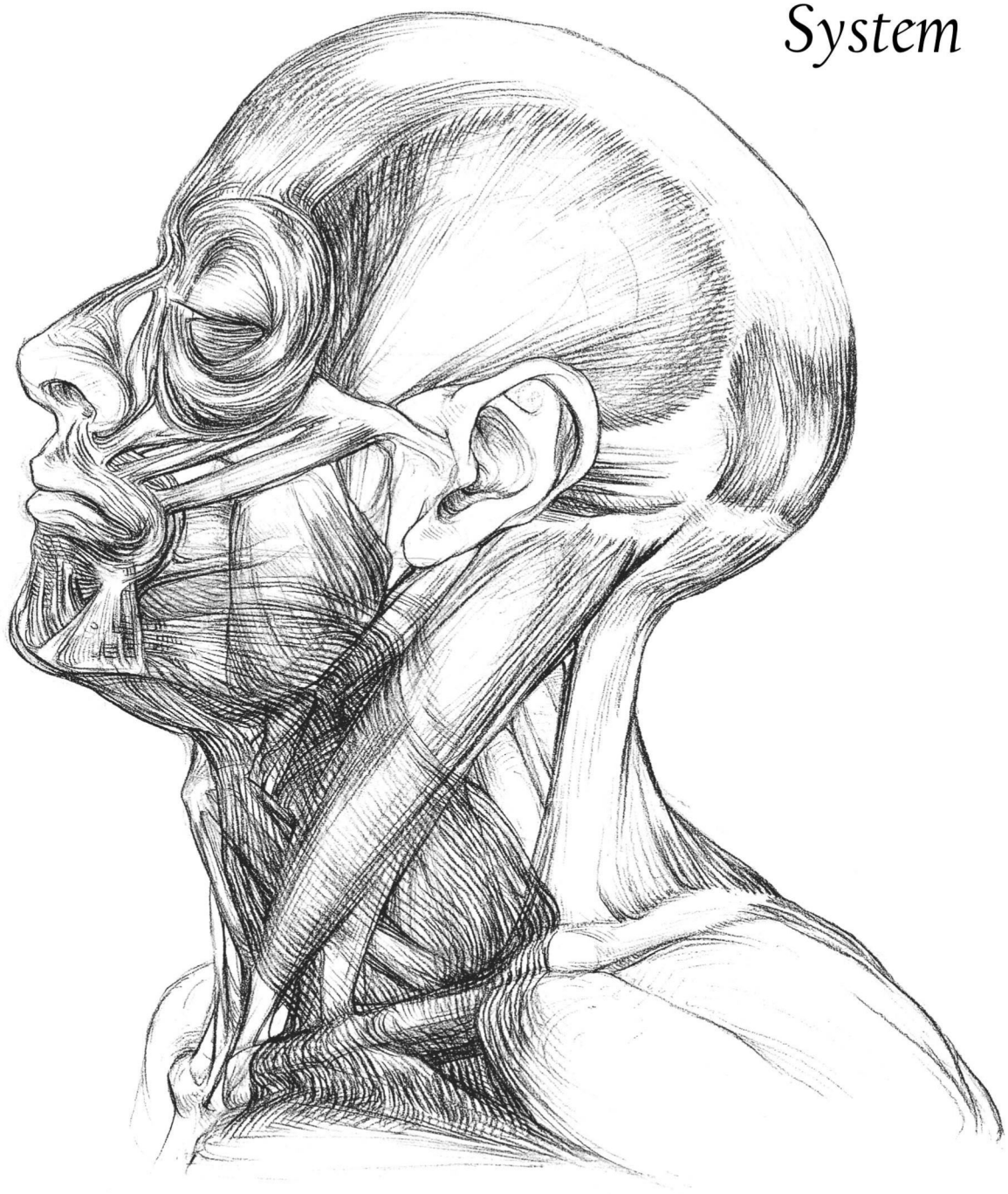
Medical Committee
The University of Jordan

The Skin and MUSCULOSKELETAL System



PHYSIOLOGY

SLIDES ☐
SHEET ■
LECTURE # 4

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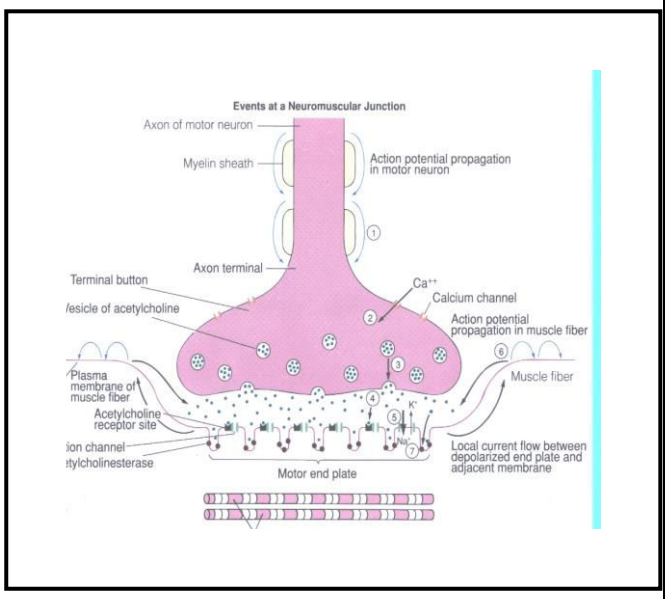
Skeletal Muscles (cont.) & Smooth Muscles

I think you know the summation process that we have talked about and I think you were given everything also ; we said that we can have two types of summation :

1- **Frequency summation** (**Wave summation**).
2- **Motor unit summation**.

Now , what we mean by it ? and how there are more than one motor unit involved in contraction ? We will see ☺.



I think you also know this structure , which is the **(NMJ)** at the level of each muscle fiber. We have one terminal ending with one muscle fiber. Notice the membrane of the muscle which is called **Sarcolemma** , forming what we are calling **neuromuscular junction (NMJ)**.
So once we have a motor neuron generating an action potential and reaching that terminal , we are getting release of neurotransmitters ; actually by activation of calcium channels that we are having , here, at the terminal membrane . After the entry of calcium to the terminal ,these vesicles will be triggered to fuse with the terminal membrane . Then , **exocytosis** is induced , so there will be an increase in the concentration of acetylcholine in that synaptic cleft.
At the level of that muscle membrane , which is very specialized part , there is a part called Motor End Plate .

At Motor End Plate , we have receptors for ACH . What type of receptors we have for ACH to bind ?

A: **Nicotinic Receptors**

Those receptors on Motor End Plate (nicotinic receptors that ACH bind to) are linked to Sodium (Na^+) channels . Once ACH molecules bind to their receptors ,those sodium channels will be activated .

Now this activation of sodium channels will result in What ?
** Are you getting action potential ?? – No , not yet .
But rather , we have developing small depolarizations (sub-threshold) which are generated at the motor end plate , so they are called motor end plate potentials.

-Motor end plate potentials are similar to the excitatory post-synaptic potentials that we are having in the synapse .
Even if they are similar , we still calling them motor end plate potentials .

Now these potentials undergo summation , like electrical summation we took 3 weeks ago .We are getting summation , and if the summation reaches threshold , we will have action potential at the sarcolemma .

That action potential ,now, will spread all over the sarcolemma . In addition, we have a structure called acetylcholine esterase to destroy the ACH . If we don't destroy it , ACH concentration will increase , generating more potentials , generating more action potential and so the muscle will keep contracting all the time . So we have to destroy ACH as fast as possible, that's why the enzyme is very active , very fast .

So If we're getting another action potential , another release of neurotransmitter then another action potential will be generated at the muscle membrane .
When we have no stimulus , the release of ACH is very low , and that's not enough to stimulate all the Na+ channels ,in order to make a depolarization that can reach the threshold (action potential) .

Myasthenia Gravis : it is a disease that result in the destruction of the sodium channels so we have few number of active sodium channels .

In this case , the transmission of action potential from the terminal toward the muscle is Much Less , so the muscle becomes weaker .

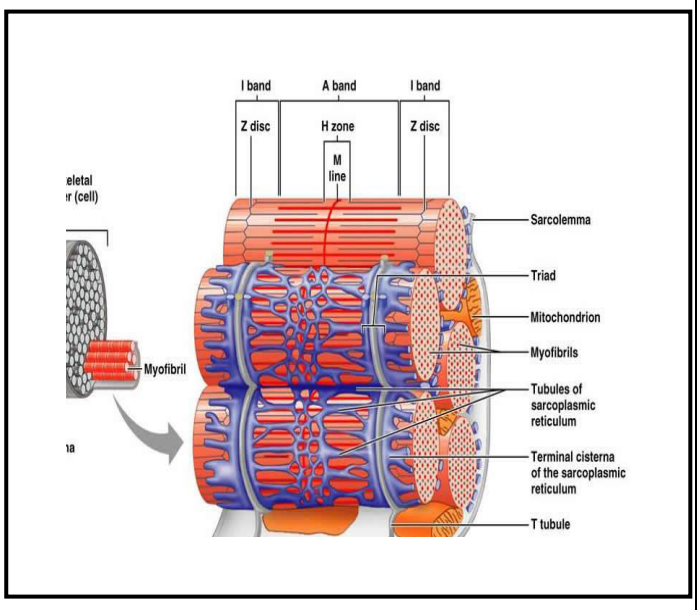
To increase that transmission , we increase the ACH concentration in the synaptic cleft , sometimes by giving the patient acetylcholine esterase inhibitors. As a result , ACH concentration increase in order to get much higher probabilities in binding and activating the few channels that are available there .If this activation happens , we will generate action potential .

Again , this disease is an autoimmune disease that result in antibodies that destroy the sodium channels , so less transmission of action potential is achieved . And weakness in the muscle will develop .

The doctor talked that there is drugs ; some of which increase the transmission , others decrease it . He will not ask us about them .

Acetylcholine Esterase Inhibitors (that inhibit the activity of acetylcholine esterase)are one of the drugs that potentiate the transmission .
Now we have generation of action potential at the periphery by the summation , and this action potential will spread all over the sarcolemma .

Now look at the picture , we have the whole muscle fibers as you see ; notice the sarcolemma : at a certain point there is an invagination of it deeply in the muscle, forming an important structure called **Transverse tubules (T-tubules)**.



So the fluids we have in the T-tubules are cellular & extracellular fluids .

At any time we have an action potential , it will deeply (inside the muscle cell) transmitted through the T-tubules .

Also notice the sacs of sarcoplasmic reticulum (that have high concentration of calcium inside) on the both sides of each T-tubule , forming what is called : Triad .

Two sacs of sarcoplasmic reticulum on each side of one T-tubule = Triad.

In Skeletal Muscles : usually , the triad is located between the I-band & the A-band . But in Cardiac muscle , we will not find this structure (the Triad) , instead we have what is called Diad (only one sac of sarcoplasmic reticulum and one T-tubule) , and it is located in different place .

Once the action potential reaches the T-tubules , calcium will be released from the sacs beside the tubules . But how this will happen ?

- We have a protein structure , that is passing(spanning) the two membranes (first one : the membrane of the sac , the other : is the membrane of the T-tubule).
- The whole protein called : Foot Protein ; it has two parts :
  - **Dihydropyridine** receptor :the one that invade the T-tubule .
  - **Ryanodine** receptor : the one invade the sac of sarcoplasmic reticulum. It works as calcium (Ca^{+2}) channel , when the action potential reach such these receptors , it will induce conformational changes in them triggering the Ca^{+2} to release from the sacs of sarcoplasmic reticulum toward the cytosol of the cell.

-Both Dihydropyridine & Ryanodine are chemical substances found in plants , for example , but never found in our bodies .

- Then , why we still call these two parts as Dihydropyridine & Ryanodine receptors ?!

Because they found that these substances can bind to their corresponding receptors and stimulate them , that's why they called them receptors ☺

-Remember that there is a difference in Ca^{+2} between the sacs & the cytosol , in the Sacs of sarcoplasmic reticulum the[Ca^{+2}] = 10^{-3} molar But in the Cytosol the [Ca^{+2}] = 10^{-7} molar .

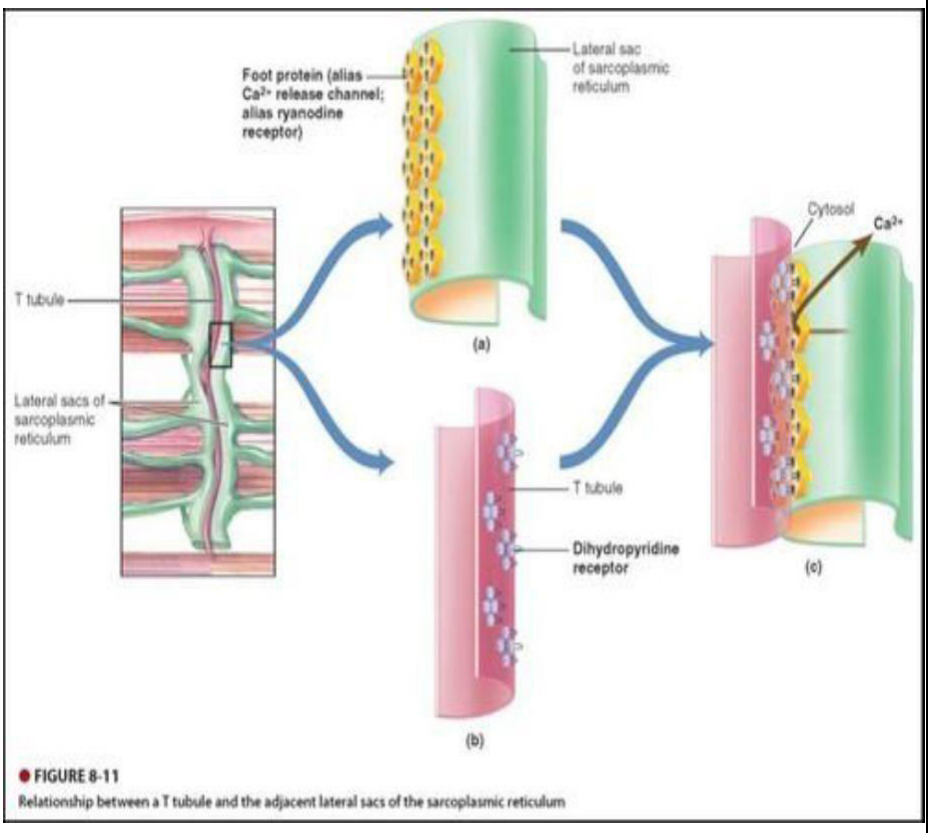


FIGURE 8-11
Relationship between a T tubule and the adjacent lateral sacs of the sarcoplasmic reticulum

So there is 10^{4} times (ten thousand fold)difference in concentration ,that's why you have a fast release of Ca^{+2} from the Sacs (from high to very low Conc.) once the Ryanodine receptors are stimulated .

** Look at the picture. and notice the Foot Protein .

You know what will happen if we increase the [Ca^{+2}] in the cytosol.

And remember that Ca^{+2} bind(4 molecules) the troponin C to permit the interaction between thin & thick filaments and so induce contraction.

So this is the story of Skeletal Muscles .

"we have neuromuscular junction and once the action potential is transmitted from the nerve terminal to the muscle fiber , it will spread all over the sarcolemma reaching deeply the muscle fibers through the T-tubules , then induce conformational changes and release of Ca^{+2} from the sacs of sarcoplasmic reticulum , then contraction will happened "

That's whole process called : **Excitation-Contraction Coupling** .

Smooth Muscle Cells

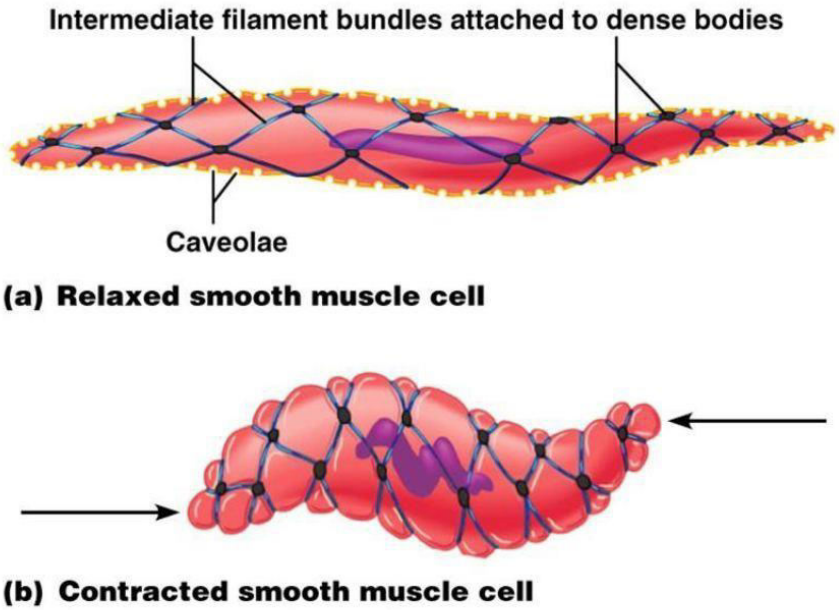
We will also take something about Smooth Muscle Cells to understand some differences between different types of muscles (Skeletal , Cardiac & Smooth)

As you know smooth muscle cells are widely distributed in our body , in most our tissues . They are found in our Gastrointestinal tract , in the uterus .. etc. In each part or place they are found in , they have different behaviors Not like skeletal muscles (that have standard function in all our body).

**Look at the pic :

- We are having , here , two smooth muscle cells: One of them is contracted (because of a stimulus) and the other is relaxed .

-One of the things you will find in these cells , a globular protein structure which are called : Dense Bodies .The function of these bodies is to hold thin filaments "actin filaments"



Are we having contractile proteins ?

Yes , we Must have . Otherwise we will not have any contraction .

But the organization of these contractile proteins isn't the same as in the skeletal muscle , that's why we don't have striations here .

-In Skeletal Muscles we have Z-disks that hold the thin filaments together , So Dense Bodies in Smooth Muscles function as Z-disks in Skeletal Muscles .

-Between thin filaments we have thick filaments , in order to induce sliding and contraction .

-The lines we are seeing , above, between dense bodies , are the thin & thick filaments .

We have a property found in smooth muscle ,but not found in skeletal muscles . Remember that in skeletal muscles , we have a nerve terminal ending at a muscle , forming neuromuscular junction (NMJ) . But we don't have NMJ in Smooth muscles , instead the nerve terminals end loosely in the space between the smooth muscles , releasing their neurotransmitters and then they bind to their receptors, inducing contraction or relaxation or whatever their function is .

Also , in smooth muscles the nerve endings aren't found in a specialized part as in skeletal muscles (Remember : it was the Motor End Plate), instead they end all over the muscle . So we have receptors all over the muscle (smooth muscles) also.

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We have two ways by which we can control the smooth muscles activity : One of these ways is : the electrical activities .

Electrical Activities : can activate Ca^{+2} channels on the sarcolemma , then Ca^{+2} release and this will result in binding of Ca^{+2} with Calmodulin , this binding will activate an enzyme called : Myosin Kinase "as the name implies , it will phosphorylate the myosin , and once it's phosphorylated it can interact with actin"

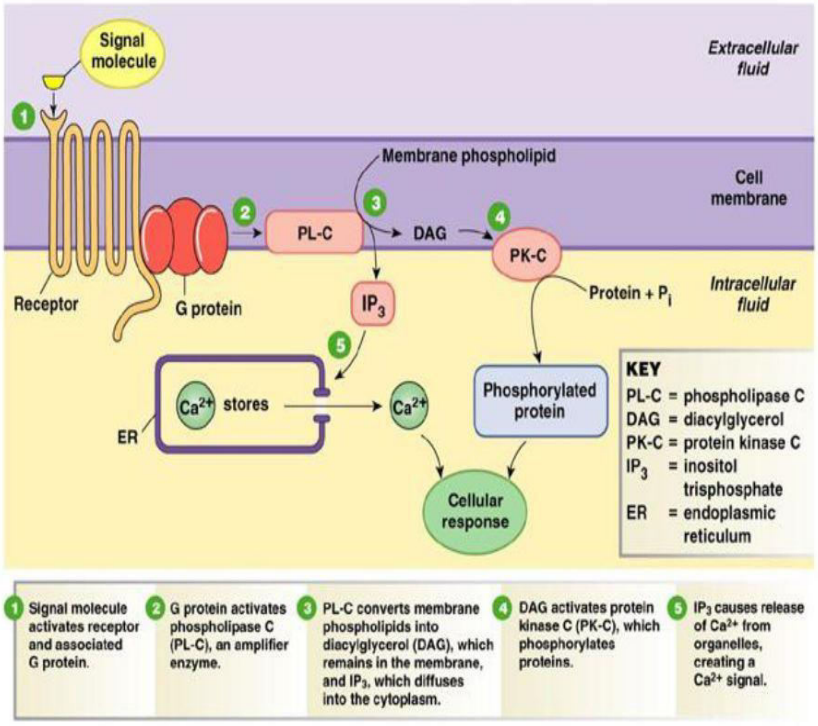
- Remember that ,also, in your Skeletal Muscles we have phosphorylated myosin .But the phosphorylation there is done by an ATP molecule which is splitted to ADP +Pi , in order to have active phosphorylated myosin molecule .

In Skeletal Muscles we have an ATP molecule .

In Smooth Muscles we have Myosin Kinase enzyme.

} To get phosphorylated Myosin that can interact with actin filament

- Once we have dephosphorylation , the interaction between thin " actin" & thick "myosin" filaments become less . So we are decreasing the binding properties between the thin & thick filaments .
- We have , in smooth muscles, two main player enzymes :
  1- The **Kinase** ,that cause phosphorylation and thus cause contraction .
  2- The **Phosphatase** , that cause dephosphorylation and thus cause relaxation.



✓ So, How we can control the activity of these calcium channels involved here in smooth muscle ? By the Electrical control

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In addition to Electrical control ,we have also another type of control for the activity of smooth muscles , which is the **Chemical Control** .

How the chemical control looks like ?! you might remember this pic from the last year .

So ,here, we have chemical substance that bind to a receptor (called G-protein Coupled Receptor) resulting in activation of phospholipase C "PL-C" , then we will get Inositol triphosphate"IP3" that bind to a receptor in the sarcoplasmic reticulum ,this binding will induce the release of Ca^{+2} to the cytosol (this is a release from intracellular) .

To sum up : we have two ways to control the activity of smooth muscles either by electrical control or by chemical control .

In addition , we said that these smooth muscle cells are having receptors , some of these receptors are Excitatory and some are Inhibitory (means causing relaxation or less contraction) . We can also have other factors to activate phosphatases to get relaxation to these smooth muscles .

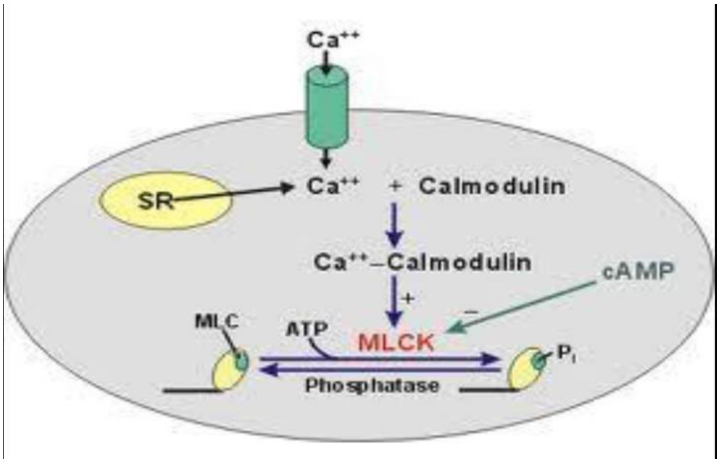
The structure of smooth muscle is highly sophisticated , as you know the activity of smooth muscle cell is important in vessels and pressure control :when you have vasoconstriction , this means you have high blood pressure . And when you have vasodilation , you have lower blood pressure .And its important also in the contraction and relaxation of the airway passage .

Also at the level of Gastrointestinal system , the smooth muscles are very important for the movements of intestines' context.

These muscles are very complex not as skeletal muscles (we have only one type of control ; they just have ACH bind to its receptor causing generation of action potential), but in the smooth muscles we can get activation of Ca^{+2} channels at the sarcolemma by the electrical control or we can get release of Ca^{+2} from the sarcoplasmic reticulum by the chemical control .

- The source of calcium is only sarcoplasmic reticulum in Skeletal muscles , but in Smooth Muscles we have more than one source (Mainly extracellular fluid , and some from the sarcoplasmic reticulum)

In this slide : we see that Ca^{+2} binds with Calmodulin , forming a complex that activates the Myosin Light-Chain Kinase " MLCK" enzyme that phosphorylate the heads of myosin .The



dephosphorylation is achieved by the phosphatase enzyme .

One thing about the Skeletal muscle , In hypocalcaemia (Less Ca^{+2} in our body fluids) , What you are expecting to happen to these muscles ? Are they affected or not ?

- There will be Tetani "prolonged contraction" in the muscle, why is that ? The problem in the motor neurons on the muscle , in one muscle there is a lot of synapses , some of them are excitatory and some are inhibitory . But the number of inhibitory terminals is much more than the excitatory ones .Now remember that we need Ca^{+2} to release the neurotransmitter from the nerve terminals to do their function .
  So in hypocalcaemia , there is low calcium concentration , so there will be much less neurotransmitters release .

To sum UP ; we have less Ca^{+2} , more Inhibitory terminals , less neurotransmitters release … what will happen ?? Remember : Inhibition of an Inhibition = Excitation .So the result is Much More Excitation , result in Tetani (which is a sign for hypocalcaemia) .

Once you have hypercalcaemia (more Ca^{+2} concentration , more release of inhibitory neurotransmitters) your muscles get more relaxed and if it was very high , your heart might stop !!

- Hyperkalemia effects are the same as hypocalcaemia ones ; so if a patient have hyperkalemia we give him calcium to prevent his heart from stop !
- Remember that Mg^{+2} is required for the activity for ATP-ase enzyme , once there is hypomagnesaemia you will have the same signs as if you have hypocalcaemia .

So as you see , the problem with fluids and these ions are very very complicated !!

Sorry For Any Mistake

GOOD Luck :)