Course: Electrophysiology of Heart

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Lecture 3: Physiology of voltage gated channels

Hello everyone. So, today we will start our next portion of Physiology of Voltage Gated Channels. Last lecture we had learnt about the sodium channel voltage gated sodium channels. So, today we will see about the potassium channels and the calcium channels. Now, as we had seen in the sodium channels they are the transmembrane proteins. So, similar is the potassium channels they are the membrane spanning proteins.

Now, mainly potassium channels is meant for efflux of the potassium ions to the pore. It is just opposite of the sodium ions where there is influx of the sodium through a pore. The role in potassium channels mainly cardiac repolarization, smooth muscle relaxations besides this main two important actions that is repolarization and smooth muscle relaxations they are also important for neurotransmitter release as well as insulin release. So, these are also the important functions of potassium channels.

So, hence the potassium channels belong to the largest and the diverse class of the ion channels. If we go through the structure of the potassium channels mainly it consists of the four alpha subunits and beta units. Now, alpha subunits as we have seen in the sodium channels they are the main functional part of the channels voltage gated sodium channels. And they because they constitute the pore, the pore domain is present in the alpha units. Whereas, the beta units they usually modify or regulate the channel activity which means the alpha units will play a role by sensing the voltage or the change in the membrane potential.

So, thus alpha units they respond to the membrane potential or the voltage change and also they form homotetramers or heterotetramers. So, in this way they form channel complexes the pore is kept in the center and the tetramer is formed by the alpha subunits and this form mainly the functional domain. Now, the beta subunits they are nothing, but auxiliary subunits or the parts of the potassium channels they modify the properties of the channel. So, this is the linear schematic representation of a voltage gated potassium channel. Here we can see the four alpha subunits are making tetramer homotetramers

and in the between we can see this pore.

So, in this way the tetramers are formed in a potassium channel voltage gated potassium channel. And as we had already seen in sodium channels that each alpha subunit they consist of various transmembrane segments. So, here also we have six transmembrane segments S 1, S 2, S 3, S 4, S 5 and S 6. The six transmembrane segments they each you can see one end is accompanied by N terminal the other one is accompanied by C terminal. Now, in between this is trans membrane alpha helix which consist of phospholipids bilayer.

The S 5 and the S 6 segments these constitute the selectivity filter. This already we have discussed in the sodium channel also the selectivity filter or known as P loop. Now, the selectivity filter is mainly meant for the identification or selectively passage of a particular ion. In this case since it is a potassium channel. So, it will pass only the potassium ions and it will not pass any other ions.

And this also constitutes the pore domain which cause the ion permeation to occur. And the S 4 segment this constitutes the highly positive arginine residues it is electro positive in nature. And this functions as the voltage sensor domain. The voltage sensor domain in the alpha subunit of any ion channel whether it is sodium channel or potassium channel or calcium channel. They mainly are responsible for the bringing about the conformational change in response to the voltage.

So, this is all about the schematic representation of the potassium channel voltage grid potassium channel. Now, what are the types of potassium channels? Mainly we have 6 transmembrane voltage grated potassium channels, 2 transmembrane in what rectifier potassium channels. Mainly we denote it as K i r and it also consists the ATP sensitive potassium channel also ATP sensitive potassium channels. And also we have the 4 leaky channels 4 leaky channels means 4 transmembrane leaky channels. Now, this 4 transmembrane leaky channels if you could remember the genesis or the ionic basis of resting membrane potential is the leaky channel.

So, this leaky channels mainly responsible for the genesis of the resting membrane potential in any cell. So, 6 transmembrane voltage grated potassium channels, 2 transmembrane in what rectifier potassium channels and 4 transmembrane leaky potassium channels. So, we will see the structures as we can see these are the 6 transmembrane in 6 segments are there. So, that they are 6 transmembrane voltage grated potassium channels. And we have the 2 transmembrane these are the potassium inward rectifier potassium channels and 4 transmembrane these are the leaky channels.

Now, ATP sensitive potassium channels these also constitutes in the inward rectifier potassium channels. These are present mainly in the beta cells of pancreas the cardiac muscles smooth muscles. So, pancreas means specifically beta cells because I had told you it is play it plays a very important role in the insulin release. So, the stimulator for this potassium channels ATP sensitive potassium channel is minoxidil very rampantly used for the hair fall treatment. Then we have adenosine.

Now, adenosine in heart acts by shortening the cardiac action potential duration by shortening the cardiac action potential duration. Now, what is cardiac action potential duration what is cardiac action potential that we will discuss in the further lectures regarding whenever we will discuss the cardiac action potential phases. So, till now you remember that adenosine acts by shortening the cardiac action potential duration. The closer I mean the gate are closed by sulfonylureas used rampantly for the treatment of diabetes because beta cells respond to this potassium ATP sensitive potassium channels while releasing the insulin. So, sulfonylureas, glimin, clomide, tolubutamide.

So, these are the inhibitors of the closure of this potassium channels ATP sensitive potassium channels. Along with that this potassium channels inward rectifier potassium channels also play a very important role in the action of class 3 anti arrhythmic drugs. Class 3 anti arrhythmic drugs are nothing but the potassium channel blockers for example, amiodarone. So, whenever there is abnormality in the heart rhythms heart rate we use anti arrhythmic drugs for that and potassium channel blocker is one of the anti arrhythmic drugs which belongs to class 3 none other than potassium channel blockers example amiodarone. So, this inward rectifier potassium channel blockers are mainly responsible for that.

And the 4 transmembrane leaky channels they are mainly target for the inhalational anesthetics that is halothane. So, this much you have to remember for the different types of potassium channels coming to specifically to the voltage gated potassium channels. We have various sub families around 12 sub families of voltage gated potassium channels we do not have to remember that the initial discovery was done with the help of shaker. So, shaker protein potassium voltage gated potassium channels then we have shab shawl shawl. So, these are various types of potassium channels we have.

So, these potassium channels the main important thing is the inhibitor or the blocker of the voltage gated potassium channels are number 1 4 aminopyridine 4 AP and TEA that is tetraethyl ammonium. These two important blockers you have to remember of voltage gated potassium channels that is tetraethyl ammonium and 4 aminopyridine. Besides that if you ask me what are the different types of this voltage gated potassium channels these are nothing, but some are known as fast activating potassium channels some are known

as slow activating potassium channels it depends on the speed. So, fast activating potassium channels are nothing, but it is like fast activating potassium channels very rapidly these are occurring the very common example is shaker. And while shawl we have delayed response potassium channels.

So, these are slow activating or delayed activating potassium channels. So, this is how the voltage gated potassium channel acts whether they act rapidly or slowly depends on that the names are given various. So, what we have to remember that is the blockers of the voltage gated potassium channels that is tetraethyl ammonium and 4 aminopyridine. Now in the potassium channels they remain the potassium ions they are they are very much permeable to the cell membrane we know. Because they usually stay in initially hydrated state we can see the various bonds.

So, initially they stay in hydrated states and whenever they pass through the potassium channels they usually get linked to the carbonyl oxygen ions. So, carbonyl oxygen ions which get linked to the potassium ion. So, this bond is very much seen in potassium ion which is not present in case of sodium ion. So, that makes potassium highly selectively permeable through the cell membrane. Now, what is the action mechanism of action or how the gates open or function in case of or regulate in case of potassium channels.

Now, in case of sodium channels we have seen there are mainly 3 states of the gates they remain in the closed state. Then they open then they get inactivated then they again they have to move to the closed state. So, closed open inactivated. So, this is this 3 states are present in case of sodium. But in case of potassium channels this inactivated state is not present it is only closed and open state.

So, from closed to gate open when the gate is closed and the gate needs to get open we require depolarization. And when we are supposed to close the gate we require repolarization. So, these are only 2 states there is no inactivation state in the potassium channel which we had already seen in the sodium channel. Now, what happens how this gates open. So, initially when the gate is closed that means, here electro negative charges are present inside the cell.

We have negative charges inside the cell and we can say this is nothing, but the voltage sensor domain of S 4 segment which is highly electro positive. So, when electro negative charges present inside the cell and this voltage sensor domain is highly electro positive. So, there is an attraction between the 2. So, this attractive force will keep the gate closed, but whenever there will be depolarization as we can see in depolarization there will be electro positive charges inside the cell because of the influx of the ion. So, whenever there is depolarization or the electro positive charge inside the cell this electro positive

domain that is voltage sensor domain this will not get not stay attracted rather repel from each other.

And whenever these the flaps will get repel the gate will open and potassium will move outside. So, this is the mainly mechanism of closing the gating mechanism of the voltage gated potassium channel how the gates open and get closed. So, it is mainly because of the change in the voltage potential and the relation of the voltage sensor domain that is S 4 segment with the voltage put a membrane potential. So, what is important significance of the clinical aspects of potassium channel already we had discussed in sodium channels various syndromes like long QT syndrome short QT syndrome Brugada syndrome. In potassium channel also we do not have to remember all what is important is K cn Q 1 gene.

Now, this K cn Q 1 gene usually codes for the voltage gated potassium channels and that mainly results in the long QT syndrome short QT syndrome and the Brugada syndrome. The same we have seen with the SCN 5 gene that is for the sodium channels. So, this long QT syndrome short QT syndrome or Brugada syndrome this will cause nothing, but cardiac various cardiac arrhythmias then the other than polymorphic ventricular tachycardia then ventricular fibrillation. So, these are the various types of arrhythmia which is usually seen in case of these syndromes. Now coming to the calcium channels now calcium channels the main functional domain is alpha 1 unit the principle 1 big large alpha unit is same over here along with that there are all auxiliary units.

We have alpha 2 segment, we have gamma segment, we have delta segment, we have beta segments. So, these are all auxiliary units which only function secondarily that is the modulate the activity, but the main function is done by the alpha 1 subunit the basic physiological electrophysiological and the pharmacological properties are present in the alpha 1. Now, this is again the linear schematic representation of calcium channel. Now, in case of calcium channels already in the alpha 1 subunit 4 domains are present and each domain as I told you the same structure usually is seen in other ion channels also sodium potassium each domain consist of 6 transmembrane segments. And S 4 segment is the voltage sensor domain the pore or the selectivity filter is formed between S 5 and S 6.

So, similar arrangement we also see in case of calcium channel besides that again each is having N terminal and C terminal besides that in calcium channels we have the auxiliary units. We can say this is the gamma unit which is present the transmembrane level then intracellularly we have this beta unit this is the side for the phosphorylation. Then we have the alpha 2 subunit and with the disulfide bond with delta subunits and this zigzag line is for the glycoposphate tidal inositol anchor. Whenever calcium channel

is involved we are mainly concerned with the second messenger system we have DAG diacylglycerol or inositol phosphate 3 which acts. So, that is mainly responsible for this other subunits, but the main role the ion channels which is important for signal transduction that is alpha 1 subunit and this is same as that of the other ion channels.

Now, what are the types of voltage gated calcium channels the voltage gated calcium channels are mainly high voltage and low voltage gated calcium channels. So, high voltage we have k c a v that is voltage gated calcium channels 1.

1, 1.2, 1.3, 1.4. Then also we have calcium voltage gated calcium channels we have 2.1, 2.

2, 2.3 and we have low voltage gated 3.1, 3.2, 3.3. For that these are divided into this 1.1 to 1.4 is known as L type of calcium channels or they generate L type of current.

This L type is mainly coming from the word long lasting. So, this is L type of current seen in this calcium voltage gated channels ranging from 1.1 to 1.4.

Then we come to calcium voltage gated channel 2.1 this is mainly N type. Then we have 2.2 this is mainly P or Q type.

Then we have 2.3 this is mainly R type. We will discuss this further in further slides. And 3.1 to 3.3 this all comes under T type of calcium channels. The name as suggest T means transient calcium channels transient.

So, L is long acting and T is for short acting or transient opening of the channels. So, low voltage is T type the other two categories are high voltage which consists 1 to 1.

4 L type and 2.1, 2.2 and 2.3. Now, this L type as I told you they have slow voltage dependent inactivation and they are long lasting or in a way they get activated at high voltage. So, that is why they are high voltage calcium channels. And also this L type calcium channels are regulated by second messenger activated protein phosphorylations. So, this we will see further in whenever the cardiac muscle contraction will discuss. So, L type of calcium channels in comparison to L type of calcium channels the T type of calcium channels are transient type.

So, they usually get activated at much more negative voltage. Suppose L type get activated at plus 20 milli volt while a T type will get activated at minus 10 milli volt. So, they get activated at much more negative membrane potentials. They get inactivated very rapidly deactivated slowly they have small single channel conductance and also they are

insensitive to conventional calcium antagonist. Now, usually the L type of current or the L type of voltage educated calcium channels they are sensitive to blockers.

So, the calcium antagonist the most common calcium antagonist is dihydropyridine. So, that is why the other name of this channels that is dihydrodhpr dihydropyridine receptor. So, this dihydropyridine receptor blockers are nothing, but they act on the L type of calcium channels. But as such T type of calcium channels they do not have any such blockers. So, since their name they are dependent on the further negative voltage and T type of calcium channels are mainly responsible for the transient opening and short openings.

In contrast to this we have N type of calcium channels. Now, N type of calcium currents are mainly distinguished by their intermediate voltage dependence. They fall in between L type and T type which means they are they are not totally dependent on high voltage neither they are dependent on much negative voltage. They are in between the L type and T type. Whereas, P type of calcium currents they are first recorded in the Purkinje neurons. Q type of P name suggest from Purkinje, Q type of calcium currents they are first recorded in the cerebellar granule cells or cerebellar granule neurons.

Whereas, R type of calcium also currents they are also seen in cerebellar granule neurons and they are resistant to the peptide calcium channel blockers. So, this is the mainly signal transduction which is done by the voltage gated calcium channels. We can see this alpha subunit is mainly responsible for the calcium channel for the signal transduction. And they mainly perform contraction secretions of synaptic transmissions that is secretion of the neurotransmitter, phosphorylation of proteins, various intracellular activities on undergoing over here enzyme regulations and gene transcriptions. Now, one thing is very important over here the neurotransmitter release which is done from the vesicles.

And there during the synaptic transmissions this calcium plays a very important role in the fusion of the vesicles and also integration between the synaptic the vesicular proteins as well as the membrane vesicular proteins. So, we have the name that is snare proteins. So, the snare proteins interactions or the neurotransmitter release from the vesicles is mainly done by n type of calcium channels and p by q type of calcium channels. It is not done by l or t type, it is done by n type of calcium channels or p by q type of calcium channels. That means, this n type or p by q type plays a very important role in the synaptic transmission.

So, next we will see what are the diseases which are related to the calcium channels. So, this is the table which is depicting l type as we have already seen 1.

1, 1.2, 1.3, 1.4. This channels I had already told you they are l type of calcium channels. And the blocker for this calcium channel is nothing but DHP or dihydropyridine. So, DHP or dihydropyridine the very famous dihydropyridine blocker drug is known as amlodipine. Now, this amlodipine is used mainly as an anti-anginal drug or anti-hypertensive drug, but antiarrhythmic drug also we use l type of calcium channel blocker, but that is not dihydropyridine blocker. So, dihydropyridine blocker is amlodipine which we generally use for anti angina medications or hypertension medications.

So, the functions of this l type of currents that is excitation contraction coupling in skeletal muscles and hence the disease hypokalemic periodic paralysis. Then mainly 1.2 if we are concerned with the cardiac muscles. So, here calcium get voltage-glute calcium channel 1.2 plays a very important role because they play an important role in the cardiac muscle contraction and hence the disease cardiac arrhythmias and Timothy syndrome.

The next calcium voltage-glute calcium channel 1.3 this is also mainly responsible for cardiac pacemaking. That means, it is also present in the nodal tissue apart from the atrial and the ventricular musculature which is seen for the voltage-glute calcium 1.2. So, this 1.3 is mainly present in the nodal tissues and cardiac pacemaking is very important function over there and that is why any abnormality to this voltage-glute calcium channels will result in arrhythmias.

Any types of arrhythmia can occur ventricular tachycardia ah fibrillation ventricular fibrillation also it is very important ah for the auditory transduction and endocrine secretion this you have to remember. And for visual transduction also calcium voltage-glute calcium channel 1.4 is very much responsible and ah since it is responsible for visual transduction. So, any abnormality with this channel will result in night blindness.

Next we come to the p by q type of calcium channel that is 2.2 the blocker of this p by q type of calcium channel is agatoxin omega agatoxin. And as I told you that is p by q type of ah voltage-glute calcium channel is mainly responsible for neurotransmitter release. So, any abnormality related to this ah voltage-glute calcium channel will result in non-release of the neurotransmitter. So, whenever there is non-release on neurotransmitter the impulse will not get transmitted there will be hampering in the nerve impulse transmissions and thus contraction and relaxation of the muscles. So, that inherited disease we get from the mutations of this voltage-gated channels that is familial hemiplegic migraine.

We see familial hemiplegic migraine and t type of calcium channels that I already told you that is they are not sensitive or insensitive to the ah conventional ah antagonist or the calcium channel blockers. So, they are we do not have any blocker as such for the t type of or the transient type of calcium channel blockers. But this t type of calcium channels are also are very much present in the pacemaker firing. It is one of the basis for the ah pacemaker potential we will see in the ah action potential of the cardiac muscles. And so, any abnormality with this t type of calcium channels will also again result in the arrhythmias and also since it is present in the ubiquitously it is present in the ah brain.

So, it results in absence seizures. So, these are the inherited disease which occur due to the mutations of the alpha subunits of the calcium channels voltage-gated calcium channels. We have to remember mainly the blocker of the calcium channel l type of calcium channel is dihydropyridine and the drug is amlodipine. The anti arrhythmic drug which is ah commonly used that is diltiazem or verafemil this is non dihydropyridine blocker. I mean this does not act in ah the dihydropyridine receptor.

So, that is only the amlodipine. This drugs are used for anti arrhythmias whereas, amlodipine is used for anti angina and ah anti hypertensive medications. So, with this I would like to conclude today's topic. In this lectures we had discussed the role and functions of potassium channels, the mechanism of actions of the calcium channels, the gating mechanisms and various disorders inherited disorders related to the ah 2 channels potassium channels and calcium channels. Thank you.