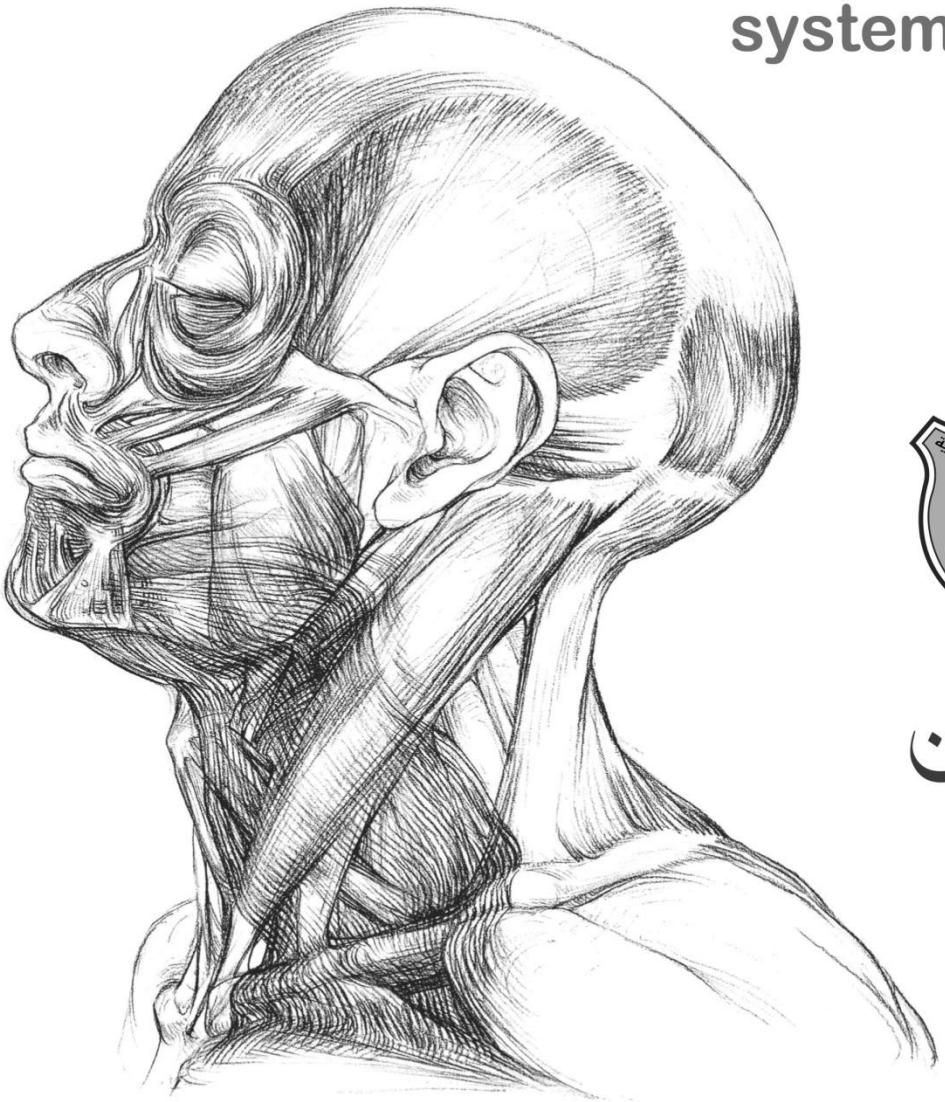
The skin & Muscloskeletal system



PHYSIOLOGY

SLIDES ☐
SHEET ■
LECTURE # 4

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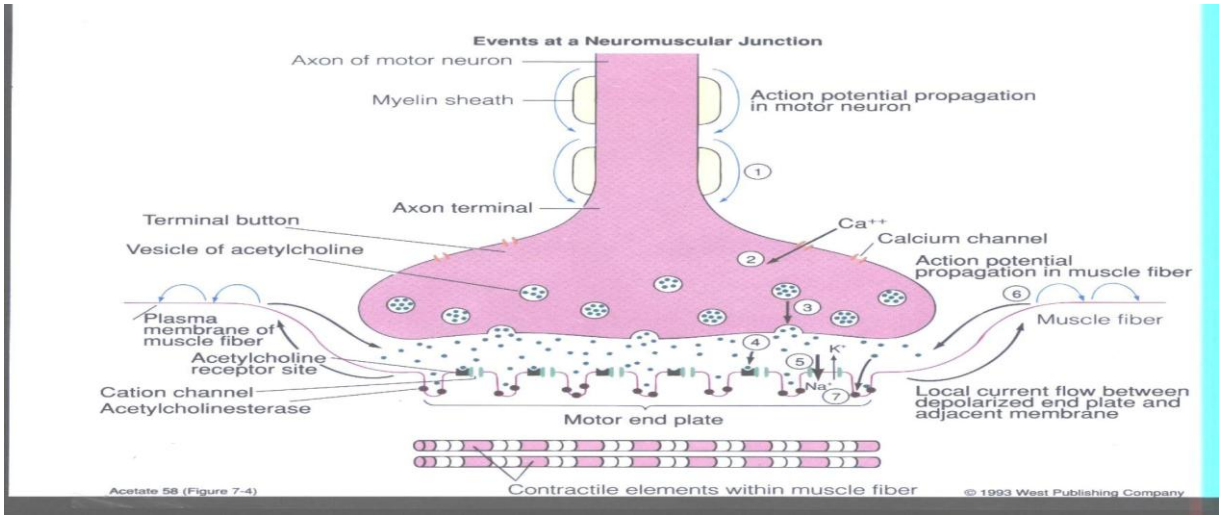
In the previous lectures we discussed action potential, structure of skeletal muscles, summation of action potentials, and muscle mechanics. In this lecture we'll be discussing Neuromuscular juctions, Excitation-Contraction coupling, and we'll talk generally about smooth muscles.

The Neuromuscular Junction :

Skeletal muscles are voluntary, they contract upon stimulation by motor neurons, they get stimulated by the release of a neurotransmitter at the neuromuscular junction. A **neuromuscular junction** is a chemical synapse formed by the contact between a motor neuron and a muscle fiber (i.e. it is the junction between **one** nerve terminal and **one** muscle cell). At the neuromuscular junction, nerve terminal ends into a small invaginated part of the muscle membrane **called Synaptic Gutter** (synaptic trough), at the bottom of the synaptic gutter, the muscle membrane has small folds called **sub-neural clefts**, which increase the surface area of the synaptic gutter.

The membrane of a muscle cell (the sarcolemma) has a highly specialized part which plays a role in the stimulation of a muscle fiber. What makes this part highly specialized is the fact that it has a lot of folds with receptors for the neurotransmitter (Acetylcholine) which- the receptors- are linked to sodium channels, in addition to an enzyme known as **Acetylcholine esterase**, which functions in the degradation of Acetylcholine. The enzyme is activated immediately after the release of Acetylcholine.



At the terminal of an axon, the neurotransmitter Acetylcholine is stored in vesicles; it is released by **exocytosis** upon excitation.

The mechanism by which Acetylcholine (Ach) is released:

Once the action potential reaches the terminal it causes the activation of Ca++ channels which then causes the docking (fusion) of the vesicles with the membrane and release the neurotransmitter by exocytosis into the **synaptic cleft**. A **synaptic cleft** is the small space (20-30 nm) between the terminal and the muscle membrane where the neurotransmitter is released. About 125 vesicles release their contents after each stimulus. If the stimulation of the release of neurotransmitter persists for a long time, **fatigue** of the neuromuscular junction occurs.

The binding of Acetylcholine to the receptors of the motor end plate results in the activation of **chemically** gated Na+ channels which induces the influx of Na+ into the muscle fiber and causes local change in the membrane potential. Notice that the binding of Acetylcholine to its receptors and the opening of the channels does not generate an action potential at the end plate, what is actually generated is the **Motor End Plate Potentials (EPPs).** Those are sub-threshold potentials which are similar to EPSPs. Summation of these potentials results in the generation of an action potential at the periphery of the motor end plate which then spreads across the sarcolemma.

In addition to the stimulation by Acetylcholine, the receptors can also be stimulated by other compounds such as **Methacholine, Nicotine, and Carbachol**. However, these compounds produce prolonged activation of the receptors due to the absence of enzymes that break them down (destroy them), and that results in muscle spasm.

We said that the motor end plate has the enzyme **Acetylcholine-esterase** which functions in the breakdown of Acetylcholine to maintain a low concentration of Acetylcholine at the muscular junction (synaptic cleft), to prevent the continuous contraction of the muscle (allow the muscle to relax). The enzyme can be inhibited by drugs such as **Neostigmine**, **Physostigmine,** and **Diisopropyl Fluorophosphates.**

- Ach receptor is a complex protein of 5 subunits: 2α, β, δ, and γ.
- Two molecules of Ach bind to the α subunits and cause the activation of the chemically gated Na+ channels.
- The channels are chemically gated because they respond to the binding of a chemical substance.

- The receptors are nicotinic receptors which are similar to those of the ANS but with a few structural differences. However, they can both be stimulated by nicotine and thus called nicotinic.

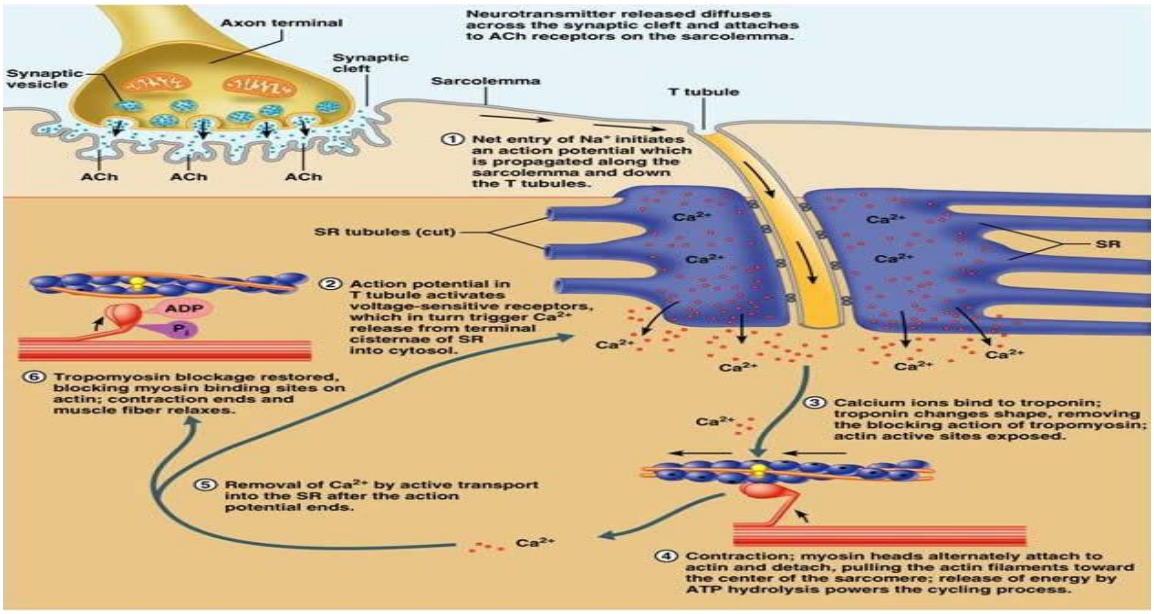
The receptors are a subject of inhibition by **curariform drugs** such **as D-tubocurarine**; D-tubocurarine can block the action of Acetylcholine on its receptors thus affecting transmission of impulse from the nerve terminal to the muscle membrane (sarcolemma).

00:00-10:00

Transmission can also fail by the destruction of the chemical gated ion channels. This appears in **Myasthenia gravis**, which is an autoimmune disease in which the body produces antibodies against Acetylcholine-gated ion channels which results in muscle paralysis. Paralysis can be partially ameliorated (made better) by anti –cholinesterase drugs such as **Neostigmine** or **Physostigmine.**

Excitation – Contraction Coupling:

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 sarcolemma. At the surface of the muscle membrane, there are small openings for small tubules that run deeply in a transverse direction in the muscle cell known as **Transverse tubules** or **T-tubules**, which contain extracellular fluid and function in the transmission of the action potential to the interior of the cell close to the myofibrils, where it stimulates the release of Ca++ into the cytosol (sarcoplasm).



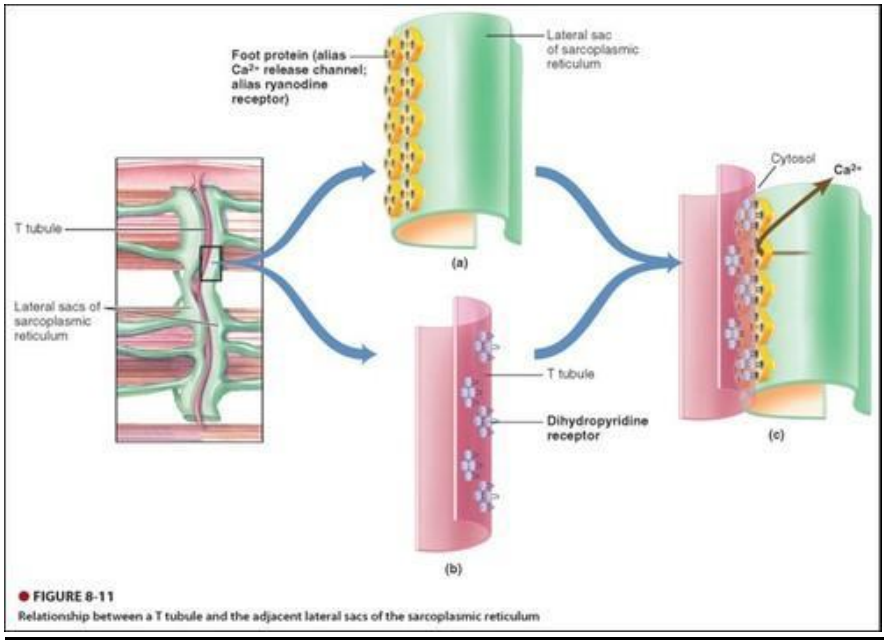
This whole process in which the membrane generates an action potential that causes the release of Ca++ which finally results in muscle contraction is known as **excitation-contraction coupling.**

Near the T-tubules we have sacs of the sarcoplasmic reticulum with high concentration of Ca++, the arrangement of the T-tubules and the sacs permits release of Ca++, these structures (T-tubule and two sacs {terminal cisternae}) form what's called a **triad**. (The purpose of generating action potential at the T-tubules is to release the Ca++ from these sacs).

Notice that there is no generation of action potential in the membrane of the sarcoplasmic reticulum, instead the release of Ca++ happens due to conformational changes that occur to a protein that spans the gap between the reticulum and the T-tubule, this protein is known as **Foot Protein.**

The foot protein consists of two parts; one is embedded in the membrane of the T-tubule and is known as **dihydropyridine receptor** (dihydropyridine receptors are voltage sensors), while the other part that is in the membrane of the sarcoplasmic reticulum and also serves as a Ca++ channel is known as **ryanodine receptor**.

-They are called so because dihydropyridine and ryanodine can bind to the dihydropyridine receptors and ryanodine receptors respectively, however we do not have either of the two chemical compounds in the human body (not produced but can be obtained from external sources or plants).



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

Once action potential reaches the T-tubules, conformational changes occur to the foot protein causing the opening of the ryanodine receptors and Ca++ is released from the sarcoplasmic reticulum. Ca++ then binds to troponin C and causes muscle contraction.

-At the membrane of the sarcoplasmic reticulum, there are highly active Ca++ pumps. These pumps keep concentration of Ca++ inside the sarcoplasmic reticulum by 10000 folds, this rapid uptake of Ca++ by the active pumps results in muscle relaxation. Ca++ concentration in sarcoplasmic reticulum = 10^{-3}M, in the sarcoplasm during rest = 10^{-7} M and during excitation of muscle = 2x10^{-4}M.

-Once Ca++ is released contraction starts, before that the muscle is in the latent period.

10:00-20:00

As you already know, even though both are striated there are some differences between skeletal muscles and cardiac muscles; here are a few which the doctor mentioned during the lecture:

	Cardiac muscles	Skeletal
Position of T-tubules	Near the Z-disk	Almost at the level of junction of the A and I bands.
Structure formed by the T-tubule and sac\s	Diad	Triad
Presence of Gap junctions between cells	Present	Absent

Smooth muscles

These muscles have their characteristics, which may differ from those of skeletal muscle; in addition to that, smooth muscles may differ from one organ to another in their organization, physical dimension, response to stimuli, and innervation. We'll talk about them more once we start with GI systems so we'll talk about them generally here.

Smooth muscles are widely spread in the human body and contribute to a wide variety of functions such as regulation of blood pressure (blood vessels are surrounded by smooth muscles), motility functions in the GI, contractile events of the uterus…etc.

They are generally 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).

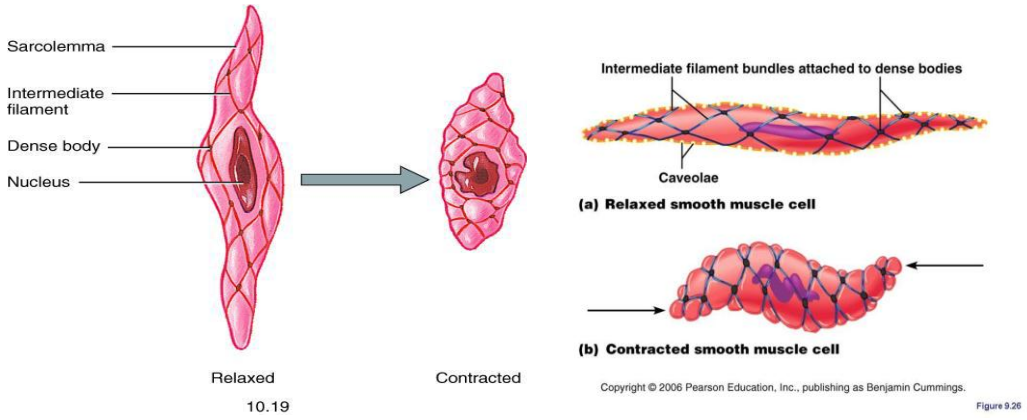
Organization of contractile proteins in smooth muscle and mechanism of contraction:

The organization of contractile proteins is different from that in skeletal muscle. The actin filaments are attached to dense structures 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 the one in skeletal muscle. When a smooth muscle is stimulated, it takes longer time than a striated muscle to induce contraction (long latent period), the total contraction time is about 30 times more than that in skeletal muscle. This happens because of the slow attachment and detachment of contractile proteins, which results in slow cycling of cross bridges.

20:00-30:00

- Dense bodies function as Z-disks.
- Once the muscle is stimulated the distance between 2 dense bodies decreases (contraction of muscle).



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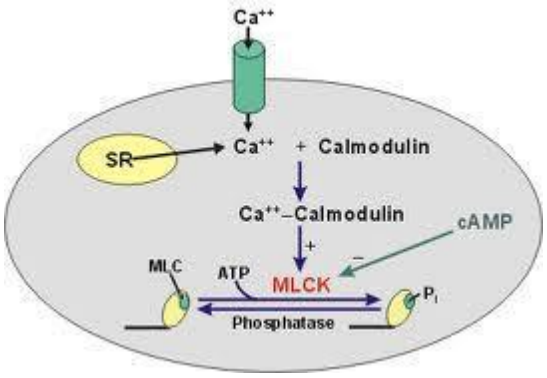
- Until now there is no proof of the presence of a neuromuscular junction in smooth muscles, instead, the nerve terminals end loosely in the space between the smooth muscles, releasing their neurotransmitters in the interstitial fluid and then they bind to their receptors which are spread all over the membrane (no motor end plate), inducing contraction or relaxation or whatever their function is.

Mechanism of contraction in smooth muscles:

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 muscles, while in smooth muscle the main

source is extracellular and some contractions 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 followed by formation of Calmodulin-Ca++ complex (4 Ca++ bind to one Calmodulin). The activated Calmodulin-Ca++ complex will induce activation of an enzyme called **myosin kinase** (myosin light chain kinase MLCK). This enzyme, as the name implies, will phosphorylate regulatory chain on myosin head. The phosphorylated myosin can interact with actin to induce contraction.
Another enzyme, **Myosinphosphatase**, dephosphorylates the head thereby results in relaxation.



- We can conclude that, an increase in the action of the kinase results in more contraction and an increase in the activity of the phosphatase results in more relaxation.

30:00-40:00

The relaxation in 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 some instances, the smooth muscles contract and their contraction is sustained. This is known as **latch phenomenon**. This is due to a 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 activated for a longer duration). A few 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. There are different types of action potentials in smooth muscle fibers:

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 is in cardiac muscles. The onset is rapid as in spike potential, but repolarization takes a longer time. This type of action potential has importance in organs where a longer contraction period is needed such as in the 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 self-excitatory. 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 waves 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 (chemical) control:

Muscle cells are innervated by autonomic fibers. 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 membranes have 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 or activation of phospholipase C. The latter results in the formation of IP3 (inositol triphosphate) and release of Ca++ from the sarcoplasmic reticulum (internal Ca++). 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

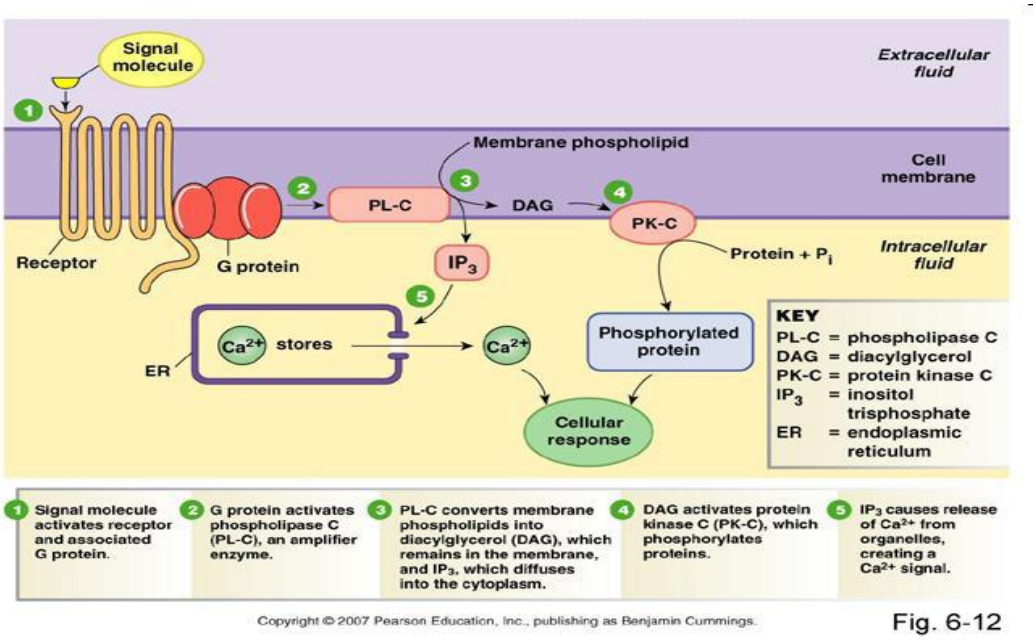


Fig. 6-12

40:00-46:00

Rock Bottom Has Built More Heroes Than Privilege

Good Luck