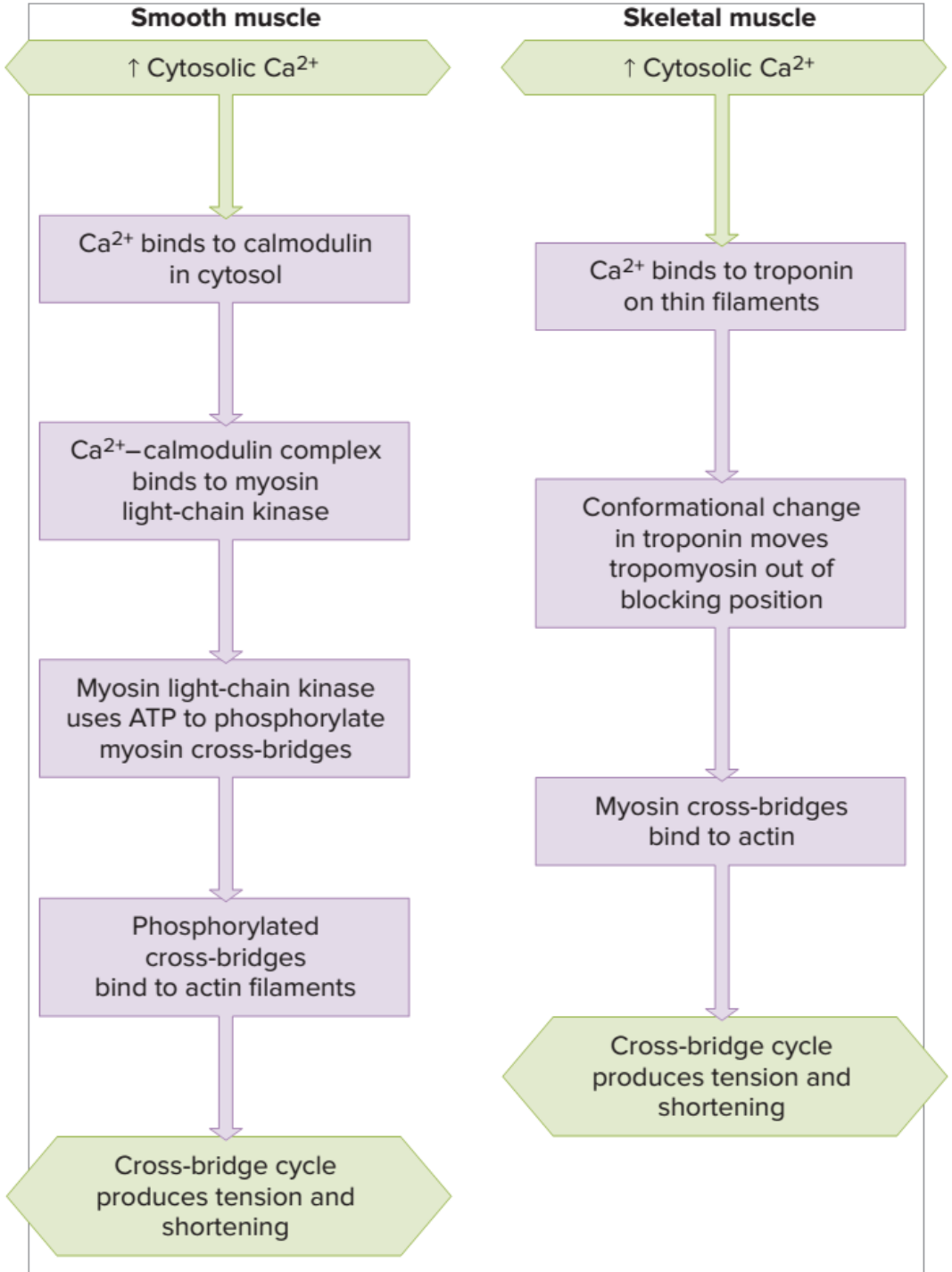
- *ATP hydrolysis determines the rate of cross-bridge cycling and shortening velocity*
- Smooth muscle myosin has very low rate of ATPase activity
  - 10-100 times less than skeletal muscle
  - Much slower muscle shortening
  - Because of slow rate of energy usage, smooth muscles does not undergo fatigue



Smooth Muscle Relaxation

- Myosin light-chain phosphatase (MLCP)
  - myosin dephosphorylation
  - continuously active
- Relaxation or contraction depends on the ratio between kinase and phosphotase
  - i.e. Cytosolic Ca^{2+}




Smooth muscle
↑ Cytosolic Ca^{2+}
Ca^{2+} binds to calmodulin in cytosol
Ca^{2+}–calmodulin complex binds to myosin light-chain kinase
Myosin light-chain kinase uses ATP to phosphorylate myosin cross-bridges
Phosphorylated cross-bridges bind to actin filaments
Cross-bridge cycle produces tension and shortening
Skeletal muscle
↑ Cytosolic Ca^{2+}
Ca^{2+} binds to troponin on thin filaments
Conformational change in troponin moves tropomyosin out of blocking position
Myosin cross-bridges bind to actin
Cross-bridge cycle produces tension and shortening

Latch State

- When stimulation is persistent and the cytosolic Ca^{2+} concentration remains elevated, the rate of ATP hydrolysis by the cross-bridges declines even though isometric tension is maintained
  - sphincter muscles of the gastrointestinal tract (prolonged contraction)
- Tension can be maintained in an almost rigor-like state without movement
- Much slow dissociation of cross-bridges from actin