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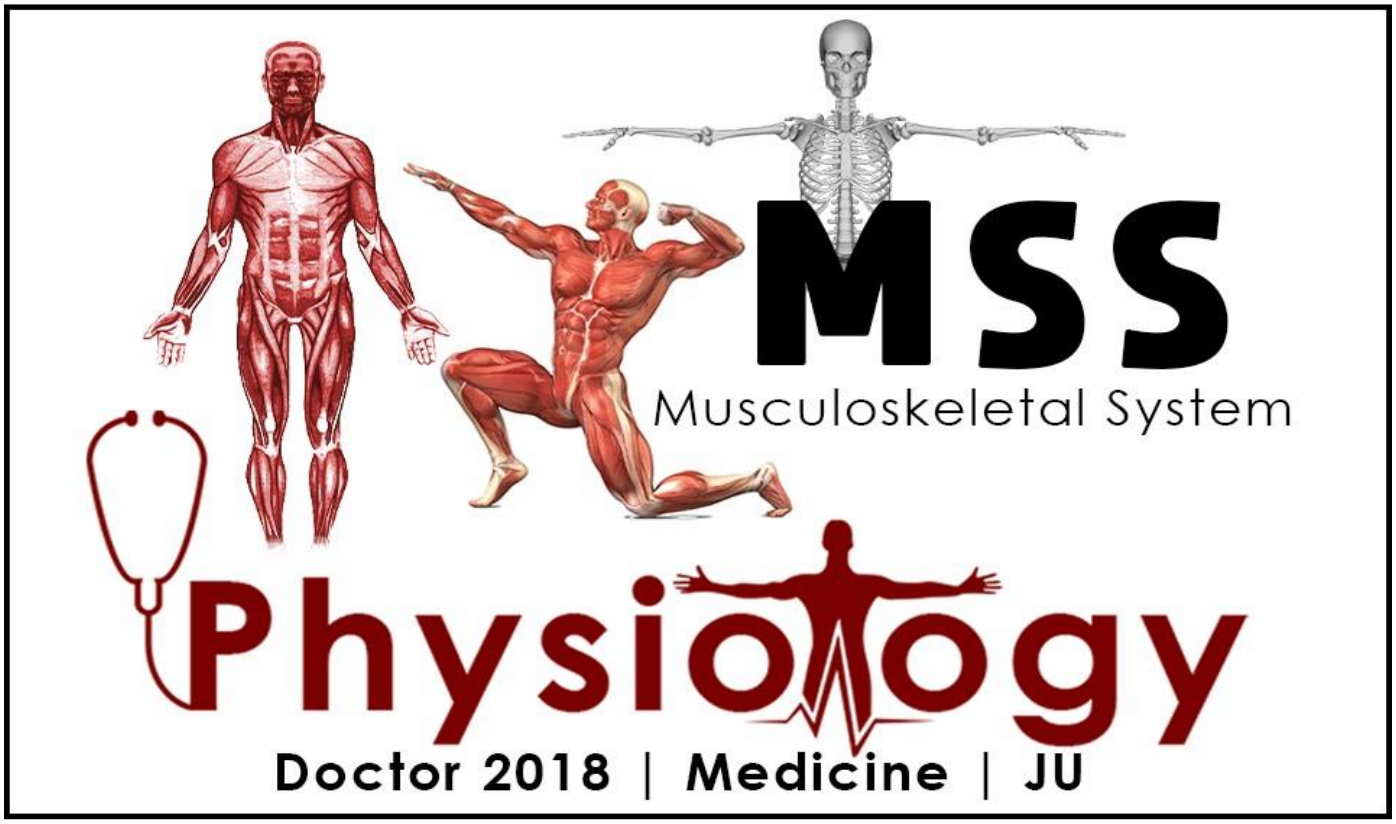


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M. Khatatbeh

# *Introduction*

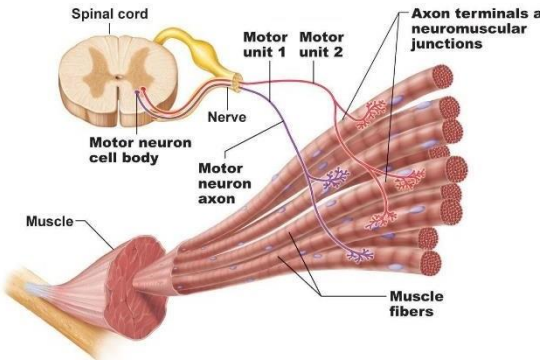
We all know that muscles contract. Furthermore, muscles contract harder if we try to move a heavier load. For example, the biceps brachii contracts more to lift 50 pounds compared with only 20 pounds. How do our muscles contract more to lift heavier loads? In short, we use only as much of a muscle as needed in order to move a load or get a job done. In this sense, a muscle works like a group of people attempting to push a car. If one person can't do it alone, maybe he'll call for another person to help. If the two of them together can't do it, then they'll call for yet another, and so on until enough persons are recruited to move the car.
Once they're recruited and the car is pushed, nobody else is needed.

As we discussed before, there are two types of summation:

1. **Frequency summation**: by increasing the frequency (rate) of action potential.
2. **Motor unit summation (multiple fiber summation):**

- Before we talk about this type of summation, what do we mean by a motor unit?

*Motor unit*: A group of **muscle cells/fibers** innervated by a single motor **neuron/nerve fiber** ***(and not a nerve !!).***
We have previously learnt the structure of a neuron and how each neuron has many axon terminals. Now, each *axon terminal* synapses with only *one muscle cell* and *the collection of all muscle cells innervated by a single motor neuron is called motor unit*.



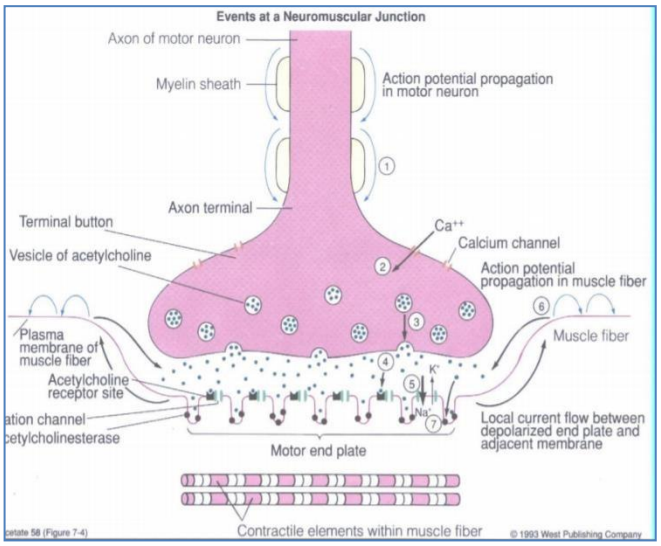

Notes: 1) It's important to know that not all motor units are the same size. Different muscles contain different sizes of motor units (muscles of the eye have small motor units compared to biceps, for instance).

2) Each motor unit contracts in an all-or-none fashion. In other words, if the motor neuron is excited, it will stimulate all of the muscle fibers to contract - that is, all of the muscle fibers within that particular motor unit.

- So, by the activation of more motor units, we will guarantee the activation of a larger number of muscle cells resulting in more forceful/powerful muscular contractions, Leading to an increase in the amplitude of simple muscle twitch.
- Now after we have talked about ''Motor Units'', we can readily go over the meaning of motor unit summation.
  **Motor Unit Summation**: The recruitment of additional motor units to generate more contractions.

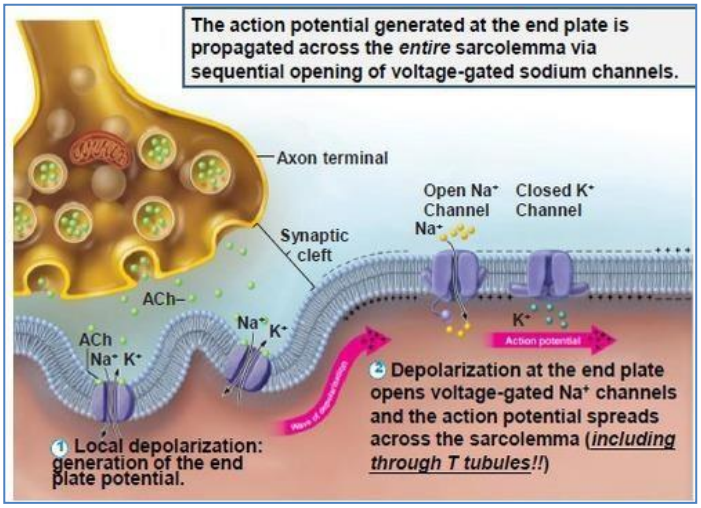
## Excitation-contraction coupling: the sequence of events through which the nerve fiber stimulates the skeletal muscle fiber causing its contraction.

***Secretion of Ach from the terminal***




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 they bind to ACh(ligand) causing Na+ influx (depolarization). 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.

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

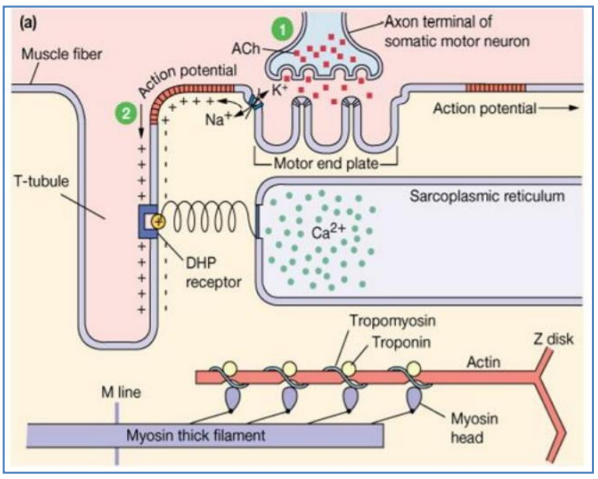



The motor end plate potentials are summated together, and if the depolarization was sufficient to reach the threshold, then the **voltage** gated ***sodium*** channels open and the action potential will be generated and spread throughout the sarcolemma.

- 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.

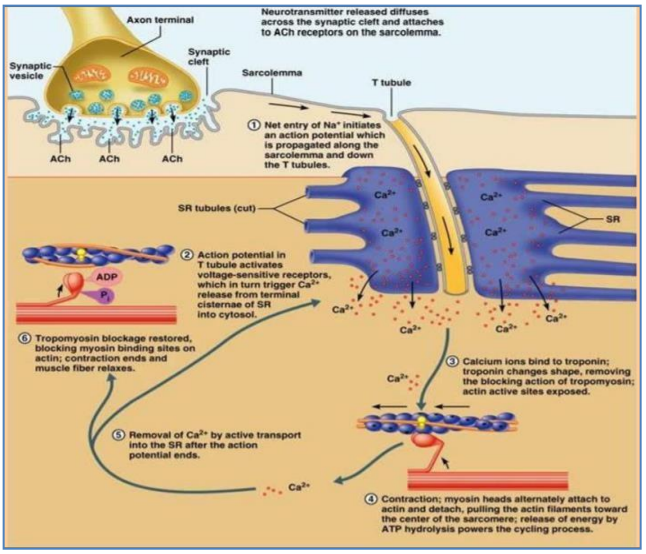
# CONTINUE

At the surface of muscle membrane, there 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. Once action potential reaches there, 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***. 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.




## Muscle Relaxation

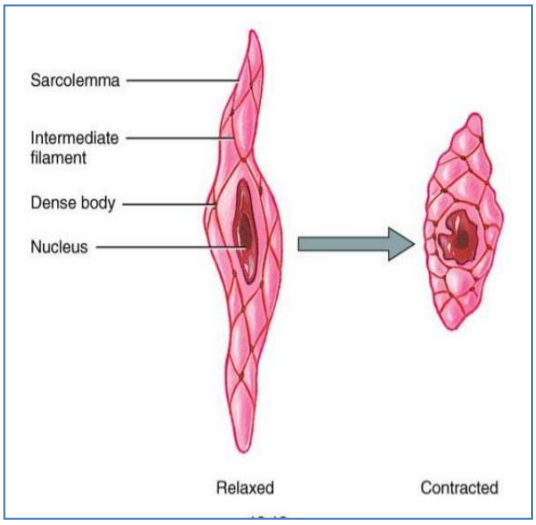
- At the membrane of sarcoplasmic reticulum, there are also highly active Ca++ pumps. These pumps concentrate Ca++ **inside** the sarcoplasmic reticulum by 10000 folds (Ca++ concentration in sarcoplasmic reticulum = 10^-3molar, in the

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.

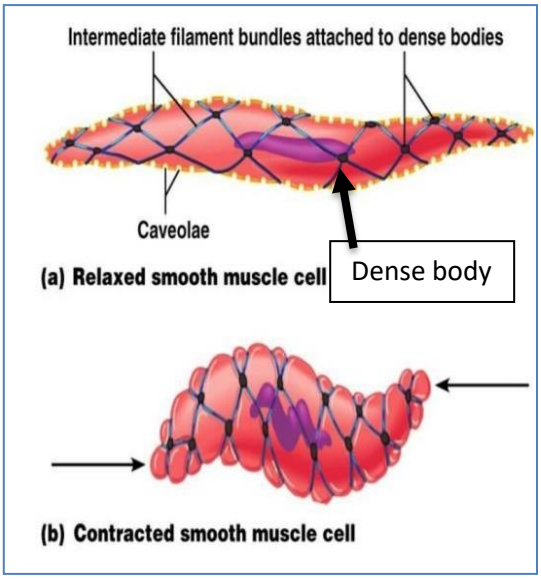
**Notes**:

- ***Myasthenia gravis*** disease occurs when the sodium chemical gated channels are destructed.
- Acetylcholinesterase plays a role in this process as it breaks down ACh, limiting the amount of ACh in the cleft at resting state.
- the T-tubules have both **sodium** and **potassium gated** channels, so they can generate action potential.

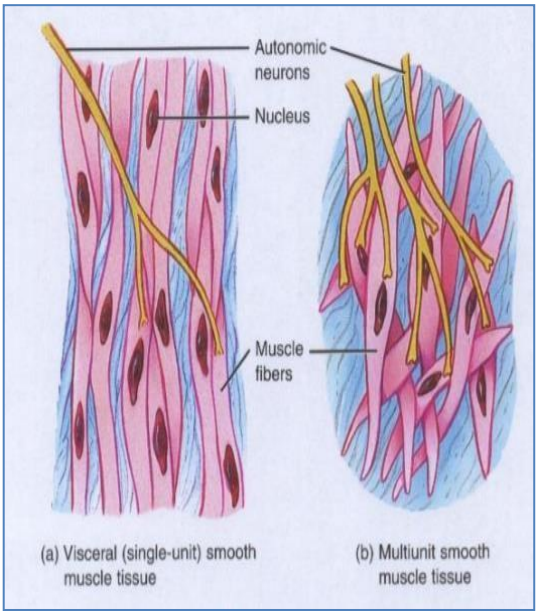
## ***Smooth muscle***:




- 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. 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.




## Smooth muscle control:

Smooth muscles can be stimulated either **chemically** or **electrically**.

### 1. Chemical control of smooth muscle:

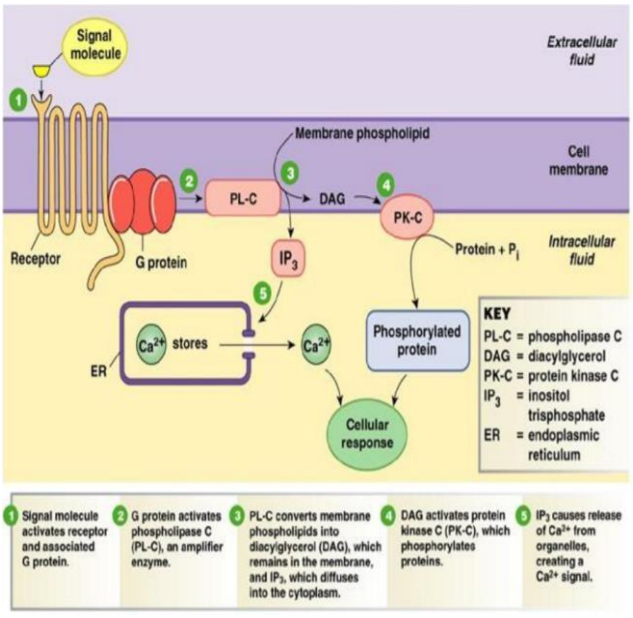
A. Smooth muscle receptor ***binds*** to a chemical compound/ligand.

***B.*** ***''Activated'' phospholipase-C*** splits the membrane phospholipid to Inositol trisphosphate ***($IP_3$)*** and diacylglycerol ***(DAG)***

***C.*** $IP_3$ 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.

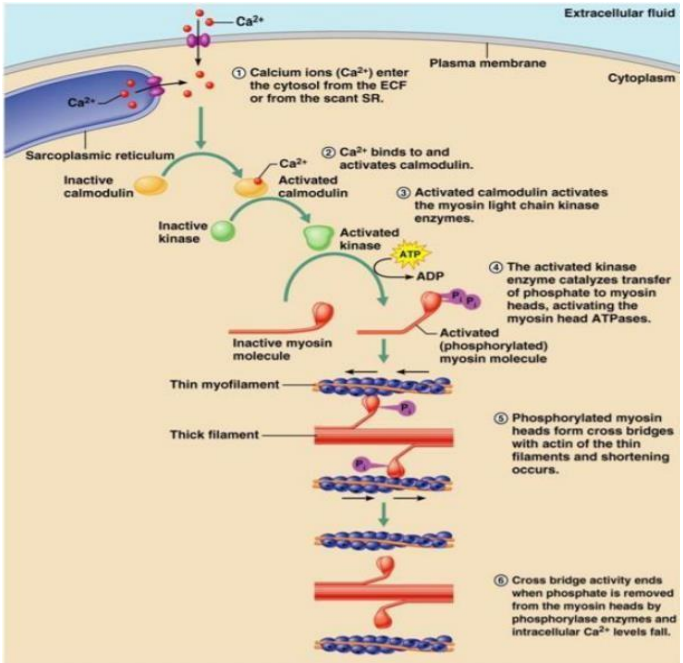


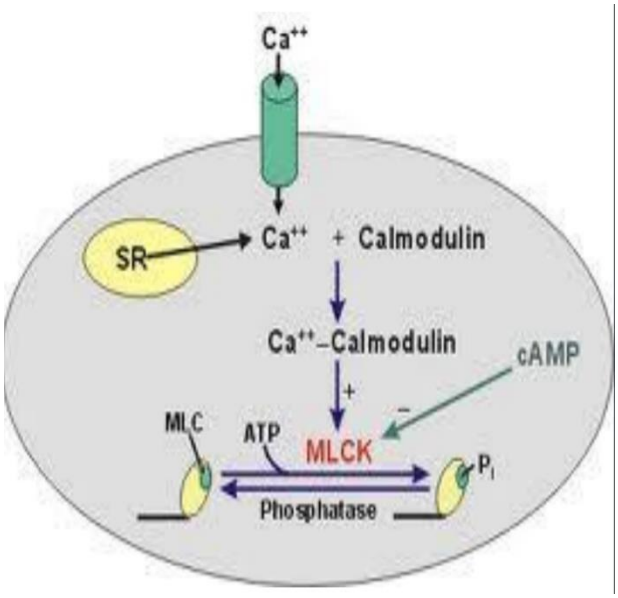
## 2. Electrical control of smooth muscle:

- Smooth muscle cells have voltage gated $Ca^{2+}$ channels on the sarcolemma, and these channels are under the control of potential changes, so the electrical control can activate $Ca^{2+}$ channel and cause influx of $Ca^{2+}$ .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



# ***QUIZ***

**Q1) After the T-tubules are depolarized**:

A. Calcium leaves the T-tubule through dihydropyridine receptor
B. Calcium leaves the T-tubule through ryanodine receptor
C. Sodium leaves the terminal cisternae through ryanodine receptor
D. Calcium leaves the terminal cisternae through calcium pumps
E. Calcium leaves the terminal cisternae through calcium channels

**Q2) The event that is not expected to induce or accompany contraction of a smooth muscle cell is:**

A. Inhibition of Adenylyl Cyclase
B. A decrease in the length of the I band
C. Myosin light chain kinase activation
D. Phospholipase C activation
E. None of the above

**Q3) Termination of smooth muscle contraction is observed after:**

A. Inhibition of myosin phosphatase
B. Efflux of Ca2+ outside the cell
C. Dephosphorylation of the actin heads
D. Decrease in cAMP concentration
E. More than one of the above

**Q4) Choose the correct statement regarding frequency summation:**

A. Involves increasing the number of muscle fibers innervated by a single neuron
B. It is the summation of contractions of a muscle fiber due to stimuli emerging from multiple nerve fibers
C. In extreme cases, it can lead to tetanization
D. Is dependent on the frequency of neurotransmitter exocytosis from a nerve ending
E. More than one of the above

**Answers**:

Q1) E
Q2) B
Q3) B
Q4) E

# ***GOOD LUCK***