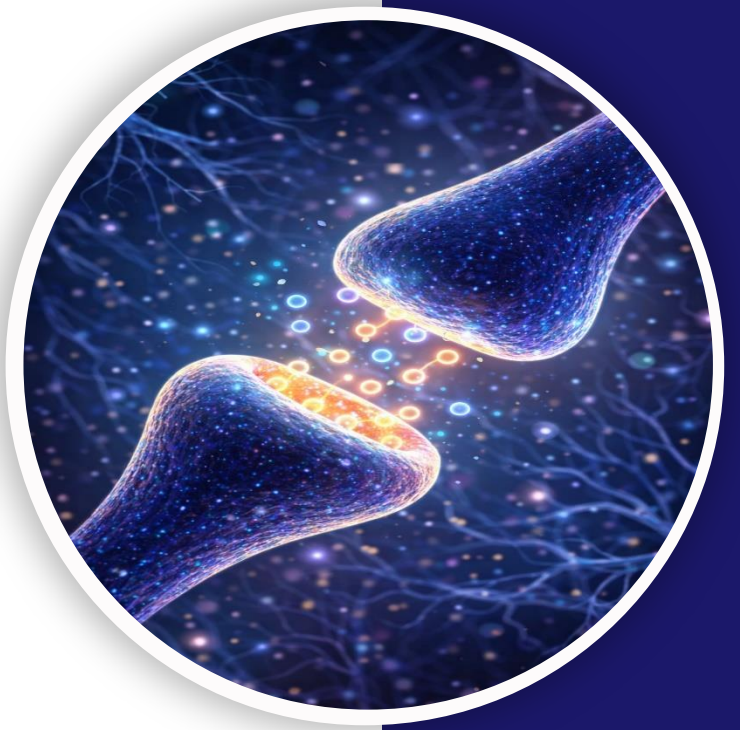
بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)



Physiology | MID 4

Muscle physiology pt. 3

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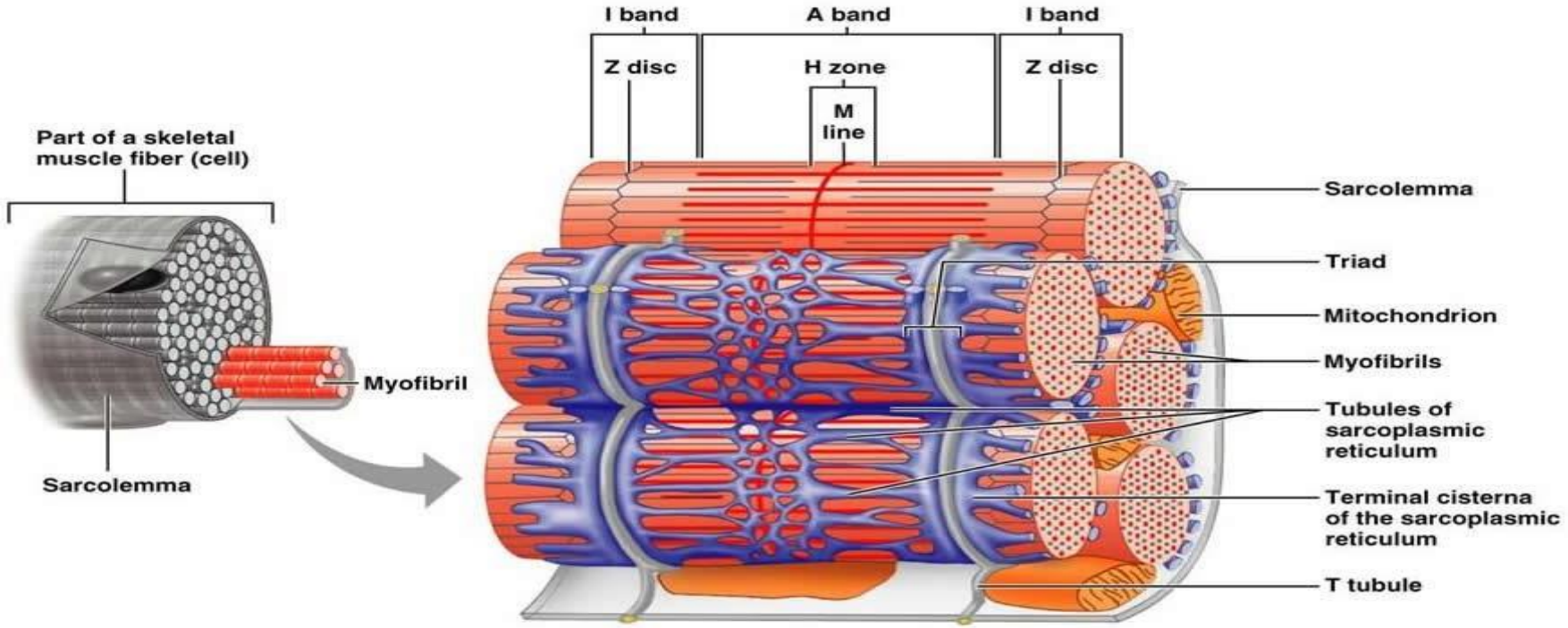
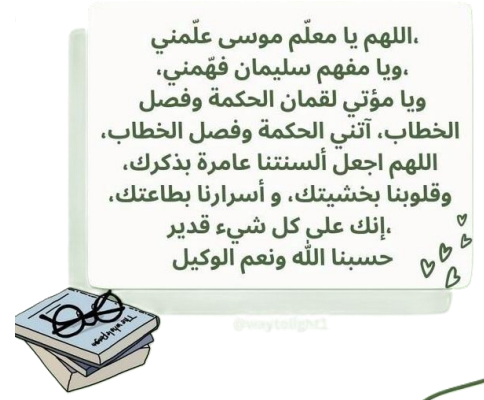
مبارك عليكم الشهر

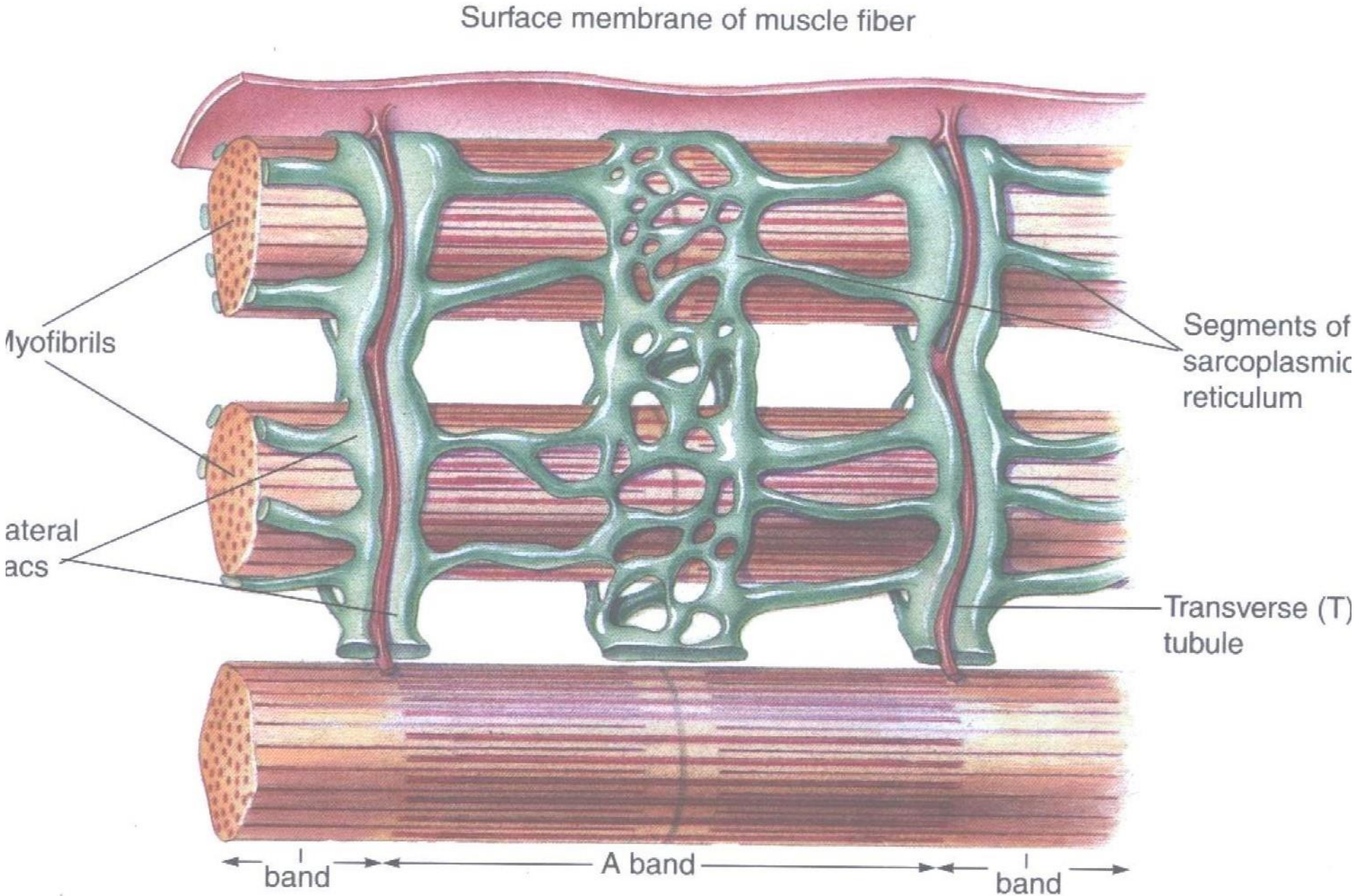


As previously discussed, skeletal muscle fibers contain specialized membrane structures known as **transverse tubules (T-tubules)**. Adjacent to these T-tubules are enlarged regions of the **sarcoplasmic reticulum (SR)** called **terminal cisternae**, which serve as major storage sites for calcium ions (Ca^{2+}).

Under resting conditions, Ca^{2+} concentration is maintained at a high level within the sarcoplasmic reticulum and at a very low level in the sarcoplasm (cytosol). The primary function of the action potential in skeletal muscle is therefore to trigger the release of Ca^{2+} from the sarcoplasmic reticulum into the sarcoplasm.

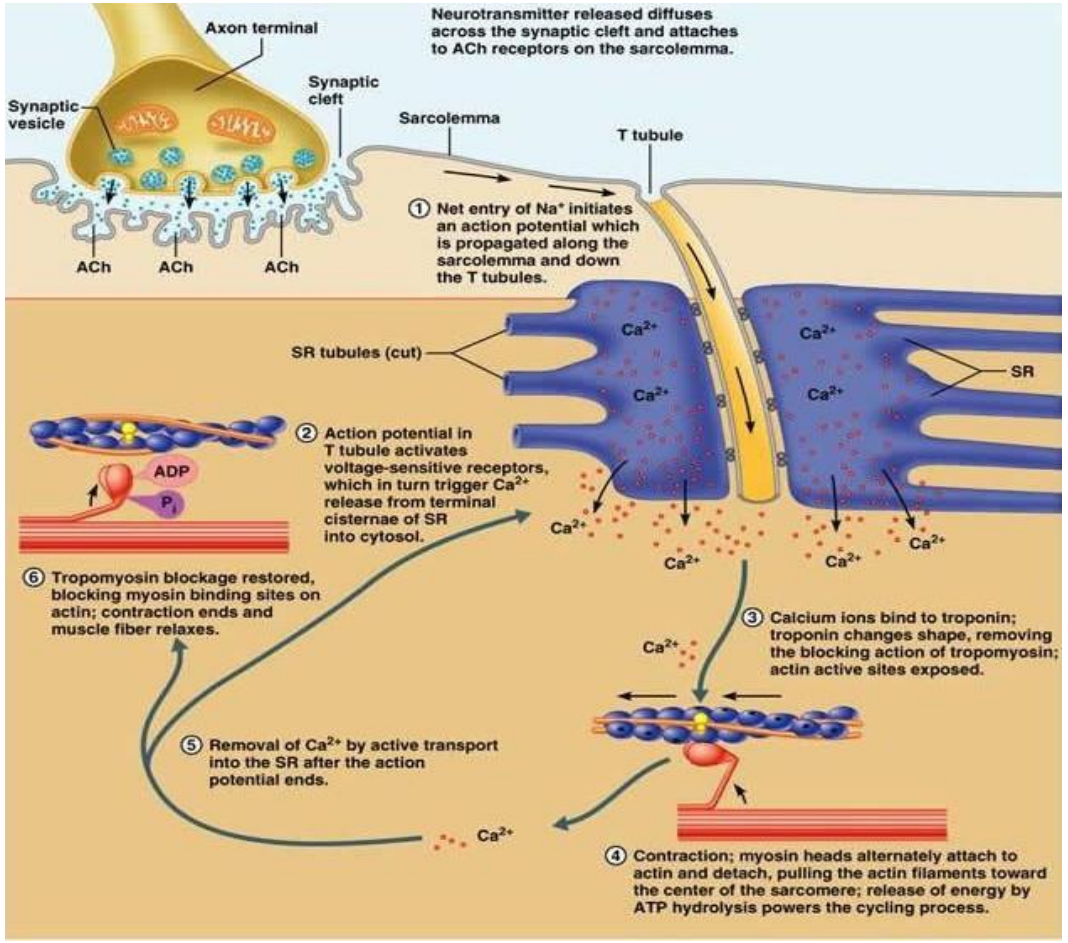


T Tubules and Sarcoplasmic Reticulum in Relationship to Myofibrils



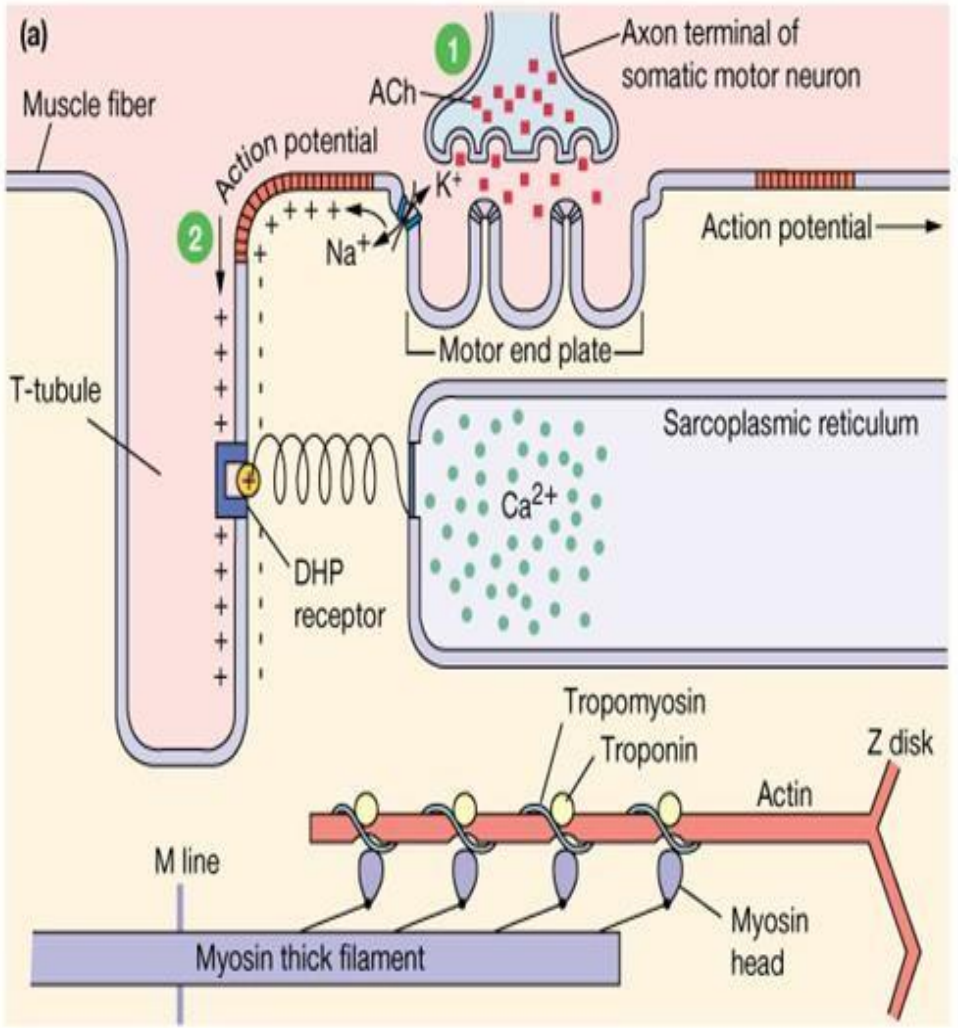
te 65 (Figure 8-10)

T-tubules are invaginations of the sarcolemma (muscle cell membrane), meaning they are continuous with the extracellular space. Consequently, the fluid within the T-tubules resembles the **extracellular fluid (ECF)**.
Because the T-tubule membrane is derived from the sarcolemma, it contains voltage-gated ion channels, including:
•Voltage-gated Na^+ channels
•Voltage-gated K^+ channels
Thus, T-tubules are capable of conducting action potentials.
When an action potential propagates along the sarcolemma and enters the T-tubules, the electrical signal is transmitted deep into the muscle fiber rather than remaining confined to the surface membrane.
Sarcolemma does not have voltage-gated Ca^{2+} channels



The membrane of the T-tubules is **closely apposed but not fused** with the membrane of the sarcoplasmic reticulum. These membranes are mechanically linked by specialized protein structures referred to as **junctional proteins (historically called "foot proteins")**.
These junctional complexes connect:
•The T-tubule membrane
•The sarcoplasmic reticulum membrane

A portion of the junctional protein embedded within the T-tubule membrane is known as the:
Dihydropyridine receptor (DHP receptor)
(more precisely: L-type voltage-gated Ca^{2+} channel acting primarily as a voltage sensor in skeletal muscle)
The corresponding protein embedded in the sarcoplasmic reticulum membrane is called the:
Ryanodine receptor (RyR)
(functions as the Ca^{2+} release channel of the SR)
Clarification:
Despite the name, dihydropyridine is **not a natural ligand in the body**. The receptor is named based on its sensitivity to pharmacologic agents (dihydropyridine drugs). Similarly, ryanodine is a plant-derived compound; the receptor name reflects drug interaction rather than endogenous physiology.



Mechanism of Calcium Release

When an action potential travels through the T-tubules, depolarization induces a **conformational change** in the DHP receptor. This mechanical change is directly transmitted to the ryanodine receptor in skeletal muscle.

As a result:

- The ryanodine receptor opens
- Ca^{2+} is rapidly released from the sarcoplasmic reticulum into the sarcoplasm

Importantly, in skeletal muscle:

(Ca^{2+} release is primarily due to mechanical coupling rather than Ca^{2+} influx from the extracellular space)

Calcium Concentration Gradient

The Ca^{2+} concentration difference is substantial:

- Sarcoplasm: ~10^{-7} M
- Sarcoplasmic reticulum: ~10^{-3} M

This represents approximately a **10,000-fold gradient**, allowing for rapid Ca^{2+} movement upon channel opening.

Physiological Consequence

Once cytosolic Ca^{2+} concentration increases:

- Ca^{2+} binds to troponin
- Cross-bridge cycling is initiated
- Muscle contraction occurs

Before measurable contraction develops, a brief delay is observed: **Latent period**

Latent period is the interval between stimulation and the onset of contraction, during which calcium is released from the sarcoplasmic reticulum.

(represents excitation-contraction coupling events, including Ca^{2+} release and binding)

At the level of the spinal cord:
Motor neurons receive both excitatory and inhibitory inputs.
Normally, there is a balance, but inhibitory control is strong enough to prevent excessive firing.
Calcium (Ca^{2+}) is essential for:
Release of neurotransmitters from presynaptic terminals and stabilizing neuronal membranes.
Result:
Controlled motor neuron activity → Normal muscle contraction
A common conceptual question is whether **hypocalcemia** affects muscle activity.
From a strictly mechanical perspective of skeletal muscle contraction, extracellular calcium is not the primary source of Ca^{2+} required for contraction. However, **clinically and physiologically**, hypocalcemia significantly alters neuromuscular function.
The explanation lies in the role of Ca^{2+} in neuronal membrane stability.
Extracellular Ca^{2+} contributes to the regulation of **voltage-gated sodium channels**. When extracellular Ca^{2+} levels decrease:
•The threshold for Na^{+} channel activation becomes lower
•Neuronal membranes become more excitable
•Spontaneous depolarizations are more likely
This results in **neuronal hyperexcitability**, which manifests clinically as:
•Muscle spasms
•Tetany
•Increased neuromuscular irritability
Thus, hypocalcemia does not directly impair the contractile machinery but instead increases **motor neuron excitability**.

Role of Calcium in Neurotransmitter Release

Calcium ions are essential for neurotransmitter release at synaptic terminals.

Normally:

Action potential → Ca^{2+} influx → Vesicle fusion → Neurotransmitter release

In hypocalcemia:

- Ca^{2+} entry into nerve terminals is reduced
- Release of neurotransmitters (including inhibitory transmitters) may be altered
- Reduced inhibitory influence can further enhance neuronal excitability

(Clarification: the dominant clinical effect of hypocalcemia is increased membrane excitability rather than simple failure of neurotransmission.)

Clinical Correlation

Patients with hypocalcemia often exhibit:

✓ Increased neuromuscular responsiveness

✓ Muscle cramps or spasms

✓ Tetanic contractions

Administration of calcium corrects membrane instability and reduces hyperexcitability.

﴿قُلْ يَا عِبَادِيَ الَّذِينَ أَسْرَفُوا عَلَىٰ أَنفُسِهِمْ
لَا تَقْنَطُوا مِن رَّحْمَةِ اللَّهِ ۚ إِنَّ اللَّهَ يَغْفِرُ
الذُّنُوبَ جَمِيعًا ۚ إِنَّهُ هُوَ الْغَفُورُ الرَّحِيمُ﴾

الزمر:٥٦

Magnesium Interaction

Magnesium also modulates neuromuscular excitability.

Abnormal Mg^{2+} levels may influence:

- Calcium handling
- Neurotransmitter release
- Membrane excitability

(Clarification: Mg^{2+} effects are complex and context-dependent, often examined in pathology/clinical physiology rather than basic ECC.)

T-Tubule Structural Organization

In skeletal muscle fibers, T-tubules are strategically positioned at the:

Junction of the A band and I band

At each T-tubule site, the membrane is flanked by two enlarged regions of the sarcoplasmic reticulum called:

Terminal cisternae

Together, these structures form: **TRIAD**

· One T-tubule

· Two terminal cisternae (SR)

Function:

Efficient coupling between electrical excitation and Ca^{2+} release.

Skeletal muscle contraction depends significantly on:

Ca^{2+} release from sarcoplasmic reticulum

Cardiac Muscle Comparison

In cardiac muscle, T-tubules are strategically positioned near the:

Z disc

DIAD

· One T-tubule

· One terminal cisterna (SR)

Additionally:

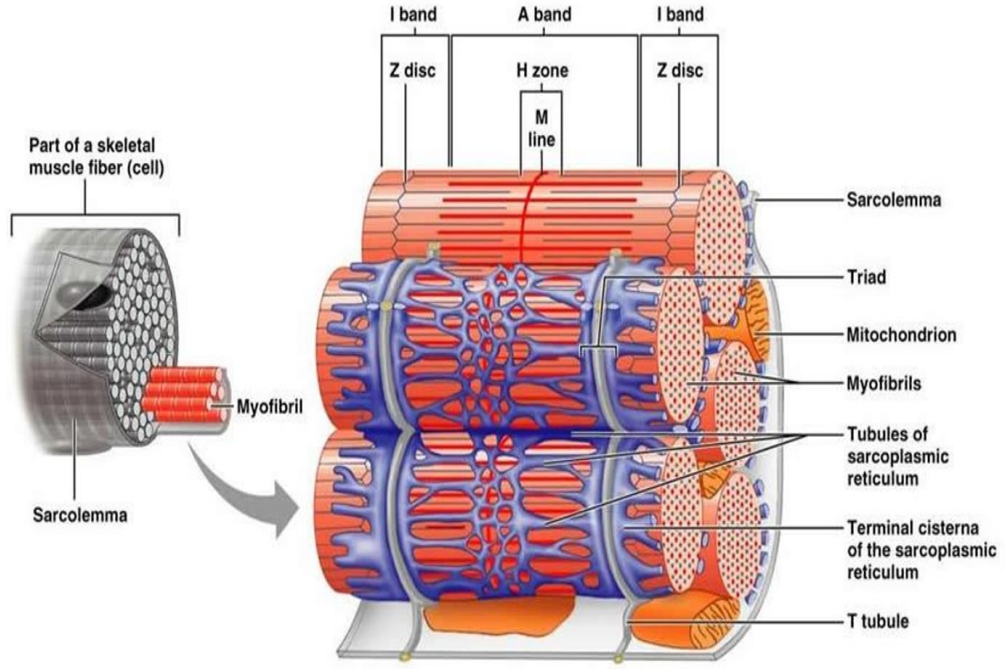
Cardiac muscle contraction depends significantly on:

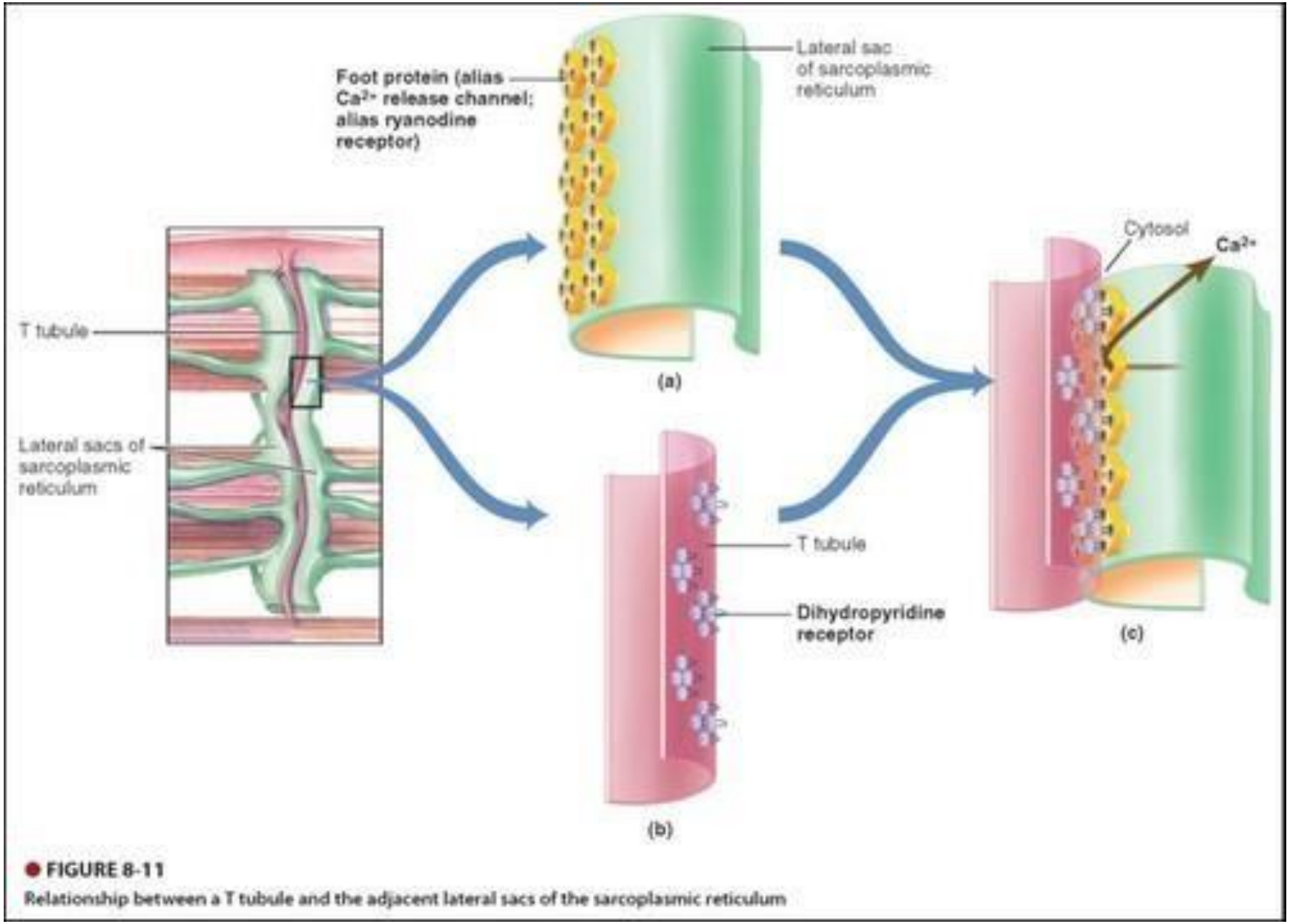
Extracellular Ca^{2+} influx not Ca^{2+} release from sarcoplasmic reticulum

Mechanism:

Ca^{2+} entry through L-type channels → Triggers SR Ca^{2+} release

(**Calcium-induced calcium release, CICR**)





● **FIGURE 8-11**

Relationship between a T tubule and the adjacent lateral sacs of the sarcoplasmic reticulum

IMPORTANT
calcium release does not need depolarization of the sarcoplasmic reticulum

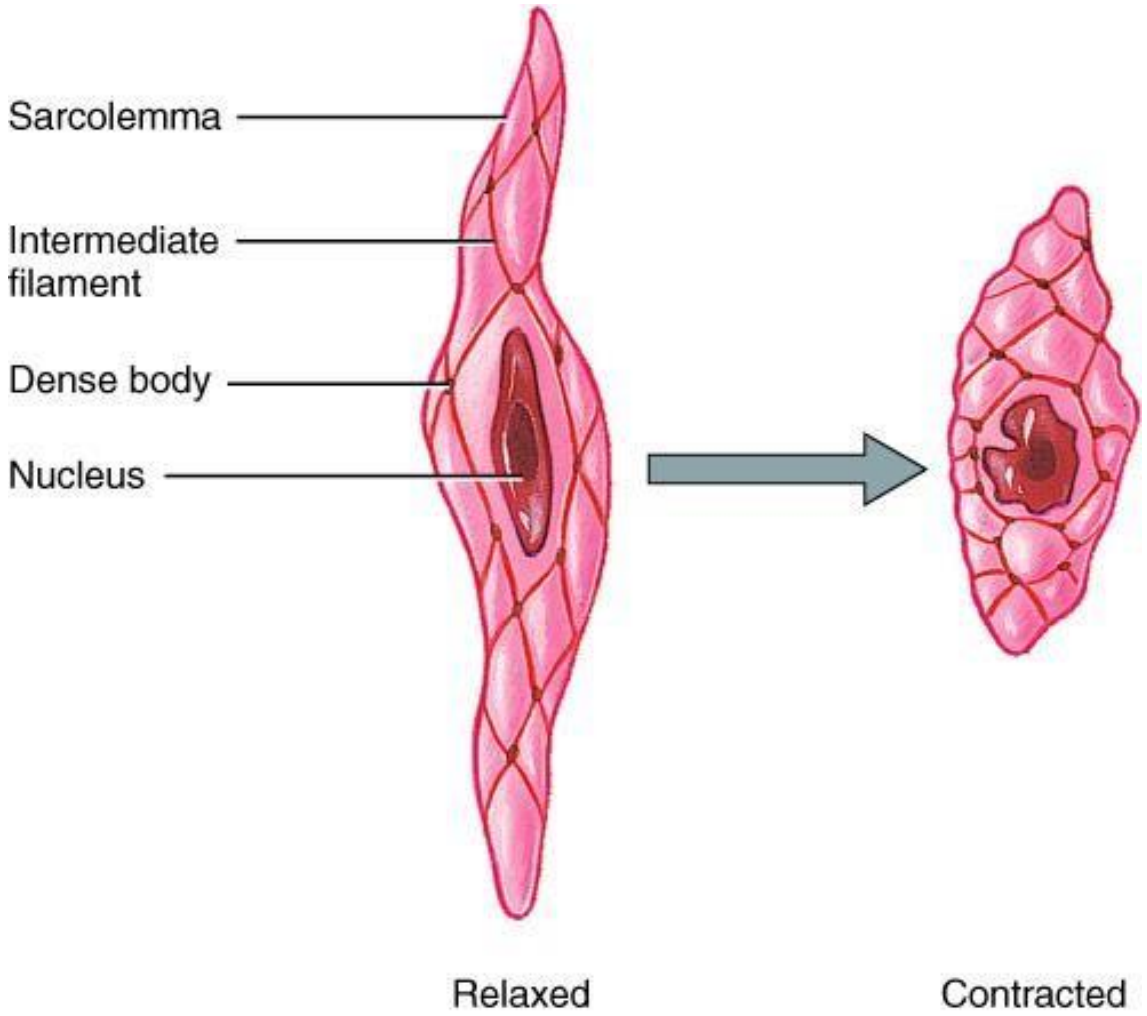
- We Have a high distribution of smooth muscle cells in many structures in our body.
- They can be found in vessels, bronchioles and so on
- The contractile mechanism in smooth muscles is more complex than in our skeletal!

SMOOTH MUSCLE CELLS

They have contractile proteins, **but the organization is different.**
So we have thick and thin filaments, but their organization is different, they are not seen as striated, and have no z-lines
and are arranged in crisscross(lattice like) patterns

So if you're viewing a smooth muscle in the relaxed state and then it gets contracted, we get an interaction between thin and thick filaments just without the organized sarcomere (striation) structure seen in skeletal and cardiac structure.

Fig. 10.19



10.19

the black dots you're seeing are called **"dense bodies"**, their function is to hold the thin filament in all direction.

Dense bodies have similar function to the z-disc in skeletal muscle.

The thick filaments are dispersed between the thin filaments.(arranged in an irregular, network like patterns)
So the lines here are present in thick and thin filaments but we don't see organized structure or striations under microscope and because of that they are called smooth muscles cells!

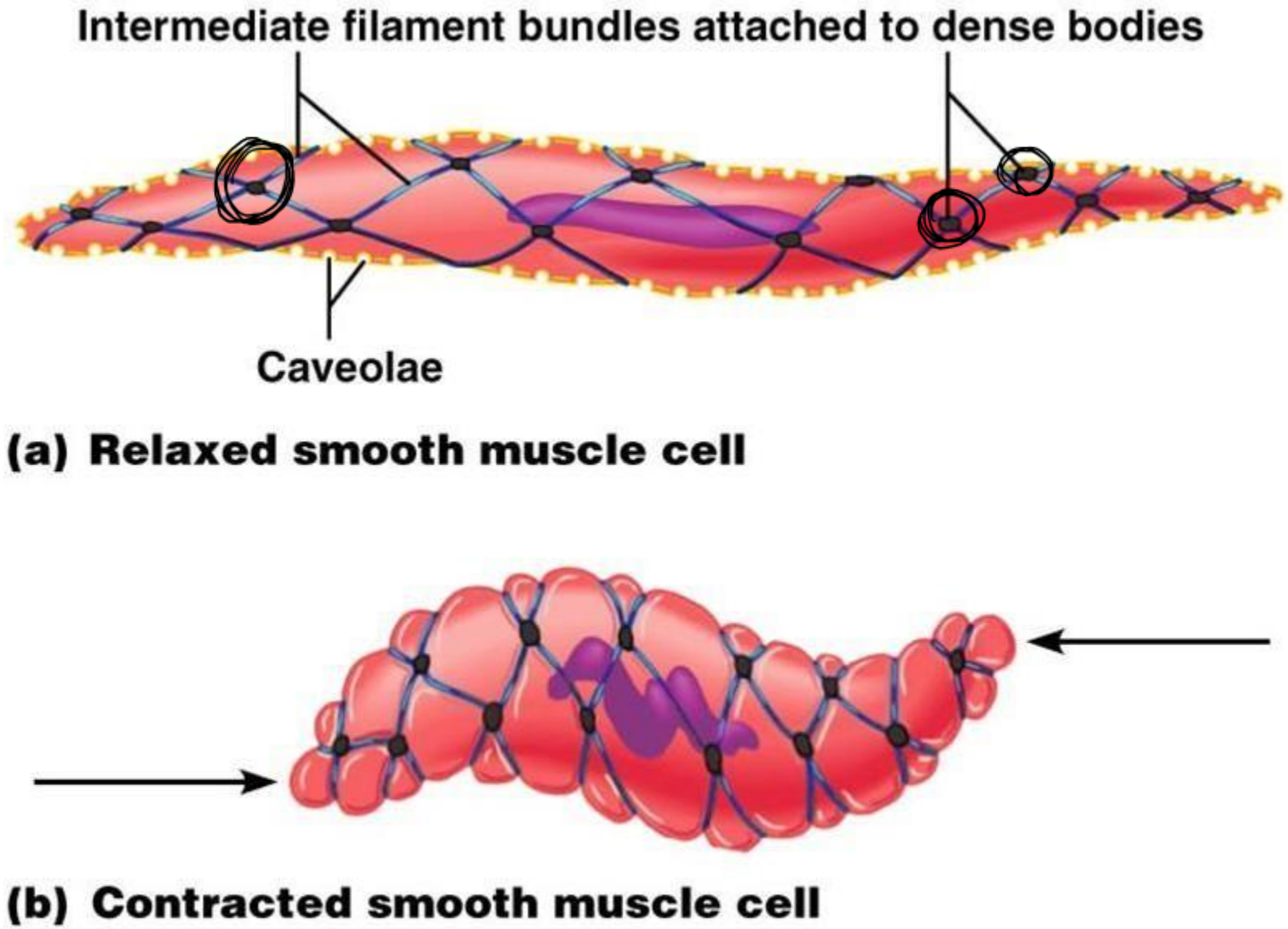


Figure 9.26

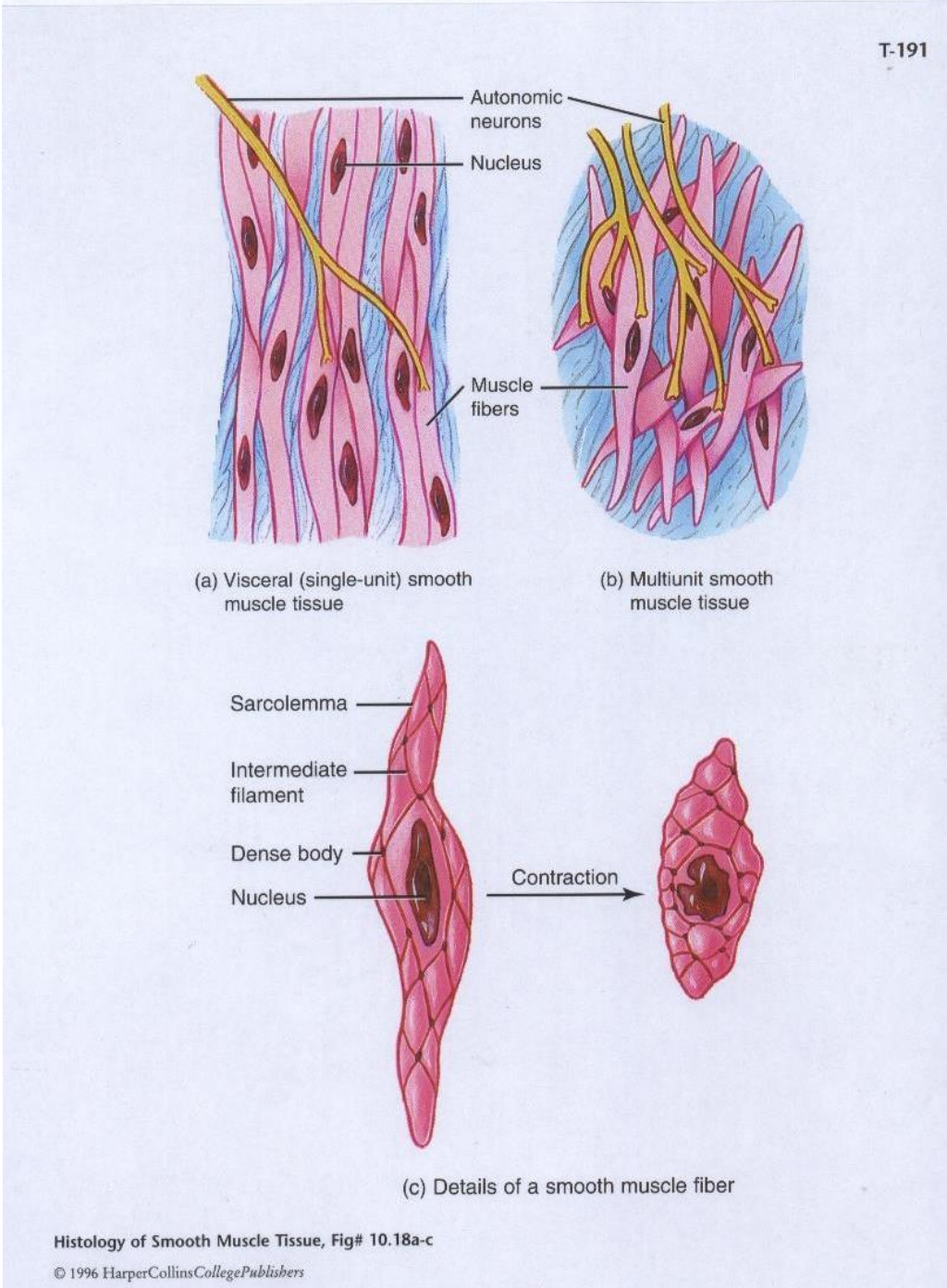
We have terminals with neurotransmitters, ending in proximity to the smooth muscle, so there will be no room for specialized structure (Like NMJ) between nerve terminals and the sarcolemma of smooth muscle cells

We get release of neurotransmitters from the terminals in the space around smooth muscle cells and the smooth muscles are now bearing receptors all over the surface, so the ligands can bind and change the activity of the muscle. :)

We can find inhibitory receptor or excitatory receptor:
Excitatory = more contraction
Inhibitory = relax
According to concentration of inhibitory or excitatory neurotransmitter.

More refined explanation from chatGTP if youre still confused:

How can we contract smooth muscles? Acetylcholine binds muscarinic receptors which activates PLC which gives me IP3 which releases calcium from sarcoplasmic reticulum, once we have calcium, we can get thin and thick filament interaction which lead to contraction!!!



In smooth muscle cells of vessels, instead of muscarinic we have alpha 1 adrenergic receptor and signal transduction mechanism, we have PLC to release calcium to get contraction. This is the chemical control by which you can control smooth muscles.

We can also add electrical control to smooth muscle, like we have calcium channels at the sarcolemma and any change in electrical activity can activate these voltage-gated calcium channels and causing contraction

Also there is chemical-gated calcium channels at the sacrolemma.

This allows for complex control over the smooth muscle

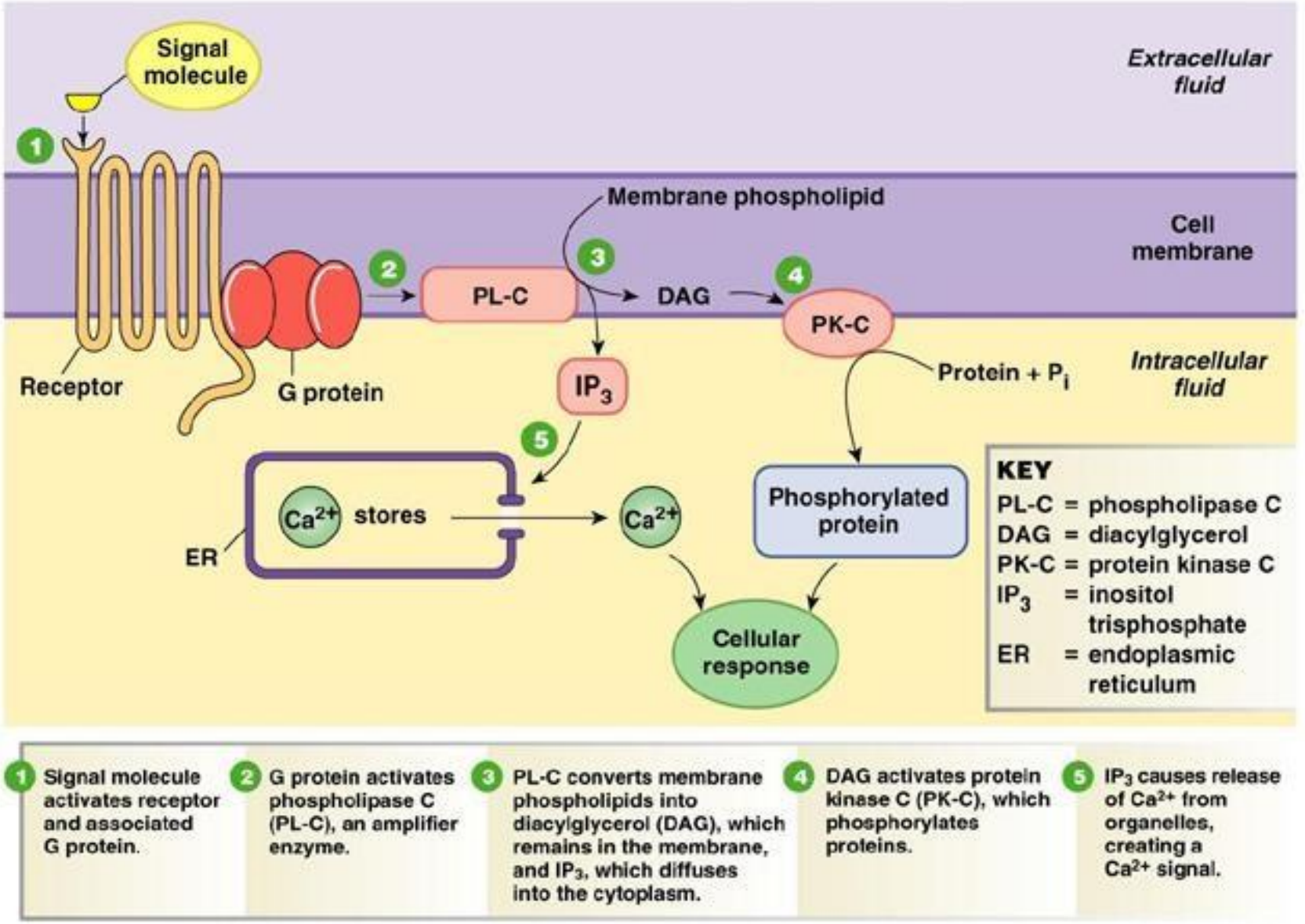
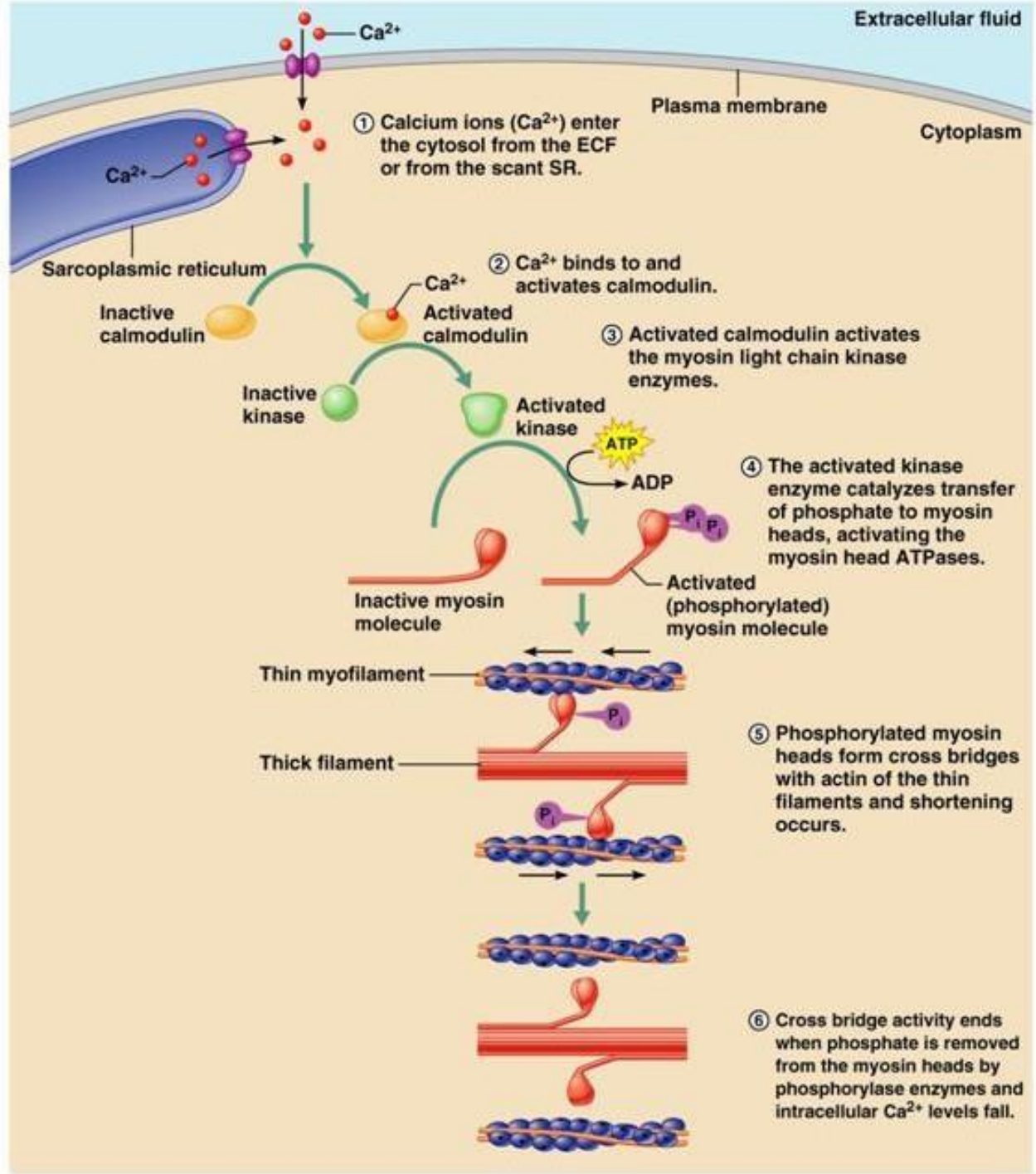


Fig. 6-12

لَا تَقْنَطُواْ مِن رَّحْمَةِ ٱللَّهِ إِنَّ ٱللَّهَ يَغْفِرُ ٱلذُّنُوبَ جَمِيعًا إِنَّهُۥ هُوَ ٱلْغَفُورُ ٱلرَّحِيمُ

Despair not of God's mercy:
behold, God forgives all sins
- for, verily, He alone is much-forgiving,
a dispenser of grace!

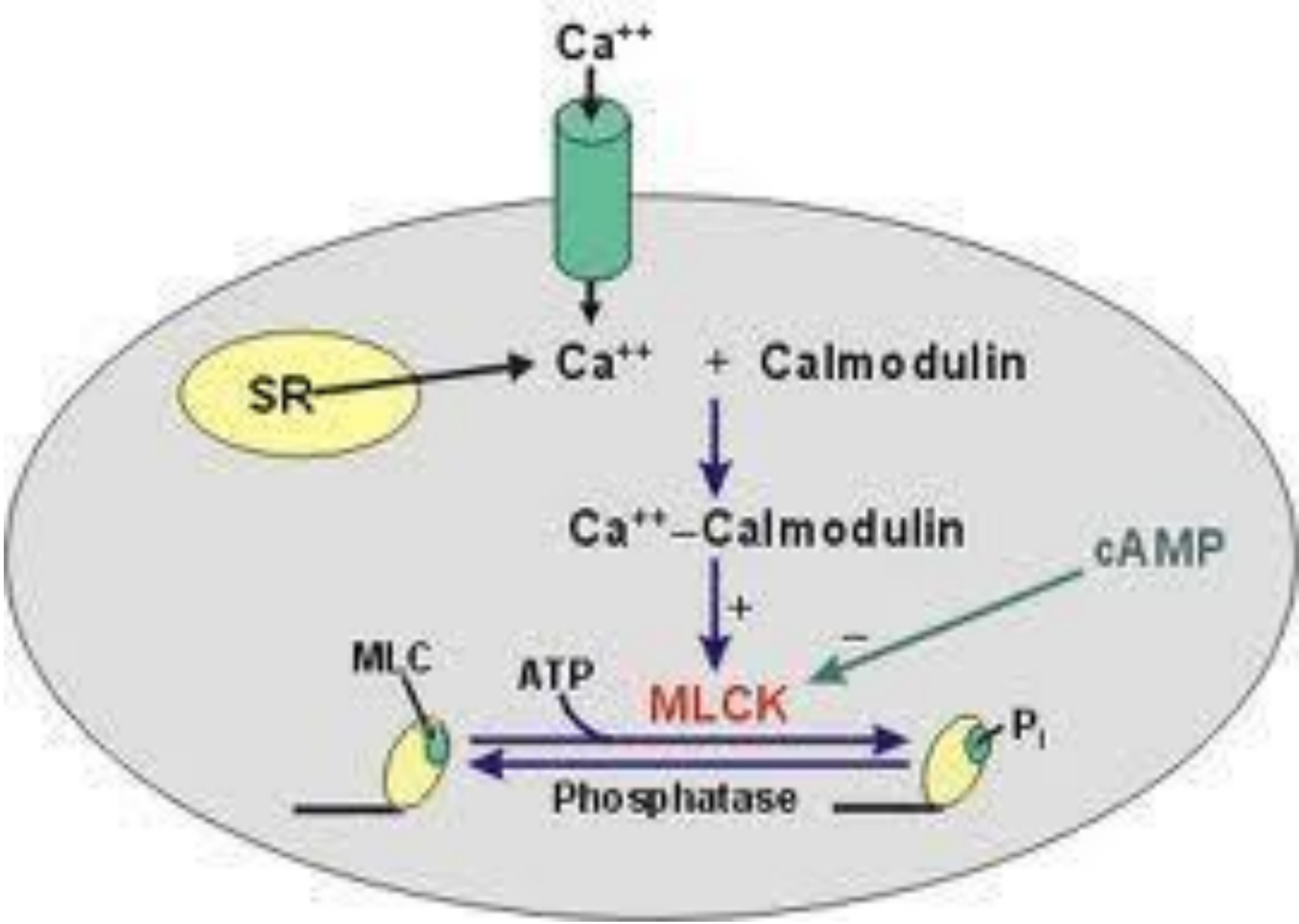
(Quran 39:53)



Now we have increased calcium Concentration inside the smooth muscle cell, the calcium will bind to calmodulin which present everywhere in the cytosol of smooth muscle cells (we don't have tropomyosin we have thin which are actin filament only and we also don't have troponin c) Forming calcium-calmodulin complex, activating MLCK, phosphorylating myosin to get contraction

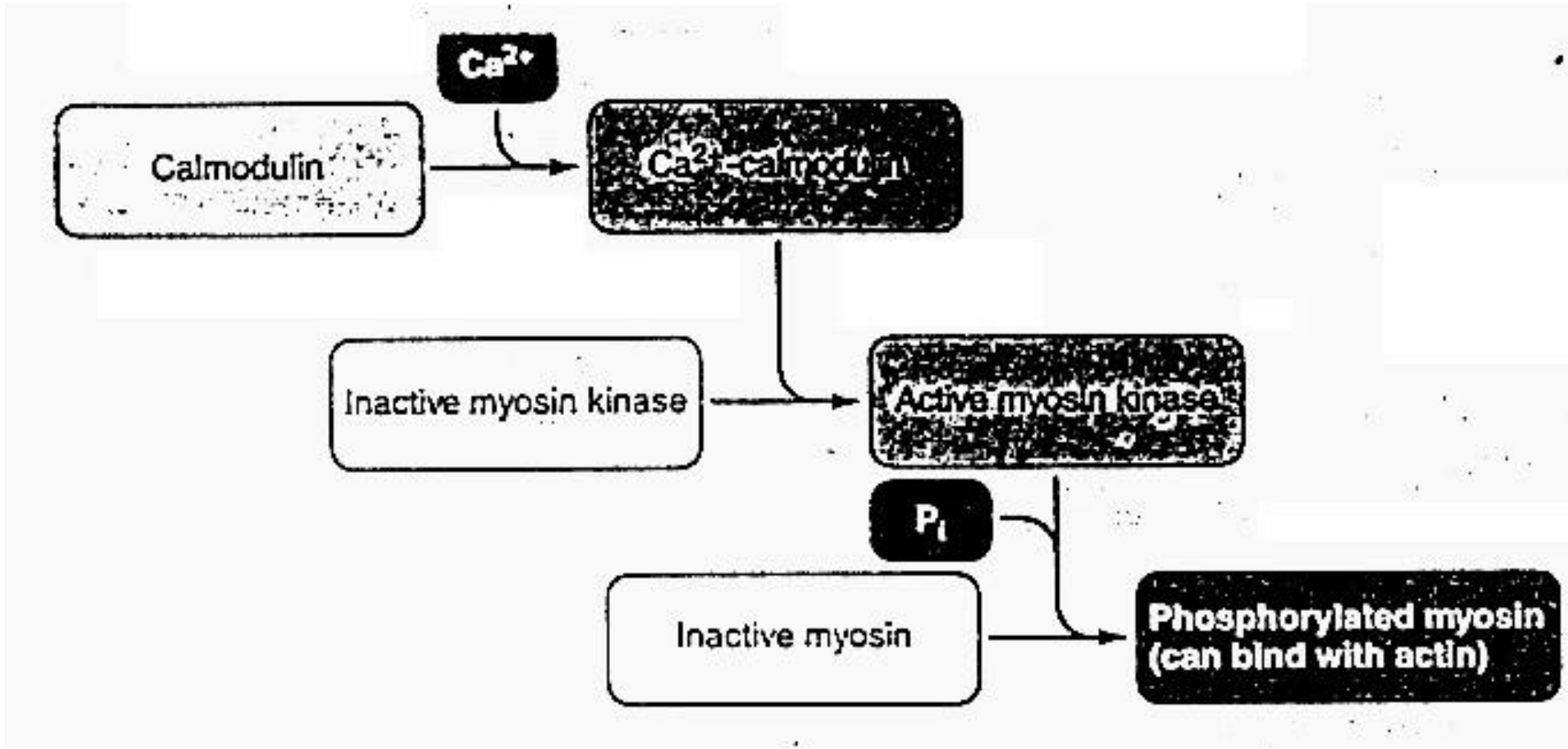
For relaxation, by reducing calcium, and reducing stimulation of kinase and activating dephosphorylate (phosphatase) and the interaction of thin and thick filament is reduced.

The control of smooth muscle is very complex, you may have some signal transduction mechanism that can inhibit MLC kinase, by increasing CAMP and decreasing activity of kinase enzyme leading to less phosphorylated myosin.



We have lots of drugs (like those used in treatment of hypertension and asthma) that work by inhibiting contractile process of smooth muscle cells, Like calcium channel blockers.

beta 2 receptor are linked to adenylate cyclase and by giving agonist of epinephrine, you can activate CAMP causing relaxation of bronchiole smooth muscle cells.


Ca^{2+}
Calmodulin
Ca^{2+}-calmodulin
Inactive myosin kinase
Active myosin kinase
P_i
Inactive myosin
Phosphorylated myosin (can bind with actin)

KNOW THE DIFFERENCES!!!!!!!!!!

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 generally present

DR.'S HANDOUT

Generation and spreading of action potential to the interior of the muscle:

The end plate potentials generated by activation of chemical gated channels will induce activation of voltage gated Na+ channels. The activation of these channels will induce an action potential, which spreads over the sarcolema. At the surface of muscle membrane, they are small openings for tubules that run deeply (in transverse direction) in the muscle cell, known as **transverse tubules** (T-tubules). These tubules contain extracellular fluid. They transmit action potential to the interior of the cell closely to myofibrils, where it stimulates release of Ca++ into the cytosol (sarcoplasm). The whole process by which sarcolemma generate an action potential that causes **release of Ca++** which results in muscle contraction is known as **excitation-contraction coupling**. The arrangement of T tubules and sarcoplasmic reticulum at the Z lines of the sarcomere permits 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 known **as ryanodine receptor**. The part of foot protein on T-tubules is known as **dihydropyridine receptor**. Dihydropyridine receptors are voltage sensors. The change in voltage of T-tubules will induce conformational changes in the whole foot protein, which results in activation 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.

At the membrane of sarcoplasmic reticulum, there are also highly active Ca++ pumps. These pumps concentrate Ca++ inside the sarcoplasmic reticulum by 10.000 folds (Ca++ concentration in sarcoplasmic reticulum = 10-3molar, in the sarcoplasm during rest = 10-7 molar, and during excitation of muscle = 2X10-4molar). The rapid uptake of Ca++ by these active pumps results in muscle relaxation.

SUMMARY: https://www.youtube.com/watch?app=desktop&v=6YvdLWgT5mg

SMOOTH MUSCLE CELLS:

These muscles have their characteristics, which may differ from those of skeletal muscles. In addition to that, smooth muscle cells may also differ from organ to organ in their organization, physical dimension responses to stimuli, and innervation. Generally, they are divided into multi-unit smooth muscle and single unit smooth muscle.

In multi-unit: each muscle fiber operates independently of all other fibers. In single unit muscles, their function needs cooperation of many muscle fibers to perform a function. Muscle fibers, in this type, are connected to each other by gap junctions to synchronize their contraction (functional syncytium).

Organization of contractile proteins in smooth muscle and mechanism of contraction:

The organization of contractile proteins is different from that in skeletal muscle. The actin filaments are attached to a dense structure

inside the muscle known **as dense bodies**. These actin filaments radiate between dense bodies. In the midway between dense bodies, few myosin filaments are found where they overlap with actin filaments. The mechanism of contraction in smooth muscle cells also involves actin myosin interaction, but with different mechanism than that found in skeletal muscle. When smooth muscle is stimulated, it takes longer time than striated muscle to induce contraction (long latent period), the total contraction time is about 30 times more than that in skeletal muscle. These appear because of the slow attachment and detachment of contractile proteins, which results in slow cycling of cross bridges.

The mechanism of contraction in smooth muscle also involves an increase in Ca++ concentration, but the source could be different than in skeletal muscle. The source in skeletal muscle is only from the endoplasmic reticulum, which has high representation in skeletal muscle, while in smooth muscle the main source is extracellular and some contraction can be induced also by the release of Ca++ from intracellular stores (sarcoplasmic reticulum), which is moderately developed in smooth muscle (not well as in skeletal muscle).

The release of Ca++ 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 kinase**. This enzyme will **phosphorylate** the regulatory chain on **myosin head**. The phosphrylated myosin can interact with actin to induce contraction.

The relaxation of smooth muscle cells also involves a decrease in Ca++ concentration by increased activity of Ca++ pumps located at the plasma membrane and sarcoplasmic reticulum. In addition to that, the mechanism of relaxation also involves dephosphorylation of myosin heads by an enzyme called myosin phosphatase.

In some instances, the smooth muscle contracts and their contraction is sustained. This is known **as latch phenomenon**. This is due to much decrease in cycling frequency of cross bridges. Which is probably due to a decrease in myosin phosphatase activity, that results in a decreased dephosphorylation of myosin head (remain longer time activated). Little ATP molecules are consumed during this phenomenon.

Membrane potential and action potential in smooth muscle cells:

The resting membrane potential in smooth muscle is less negative than in skeletal muscle. It is about -60 to –50mV in smooth muscle. The characteristics of action potentials are also different in smooth muscle. Many types of action potential are found on smooth muscle fiber:

1. Spike potentials (have short duration): these can be elicited by external stimulus.
2. Action potential in with plateau: similar to the action potential that found in cardiac muscle. The onset is rapid as in spike potential, but repolarization takes longer time. This type of action potential has importance in organs where longer contraction period is needed, such as in uterus. The longer action potential and the plateau in this type are due to activation of Ca++ channels. These channels are activated slowly, and their opening is maintained for longer time than Na+ channels.
3. Slow wave potentials: some smooth muscle cells are selfexcitatory. This property is due to rhythmic variations in membrane potential that appear at muscle membrane. These rhythmic variations are known as slow waves. These waves are probably caused by changes in Na+ pump activity, or changes in conductance of ion channels. Slow wave are not action potentials and they cannot induce contraction in smooth muscle. When the peak of these slow waves rises above threshold, they can generate spike potentials, which result in contraction of smooth muscle.

Neural and hormonal control of smooth muscle contraction:

Muscle cells are innervated by autonomic fibers. The terminals of these fibers are ending diffusely between cells and not forming organized synapses, such as the motor end plate in skeletal muscle. The transmitter in autonomic fibers is found in varicosities of the fine terminals of nerve fibers. The released transmitters from these varicosities act on their receptors to induce activation or inhibition of the contraction in smooth muscle.

In addition to neural control, some smooth muscle membrane has receptors for hormones, neuropeptides, or other factors. These also control the activity of smooth muscle cells when their receptors on smooth muscle are activated.

The mechanism by which smooth muscle cells are activated may include activation of Ca++ channels at the sarcolemma or activation of phospholipase C. The later results in the formation of IP3 (inositol trisphosphate) and release of Ca++ from the sarcoplasmic reticulum. The mechanism of inhibition may include formation of cAMP or cGMP, which induces phosphorylation of some proteins that activate K+ channels or proteins involved in relaxation, or inhibition of proteins involved in contraction.

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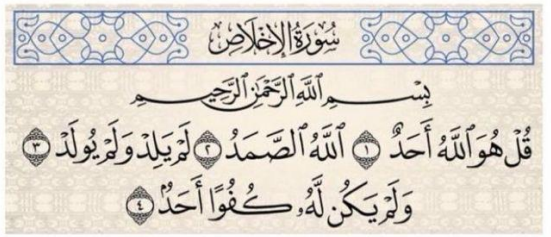

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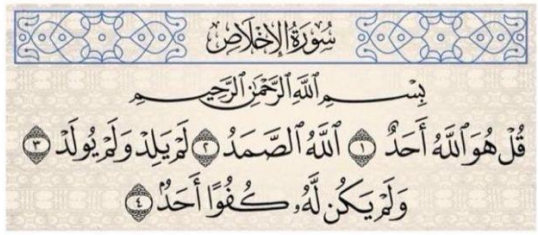

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بيت في الجنه

Last Physiology Lecture for MSS Midterm

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			