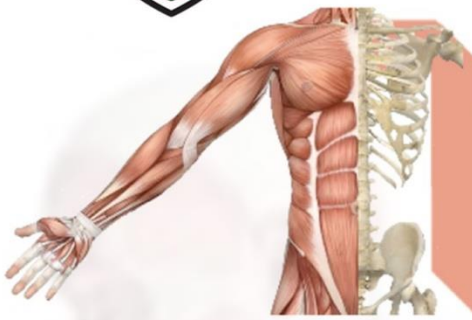

MSS

Musculoskeletal System

Doctor 2019 | Medicine | JU

Physiology

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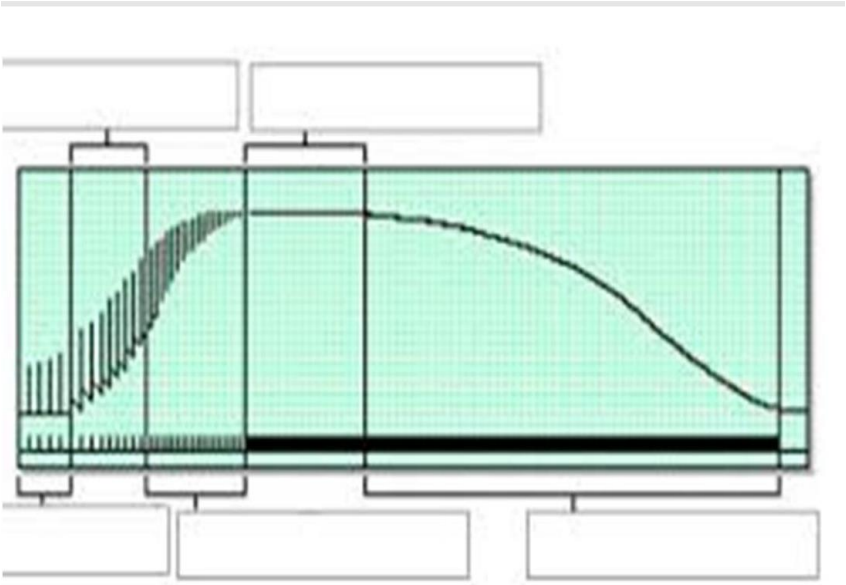
The Staircase Effect (Treppe)



*The simple muscle twitch has certain amplitude.

*After several contractions, the amplitude of simple muscle twitches increases which increases the strength of contraction. This is known as Treppe or staircase effect. (the second twitch is higher than the first, the third is higher than the second and so on)

*This effect is probably due to an increase in Ca++ concentration inside the cytosol with each muscle stimulation and inability of sarcoplasmic reticulum to recapture Ca++ immediately.

Note: The staircase effect (treppe) increases the amplitude of simple muscle twitches, it does not cause summation of twitches. The summation of twitches happens when the time between 2 twitches is less than the single twitch → summation without relaxation → tetanization.

*Remember that high concentration of calcium ions also causes uncovering of more active sites which produces sufficient contraction till we have tetanization.

*Prolonged and strong contraction of a muscle leads to the well-known state of muscle fatigue (the decrease in the graph after tetanization).

Muscle Fatigue

*Muscle fatigue is characterized by the muscle not responding to the stimulus, it is caused by depletion of ACH neurotransmitters in the neuron of the neuromuscular junction. (In the lab)

*Muscle fatigue can also be caused by other conditions such as accumulation of lactic acids (glycolysis). The muscle can still contract but with pain caused by the low PH. This is not real fatigue because the muscle is still contracting so it is still responding to the stimulus. (In the body)

*In the fatigue phase there is no direct relaxation. It is somehow similar to tetanization but with a lower contraction power, the muscle continues to have weak contractions till it reaches the relaxation period.

*During fatigue phase, we can have some contraction of the muscle through direct stimulation, but never through neural stimulation because of the depletion of ACH in the nerve ending. (In the lab)

Summation of Simple Muscle Twitches

*There are two types of muscle summation: frequency summation (wave summation) and motor summation.

*By now we are familiar with the concept of frequency summation, it happens when a muscle is stimulated by more than one stimulus and the time between 2 successive stimuli is less than the duration of simple muscle twitch. This may result in summing of the successive contractions. When the frequency of stimulation is more increased and the muscle responds by contraction without any relaxation, we can say that the muscle is in tetanization.

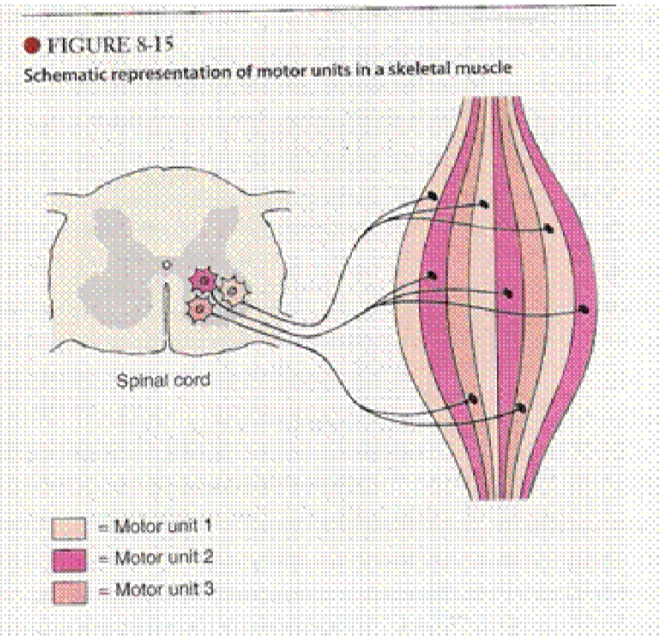


Figure 4. One motor unit can control multiple muscle cells.
Taken from Sherwook, 2004

*The motor neuron has many terminals, each terminal innervates one muscle fiber, and each muscle fiber is innervated by one neuron.

*The group of muscle cells innervated by 1 neuron is called a motor unit.
*The single muscle has more then 1 motor unit.

*Motor unit summation (multiple fibers summation) is achieved by increasing the number of motor units contracting simultaneously.

*If only few nerve fibers in a nerve that innervates a muscle are stimulated, this will induce shortening only in the muscle fibers are innervated by the stimulated nerve fibers. When the number of nerve fibers stimulated increases, this will recruit more motor units in contraction.

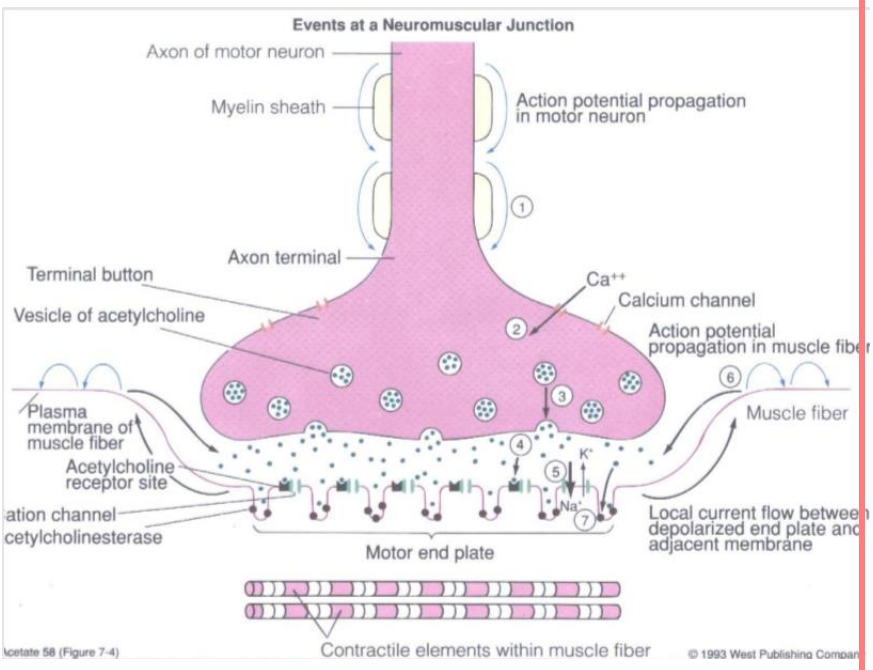
*The increase in contraction will result in an increase in the amplitude of simple muscle twitch. In human body this summation is important for gradation of forces during contraction (lifting 2kg box needs contraction of x motor units, lifting 5kg needs more than x motor units, etc)

*The number of muscle fibers innervated by a single neuron (motor unit) differs between muscles depending on the function of the muscle. Muscles of the tongue, lips and hands need fine and precise movements → small motor unit. Muscles of the back have no need of precise movements → large motor unit.

*Keep in mind that fast muscles have short-lasting simple twitches, while slow ones have longer-lasting twitches.
*The period of the muscle twitch is affected by temperature; high temp. decreases the period of twitch, and low temp. increases it.

For further explanation of Excitation-contraction coupling, watch this:
https://www.youtube.com/watch?v=LlgaziPCFU0

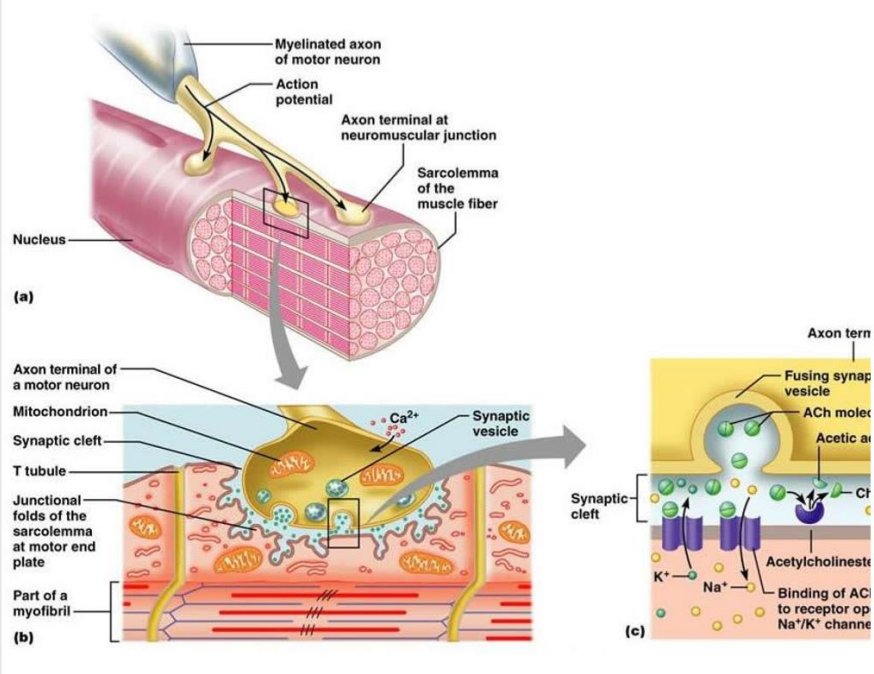
Secretion of Ach from the nerve ending into the neuromuscular junction:



In order to get the muscle contracted, we need to generate an action potential that travels through the axon of a motor neuron. And once it reaches the axon terminal (terminal button), Voltage-gated calcium (Ca2+) channels are activated, followed by the entry of Calcium ions into the terminal button and the release of Ach by exocytosis, as a consequence. Remember that the terminal button synapses with a highly specialized part of sarcolemma called motor end plate. This part contains ligand gated channels that are activated after Ach (ligand) binds nicotinic receptors causing Na+ influx (depolarization).

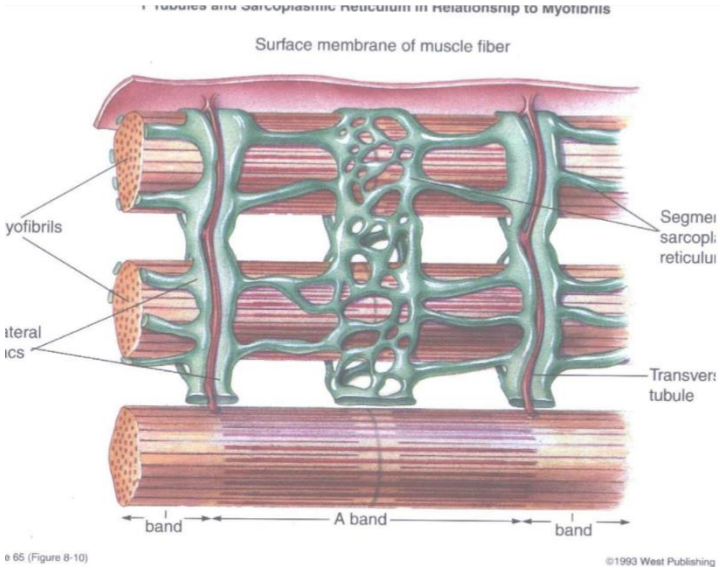
Motor end plate also has acetylcholinesterase which breaks down Ach to stop the signal.

So far, we have our motor end plate depolarized, yet we haven't generated Action potential, and we call this potential motor end plate potential (similar to excitatory post synaptic potential). The motor end plate potentials are summated together, if the depolarization was sufficient to reach the threshold, then the voltage gated sodium channels open and the action potential will be generated and spread throughout the sarcolemma.



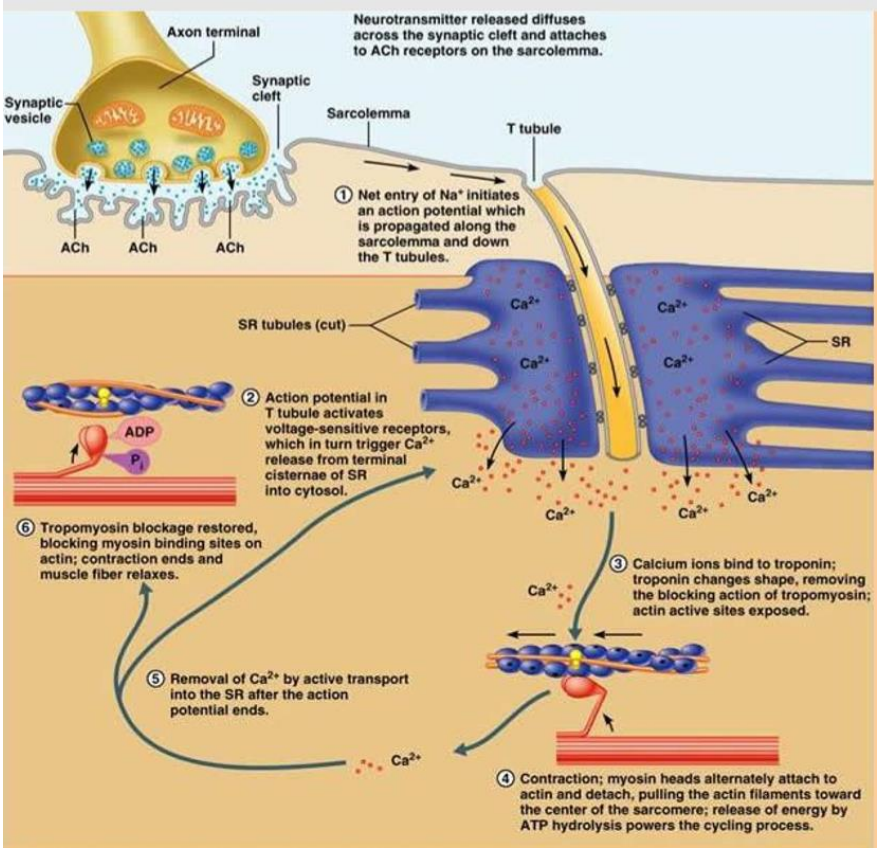
*Note: If the summation of motor end plates potentials does not reach the threshold, the action potential will not be generated, and the muscle will not contract.

*Remember the structure of the sarcomere,
-The sarcolemma which surrounds the myofibrils
-Transverse tubules which extend from the sarcolemma into fibrils to transmit the action potential. Theses T tubules contain extracellular fluid.



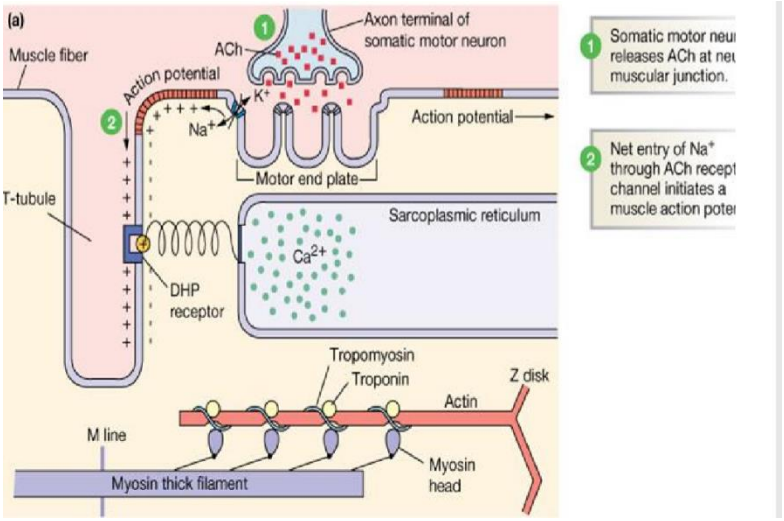
Once action potential reaches t tubules, it is transmitted to the interior of the cell where it stimulates the release of Ca++ into the cytosol (sarcoplasm).

T tubules, which are located at the junction of A and I bands of the sarcomere help in the release of Ca++ in close vicinity to contractile proteins of the myofibrils.
These structures form a triad (2 sacs (terminal cisternae) of sarcoplasmic reticulum and one T tubule).



*The gap between sarcoplasmic membrane and T tubule is spanned by a protein structure called foot protein.

*The part of foot protein in sarcoplasmic reticulum serves also as Ca++ channel and is known as ryanodine receptor. (ryanodine is existed in types of plants which makes a conformational change in this receptor)



*The part of foot protein on T-tubules is known as dihydropyridine receptor. (Dihydropyridine is a chemical substance not existed in a human body, but has an effect on this receptor)

*Dihydropyridine receptors are voltage sensors.

*The change in voltage of T-tubules (action potential) will induce conformational changes in the whole foot protein, which results in activation and opening of ryanodine receptors and rapid release of Ca++ from the sarcoplasmic reticulum into the sarcoplasm, which binds to troponin C and causes muscle to contract. (Conc. of Ca++ in the SR is 10^{-3} while it is 10^{-7} in the sarcoplasm)

****Foot protein=Dihydropyridine receptor on T-tubule + ryanodine receptor on sarcoplasmic reticulum.

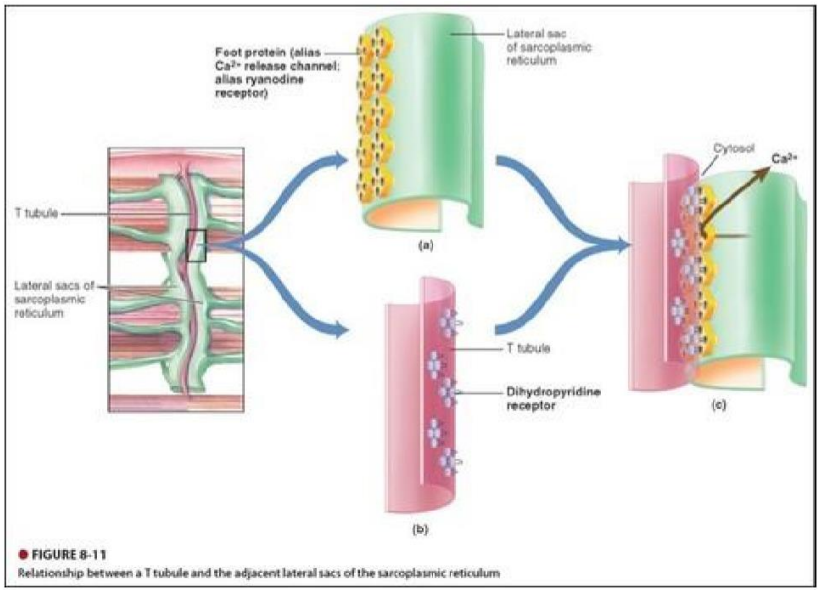


FIGURE 8-11
Relationship between a T tubule and the adjacent lateral sacs of the sarcoplasmic reticulum

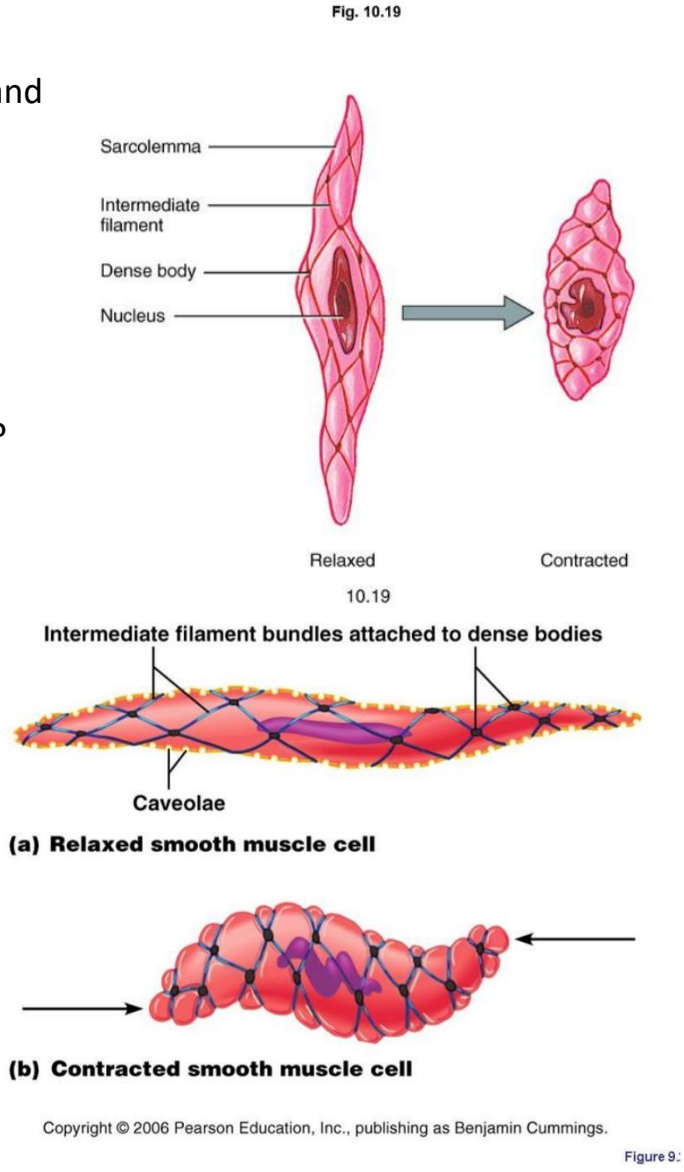
Clinical disorders

There is a disease (remember the immunology course) called myasthenia gravis (autoimmune disease), which is about producing autoantibodies against chemical (ligand) gated Na+ channels → reducing Ach transmitted to the innervated muscle.
It is treated by inhibiting acetylcholinesterase in the motor end plate → increasing Ach → facilitate the transmission of action potential.

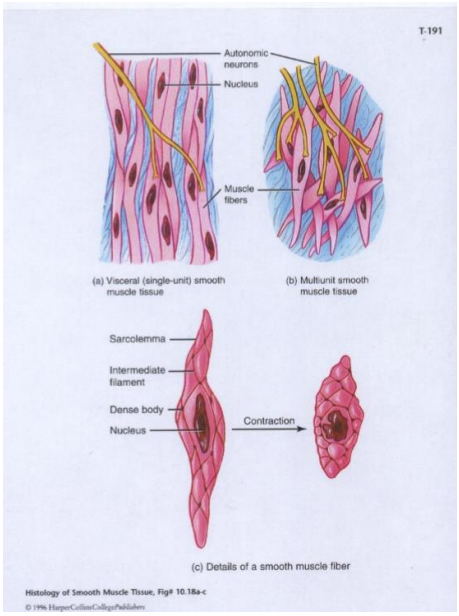
Smooth muscle cells

Smooth muscles are spindle-shaped, nonstriated and uninucleated cells.

- They are widely distributed in our body as they exist in our blood vessels, alveoli and many more sites.
- Do smooth muscles contain thick and thin filaments? YES.
- Do smooth muscles contain contractile proteins? YES, they have actin and myosin.
- Note that the black dots represent the dense bodies
- The dense bodies function is to hold the thin filaments the same way the Z-disk does in striated muscle.
- In the midway between dense bodies, few myosin filaments are found where they overlap with actin filaments.
- As we know, the interaction between the thin and thick filaments results in shortening the muscle through pulling of the dense bodies to a closer distance.



- Do we have neuromuscular junctions in Smooth muscles? No
- In smooth muscles, there are no specialized parts of the sarcolemma that contain the receptor like in skeletal muscles (motor end plate), that is why the receptors are dispersed all over the membrane. The neurons that innervate the smooth muscle cells release the neurotransmitter around the smooth muscle cells and according to the concentration of excitatory and Inhibitory NTs we could have our smooth muscles contracting or relaxing.
- Smooth muscle cells have receptors for many NTs, they even have receptors for inflammatory mediators like prostaglandins, unlike skeletal muscles which only have nicotinic receptors.



How are smooth muscles stimulated?

Chemical control of smooth muscle

A. Smooth muscle receptor binds to a chemical compound/ligand.

B. Activated phospholipase C splits the membrane phospholipid to Inositol trisphosphate (IP3) and diacylglycerol (DAG)

C. IP3 has a receptor on the ER, which is linked to Ca++ channel.

D. Once IP3 binds to its receptor, calcium channels open.

E. calcium ions move into the sarcoplasm and a cellular response is initiated.

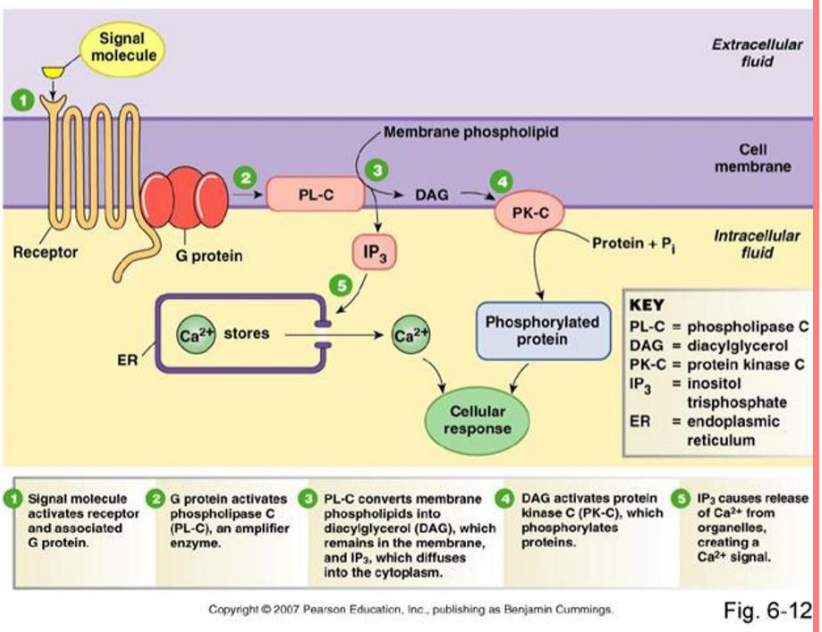
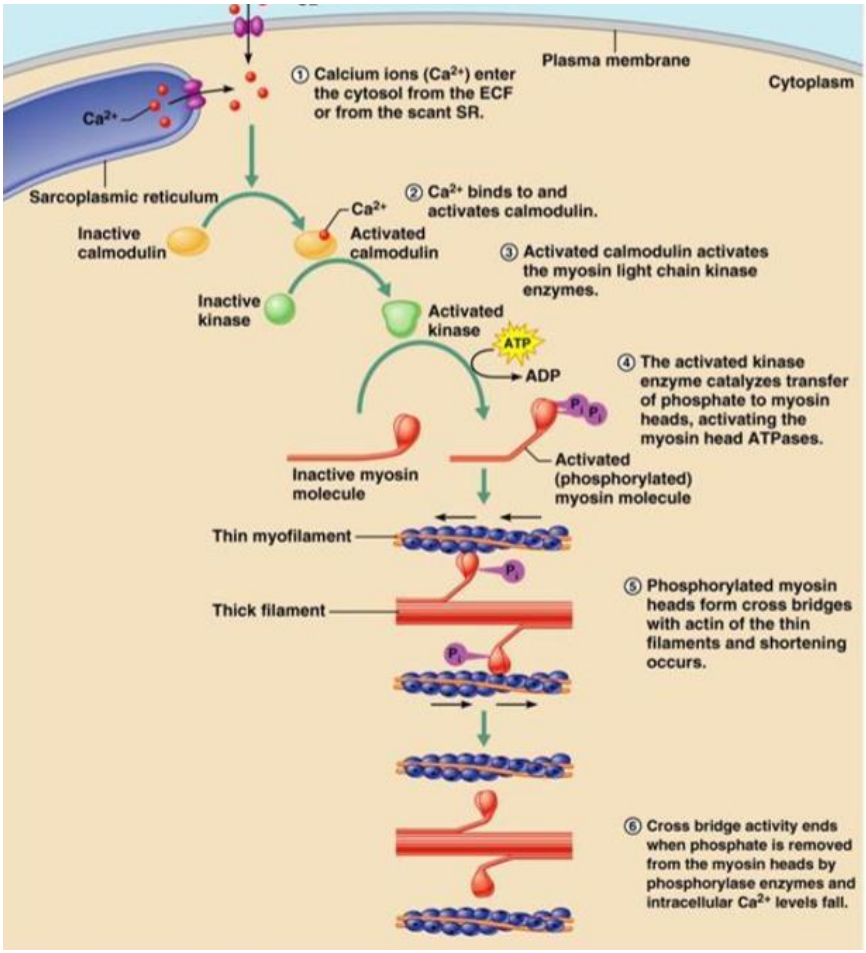
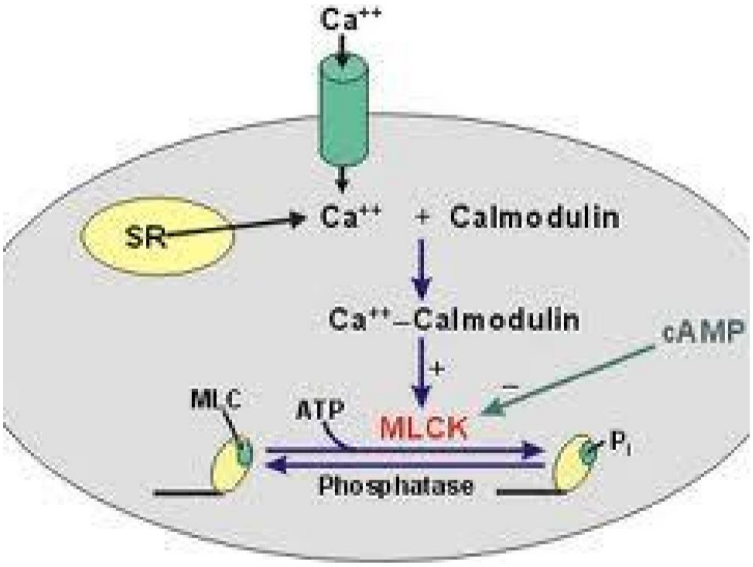


Fig. 6-12

Electrical control of smooth muscle



• Smooth muscle cells have voltage gated Ca2+ channels on the sarcolemma, and these channels are under the control of potential changes, so the electrical control can activate Ca2+ channel and cause influx of Ca2+ .The release of Ca++ whether it was from an internal (SR) or external source (ECM) into the cytosol induces activation of a protein known as calmodulin by forming calmodulin-Ca++ complex (4 Ca++ bind to one calmodulin). The activated calmodulin-Ca++ complex will induce activation of an enzyme called myosin light chain kinase (MLCK). This enzyme will phosphorylate myosin's head increasing its affinity to actin. The phosphorylated myosin can now interact with actin to induce contraction.



Notes:

• We can limit the actin-myosin interaction by dephosphorylating the myosin's head after activating the phosphatase enzyme.

• cAMP inhibit the MLCK which causes muscle relaxation.

• What does determine the activity status of the smooth muscle? Answer: The concentration of excitatory & inhibitory NTs and the balance between them. For instance, if we have more excitatory NT, this means that we will have muscle contraction and vice versa.

• The control of smooth muscle is more complicated than that of skeletal muscles.

*Activation of Ca++ channels at the sarcolemma helps in the contraction of smooth muscles (these channels are not in the skeletal muscles but existed in the cardiac muscles)
*Activation of receptors that increase cAMP → relaxation
*Activation of receptors that increase Ca++ (phospholipase C) → contraction

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 in into dense bodies and cell membrane
Well-developed sarcoplasmic reticulum and transverse tubules	Moderately developed sarcoplasmic reticulum and transverse tubules	Poorly developed sarcoplasmic reticulum; nc transverse tubules
Contains troponin in the thin filaments	Contains troponin in the thin filaments	Contains calmodulin, a protein that, when bc to Ca^{2+}, activates the enzyme myosin light-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 fluic 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 stimulatic visceral smooth muscle produces pacemak potentials; denervation results in hypersens to stimulation
Muscle fibers stimulated independently; no gap junctions	Gap junctions present as intercalated discs	Gap junctions generally present