Neural Science for Engineers
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Lecture - 16
Energy Sources of Neuronal Systems

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We will start with today's discussion with Power Systems. How is the neuronal function powered? What is the source of energy for the function of the neuronal system? What part of the system is powered and what part of it is unpowered? So, those are things which we will discuss. These have implications not only for a fundamental understanding of the nervous system function, but they also have an implication in several other things.

The most important implication which I can think of for people who are in the neurosciences from engineering background is, people who are analyzing FMRI images. So, functional MR imaging basically looks at glucose metabolism within the brain and it tries to pick up the function of the nerve in terms of the amount of glucose which is utilized by the brain.

So, it does not look at electrical activity of the brain and so that is something which we can have an understanding when we go through the need to go through power systems which power the brain. All of us are familiar with the concept that the brain as such does

not have any reserve power systems which is why it is important for oxygen and glucose to be continuously provided to the brain. Breakdown of either one of these is responsible for various kinds of diseases and death.

So, when somebody drowns there is a loss of oxygenation to the brain for about 4 minutes and that is just about the time which is required for cell death and large parts of the brain. Similar, problems are there in the management of stroke. Stroke is occlusion of a blood vessel to a particular part of the brain; if not treated within the golden period which is about an hour it causes irreversible permanent damage to the brain.

Now, why that happens, we will look at it in a greater detail, but what is being dealt here is what are the mechanisms by which the power is utilized by the cell for the generation sustain and generation of action potentials and its sustenance of function.

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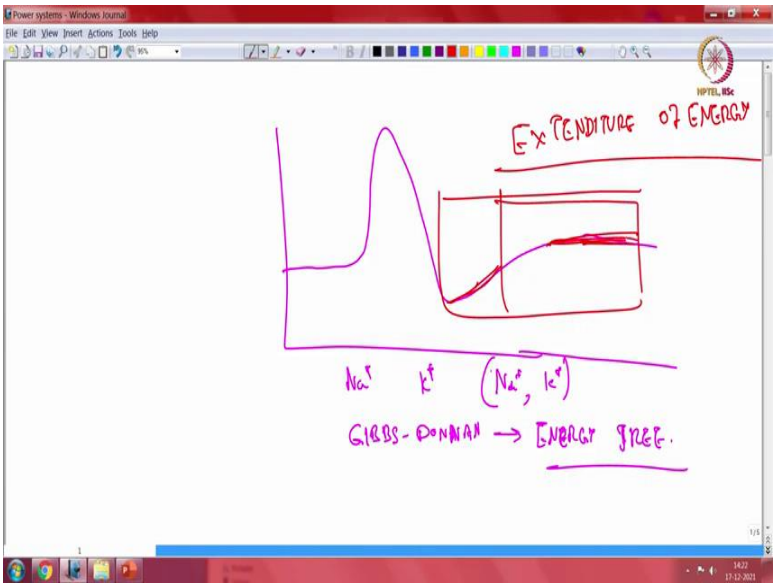

We go back to the action potential and what we have discuss so far. So, action potential has various components. Now, if you look at what part of it is; this is the sodium channel, the potassium channel and the reversal, so that is both sodium and potassium channels work. Now, we started with the Gibbs-Donnan, which basically says that membrane potential can be generated without energy.

So, you just ensure that there is a particular concentration of ions and compounds or ions and proteins on two parts of a semi permeable membrane and then you can have a

change in potential. So, that is an energy free system. It is energy free because everything happens through passive diffusion if there are channels for ions and proteins to happen and the equilibrium is maintained; it is dynamic equilibrium there is no energy expanded to maintain the equilibrium.

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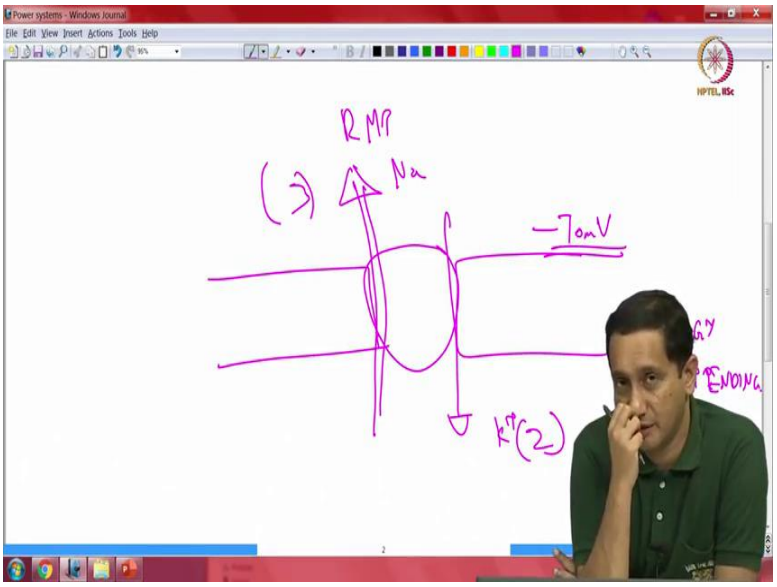

So, if you look at resting membrane potential. Resting membrane potential is against the gradient. So, we know the from the prior discussion of the sodium potassium pump and you need to pour out sodium and get in potassium, but it is 3 and 2. So, this is an energy expending process now that is the first part of this story.

So the resting membrane potential as it requires energy for it is sustenance which is one step above the Gibbs-Donnan. So, what happens when you lose energy? So, if the energy for maintenance of this pump is lost, the ability to maintain the -70 milli volts is lost which is the resting membrane potential. So, the potential gradually comes back to 0 and that in turn causes a cascade of signaling which happens.

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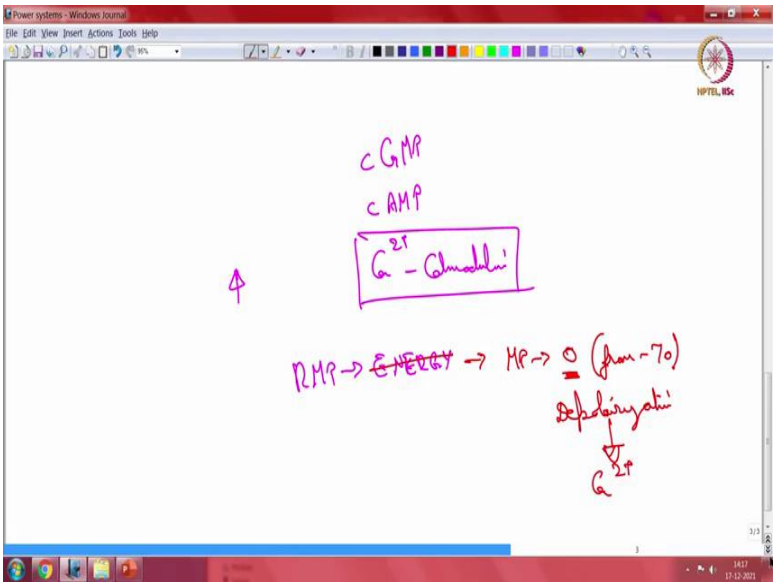

So, in the last class we have discussed the important activities of cyclic GMP, cyclic AMP and what I not discussed then is the calcium calmodulin complex. So, this in turn if there is increase in calcium. So, as I told you RMP requires energy. Now, when energy is not available it results in membrane potential approaching 0, from -70. Now, basically this is depolarization.

Now, which is happening de novo it is apart from a stimulus. So, that one of the activities which happens with depolarization is the increase or uncontrolled egress of calcium in ingress of calcium into the cell.

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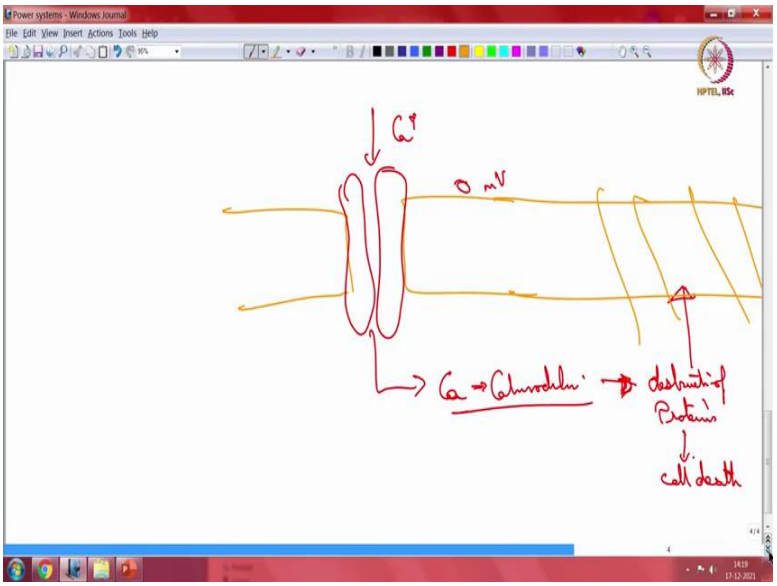

So, cell membrane, calcium at 0 milli volts and that combines with something called as calcium calmodulin and that causes series of activities. I will not dwell into those things in greater detail because it is not required. So, that produces destruction of proteins and cell death. So, power systems are responsible for ensuring that membrane integrity is preserved.

So, calcium calmodulin at some part of it also results in destruction of the cell membrane itself. So, when there is destruction of cell membrane there is uncontrolled diffusion of various molecules of various sizes and ions of various sizes across the cell membrane which should not happen and that is how cell death happens. Now, so we started with Gibbs-Donnan then with resting membrane potential and how energy is utilized for generating the resting membrane potential.

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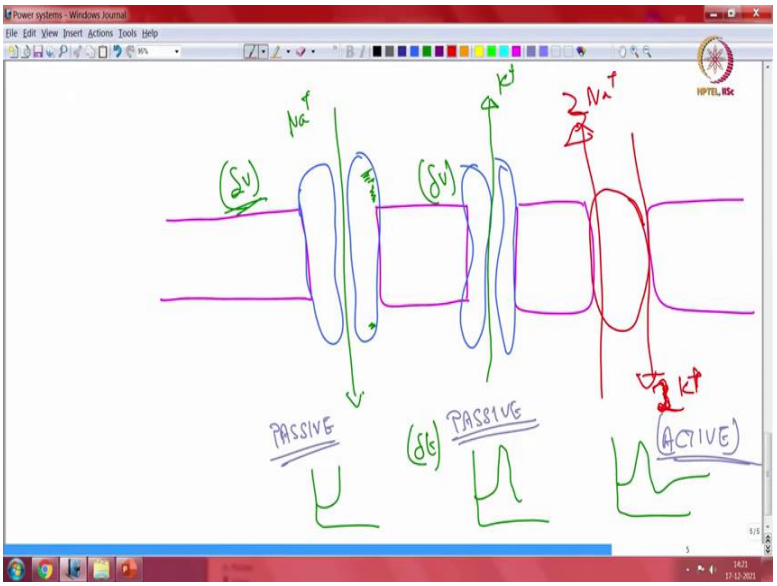

We will look at the action potential, which is something you have already dealt with, at a later point of time, but to revise in slight fashion we understand that the action potential is by one two. And so, the players in the action potential generation is the sodium channel, the potassium channel and the pump.

So, these are the players within this one action potential. So, when the action potential is triggered, sodium comes in after some duration of time, that is small amount of time t, potassium goes out and this is membrane potential goes from this one and then this one and then so, that is what happens.

So, if you look at membrane potential changed only because of a change in voltage passive. So, it is a passive event that causes a conformational change in the receptor and that causes the ion to come in, it is that same change in potential which causes the potassium channel to be activated and the potassium goes out again passive.

So, the most important parts are passive. It is the third part, which is restoration of the membrane potential is the active part of the story. So, in restoration what happens is the sodium which is got in during the action potential is thrown out, the potassium which has gone out across it is concentration gradient is built up against its concentration.

So, it is this part of the action potential which causes expenditure of energy. So, the coming back of the action of the resting membrane, maintenance of the resting membrane are the two places where there is expenditure of energy.

So, the first part of the story the signal transmission actually does it is not an expand energy expanding process; it is the correction back into this one, but we cannot look at a single action potential as I told you, axons on neurons produce strains of action potentials and they have a baseline many of these axons neurons have baseline activity.

Baseline activity, they keep changing they have a baseline level of signal generation when there is an input signal the amount of or rather the frequency of the signal changes output signal changes. So, that is how neuronal function happens it is not that zero and then you have some function it is a baseline function, increase frequency, decrease frequency and that is the output and the processing which happens within the neuron.

So, similar kind of thing happens even with the EPSP, IPSP in the dendritic part of the story, but it is ultimately restoration of the membrane potential and the sustenance of the membrane potential which is this. Now, that we have understood which part of the action potential is actually responsible for taking energy.

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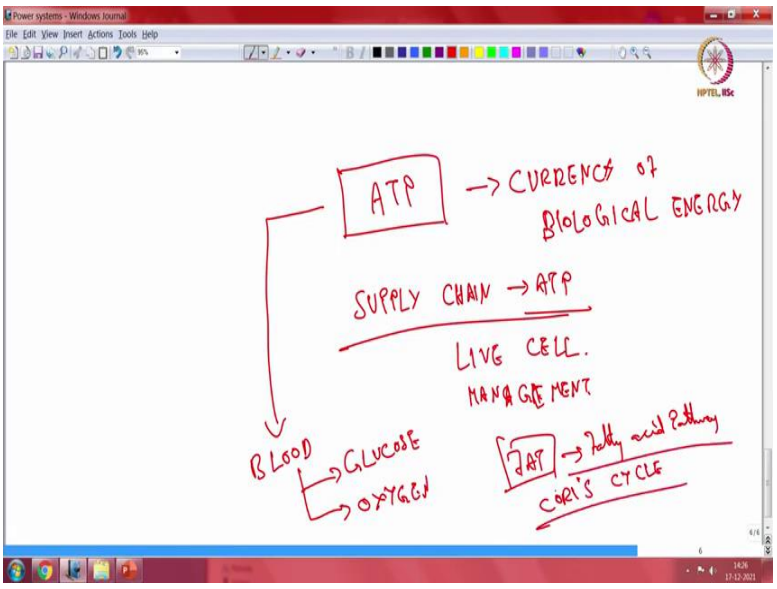

Let us look at the currency of biological energy adenosine triphosphate is the currency. It is ubiquitous. It is used for everything from manufacturing proteins, maintenance of the

membrane equilibrium; that is various pumps see I just described only about the sodium potassium pump; there is sodium hydrogen pumps and I think hydrogen pumps potassium pumps. So, various kinds of pumps are there within the membrane and there are various kinds of functions for each of these pumps.

Because for the purpose of our discussion I have just used only one or two of those pumps. So, there are multitudes of pumps, some of them even pump proteins out and they require energy because the larger molecules and to and have to be pumped against concentration gradients. So, each of this activity causes is sustained by the generation of ATP. So, free production or having a good supply chain of ATP is a fundamental requirement of a live cell.

Live cell management, ATP should be readily available it is not that you wait for a signal to arrive to decide that the ATP has to be generated, it is not like that. ATP should always be available which is taken up by the pump because of the voltage changes which happens. So, it is the other way around. So, you have to and because the brain does not have storage and it is dependent on blood for the two basic ingredients which is oxygen and glucose.

In the other parts of the body, we have fat which can be used to convert into various things. So, you have the fatty acid pathway. Then there is also the protein which is the coris cycle. These are not for current discussion, but there are other mechanisms by which other kinds of cells within the body can sustain, but for the purpose of the brain we need to know that glucose and oxygen are the two important requirements.

Now, we look at how that happens to some extent, I would not bore you with too much of details, but there should be some amount of understanding of what happens within that. Now, each one of these works which I am about to describe is has been worth a couple I think a couple of Nobel Prizes. So, that is the fundamental importance, that is for understanding.

Second thing is these systems have remained across various organisms from very small, single cell I do not know, any organism which does aerobic. Aerobic is using oxygen something which uses oxygen. Redox oxidation mechanisms to produce energy and expend energy. So, these aerobic organisms utilize this mechanism.

So, it is conserved the mechanisms the proteins are conserved across various groups of very low-level organisms to high level organisms indicating that evolution over a period of time has decided that this is efficient. It is a very efficient system; I have not figured out, I think maybe I should ask it as a question. What is the mechanical energy efficiency of a biological system, biological energy production vis-a-vis petrol, diesel, nuclear anything.

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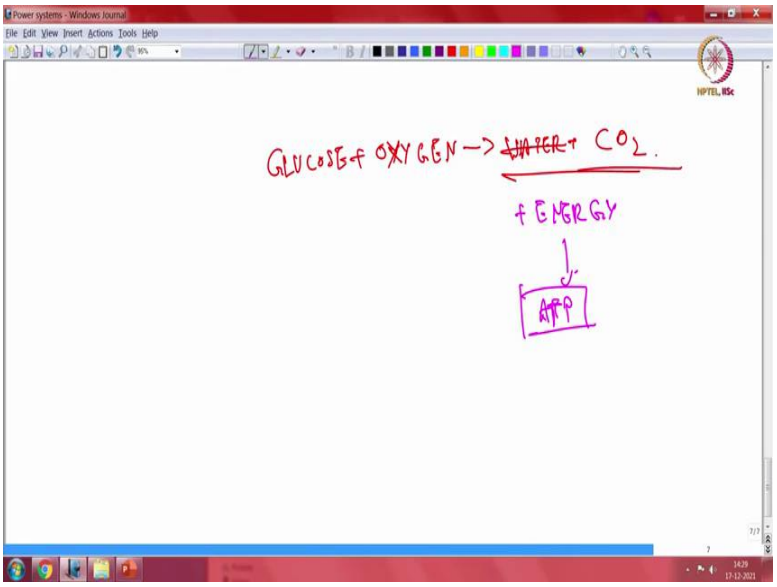

So, the ultimate results of a glucose plus oxygen is water plus carbon dioxide. So, or rather I think only carbon dioxide, plus energy of course, energy in terms of ATP generated. So, that is how glucose and oxygen is used to produce ATP. As I have discussed earlier ATP is the fundamental compound which interacts with various parts of the cell and helps to maintain the economic transactions within the cell. So, we go into those pathways.

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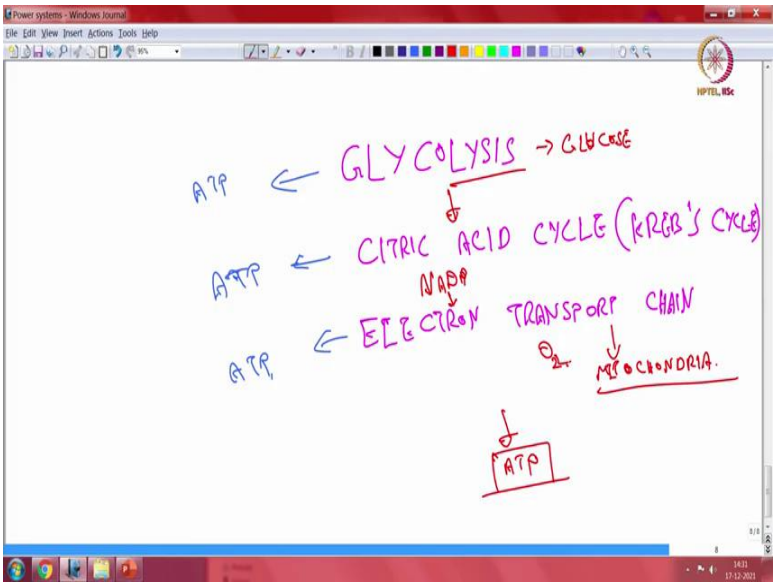

So, we look at the whole thing we need to look at the pathway in two three important steps. So, the first is called glycolysis then the citric acid cycle also called as the Krebs cycle. And then we got the electron transport chain. So, all of this produces ATP. Citric acid also produces ATP and then electron transport. Then these two function within the cytoplasm, this functions within the mitochondria.

So, glycolysis is breakdown of glucose, lysis. So, glucose is broken down into it is compounds and, in the bargain, ATP is generated some of the products of glycolysis enter into the one of the products of the glycolysis enters into the citric acid pathway and then through the citric acid pathway it produces NADP which enters into the electron transport chain and in the mitochondria.

And through there it produces for the ATP. So, this is oxygen dependent. So, that is how the cell in general is powered, not just about neuronal cells or even other cells cardiac cells for example, get power.

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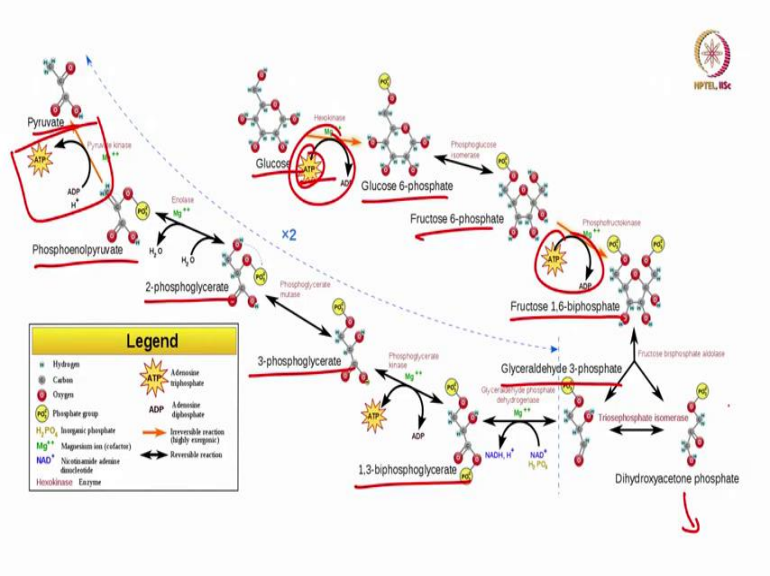

So, here I think I have to go into a little more detail. So, we look at these things. This is from Wikipedia I had to borrow because I think I will switch back and forth because I need to refer to this thing to find out glycolysis.

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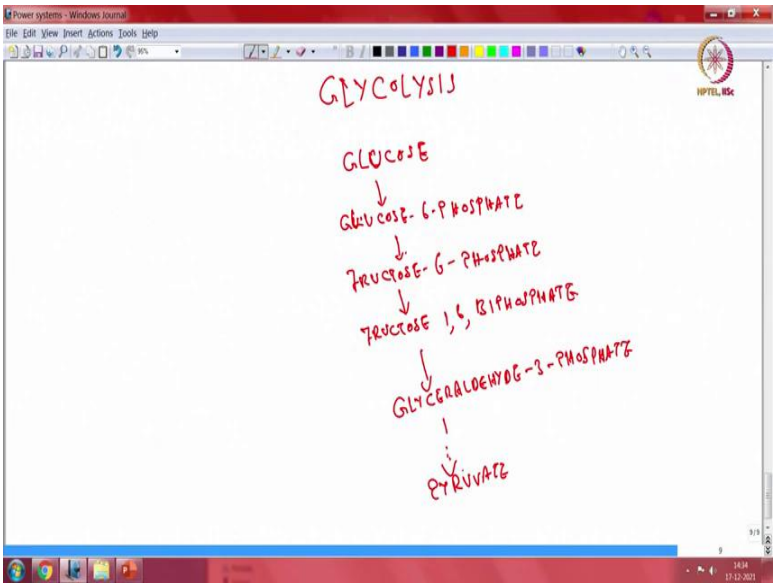

So, this is something which I had mugged up, 20 couple of years back. So, please pardon me if I make mistakes. Glucose, glucose 6 phosphate and I think it is fructose 6 phosphate, glucose 1,6 biphosphate; let me check. So, that is glucose, glucose 6 phosphate, ATP produce it is consumed. So, then glucose 6 phosphate to glucose

fructose once glucose 6 phosphate to fructose 6 phosphate, it is fructose 1, 6 4 biphosphate. So, fructose 6 1, 6 biphosphate, glyceraldehydes, something wrong here.

Because you have to end up in pyruvate, it is not ending in pyruvate. So, somewhere downstream you end up in something called pyruvate. Yeah, sorry I made a mistake here. So, glucose glyceraldehyde 3 phosphate and then you have 1,3 biphosphoglycerate I think I will anyway, I will write it out completely.

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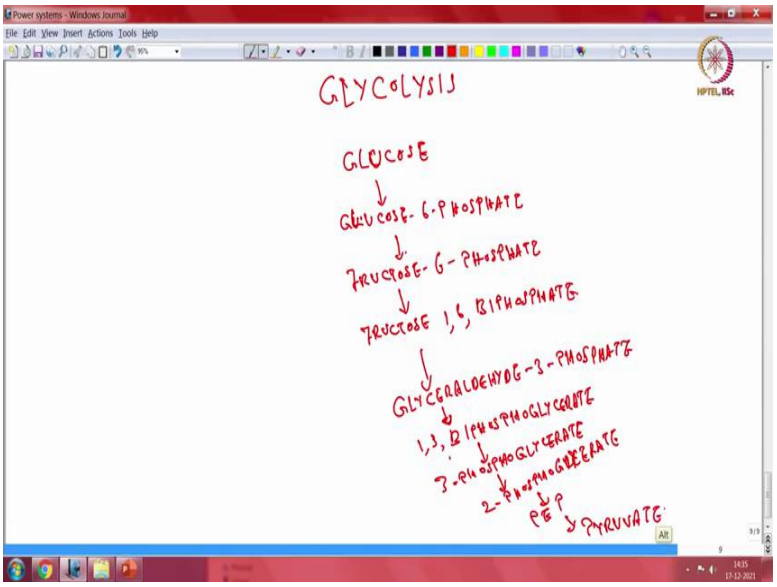

Glyceraldehyde 3 phosphate one phos 1, 3 biphos, 4 glycerate was 4 1, 3 biphosphoglycerate, 3 phosphoglycerate, 2 phosphoglycerate, phosphoenol pyruvate and pyruvate.

So, glucose, glucose 6 phosphate, fructose 6 phosphate, fructose 6 biphosphate, glyceraldehyde phosphate, d DHAP goes somewhere else 1, 3 biphosphoglycerate, 3 phosphoglycerate, 2 phosphoglycerate, phosphoenol pyruvate and pyruvate. So, this is the only step in which ATP is generated there is expenditure in here, here is this consumption ok.

So, these are this is where glycolysis takes place. So, it just purely splits glucose with the resulting ATP which is generated. So, glucose is split into it is constituent components through a series of organic biochemical reactions and that produces ATP. The various

compounds are as shown over here is from Wikipedia. So, once we have so, far seen how pyruvate is generated.

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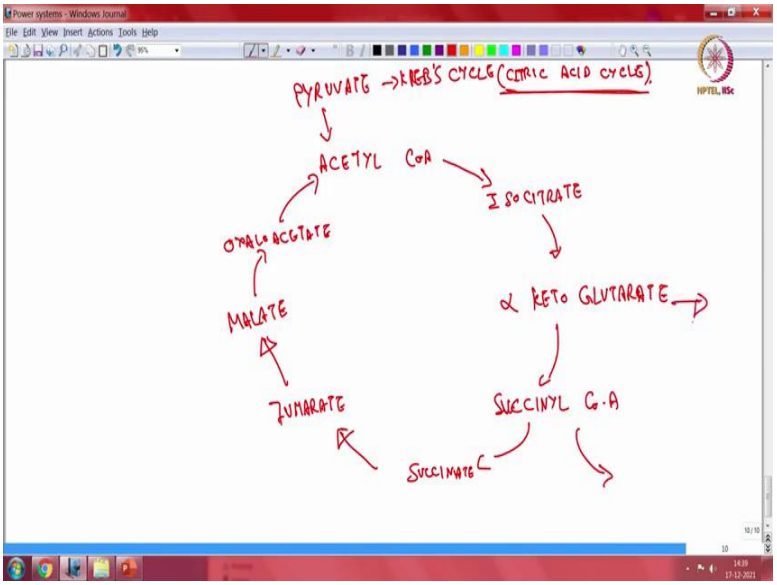

And so, what happens with pyruvate is, pyruvate enters into the Krebs cycle or the citric acid cycle. Sort of explains why it is difficult to do medicine you have to mug up all these things, it gets asked in vacuum exams and you have to be fairly thorough with all this stuff. I had been through at a point of time I unfortunately cannot tell the same thing at present. So, we will go through this and yeah so pyruvate results in acetyl CoA.

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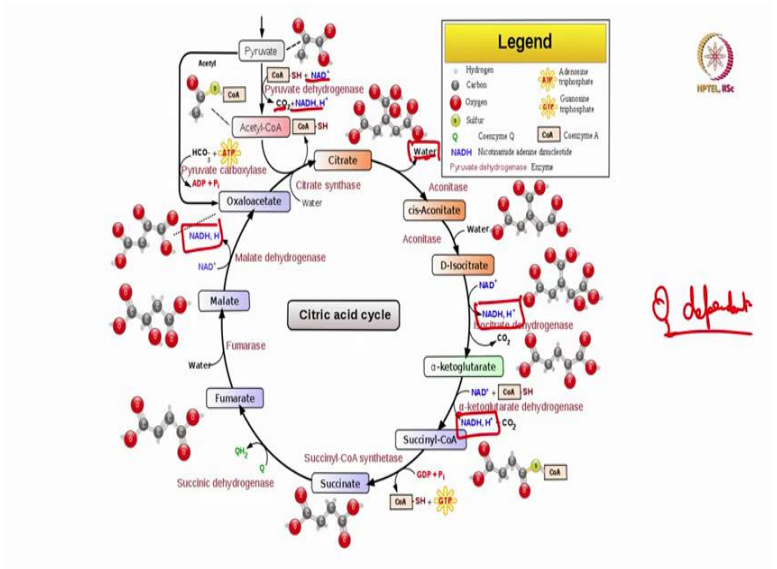

Now, acetyl CoA gets converted into isocitrate, isocitrate gets converted into; that is cisconate and b isocitrate, alpha keto glutarate; alpha keto glutarate to succinyl CoA, succinate, fumarate, malate, oxaloacetate and it gets converted back into acetylcholine.

So, this cycle keeps on continuing, there is an input from the glycolytic cycle into this. There are many of these goes into other biochemical pathways. So, Krebs cycle is a very fundamental biochemical pathway which is a very top-level pathway which provides a lot of chemicals to several other biochemical pathways necessary for several other compounds within that.

There are diseases which affect select parts of this, but in general if there is a very core problem with the Krebs cycle, the person ceases to exist or would not be born to begin with. So, that is the importance. So, we will just revise what is happening over here in terms of the ATP and NADH and NADP. So, NAD is here NADH is here carbon dioxide is produced here.

So, water is an output water is also taken back here. NADH is generated here isocitrate, alpha keto glutarate, NADH is generated here. Now, NADH goes into the electron transport system that is what I have shown earlier. So, this is how it is. So, citrate isocitrate is here, isocyanate, isocitrate, alpha keto glutarate, NADH form succinate, fumarate, another NADH is generated over here right.

So, there are 3 NADH molecules which go into the subsequent cycle. NADH is transported into; all this is in the cytoplasm and this is oxygen dependent, lot of oxygen molecules around. So, we will go to the next stage.

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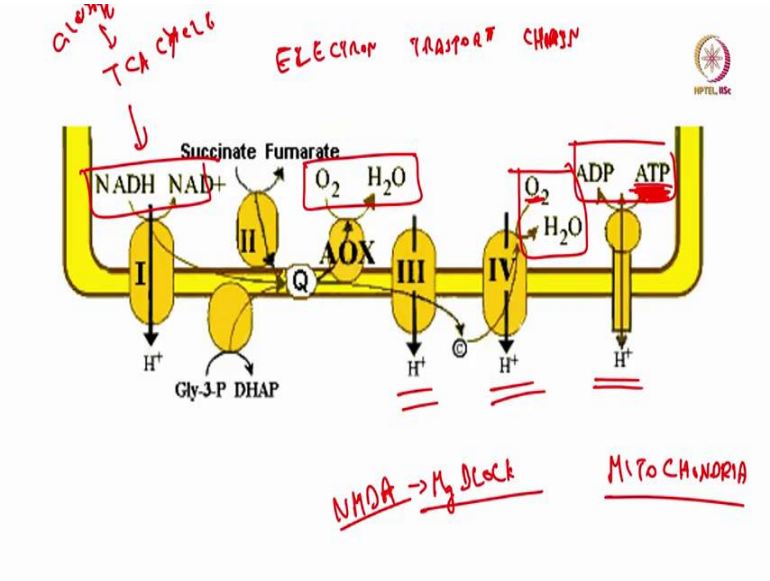

So, this is the electron transport chain. This happens in the mitochondria. So, the key things which you have to look at here is the oxygen to water. NADH which is coming from the TCA cycle. So, from the TCA cycle, citric acid cycle, NADH comes which enters into the mitochondria and the systems are very interesting.

But very difficult to remember the individual components because they do not have a very logical framework, you need to really remember those names to understand how transfers are happening from one point another. It is very difficult to understand as such. But for the purpose of this class what I am trying to highlight is I do not want people to mug up the citric acid cycle and glycolysis, it is easier to have been have done MBBS or one of the bio stuffs and be sitting rather than sit through my class.

So, the idea is to have an understanding of the background stuff. So, this background stuff. So, when glucose is used, glycolysis and that produces ATP which is taken up for currency as in the cell. The citric acid cycle produces NADH which enters into this and then produces the output in terms of ATP.

So, ATP is the ultimate factor, there is oxygen which is consumed, the glucose is consumed from here. So, glucose through the TCA cycle produces a NADH it also produces succinate over here and that in turn that in turn produces the ATP.

Please do note that. As I was saying, that there are other ions in play. So, protons are important, and these are places where they are they do not actually help in the membrane part of the story in terms of action potential transmission or anything. So, there more prominent are sodium, potassium, calcium and magnesium.

In fact, I have not spoken about the NMDA receptors. So, NMDA receptors contain something called as a magnesium block we would be discussing that later during learning when I discuss the topic. So, this is the mechanism by which energy is generated in terms of ATP.

So, through glycolysis it goes to the Krebs cycle and from the Krebs cycle it goes into form ATP. It consumes glucose, it consumes oxygen. The processes are at various parts of the cell and requires a lot of a transfer of material from the from glucose which has to be taken from outside the cell into the cell through the blood.

And it is consumed and the carbon dioxide which is there has to diffuse black into the blood where it is thrown out through the lungs and the hydrogen ions which are maintained strictly within the mitochondria and in the surrounding, they have their own pump systems to ensure that PH does not change the concentration of protons is maintained. And in the end, we have these functions which are implemented. Now, let us look at a little more detail in some other things.

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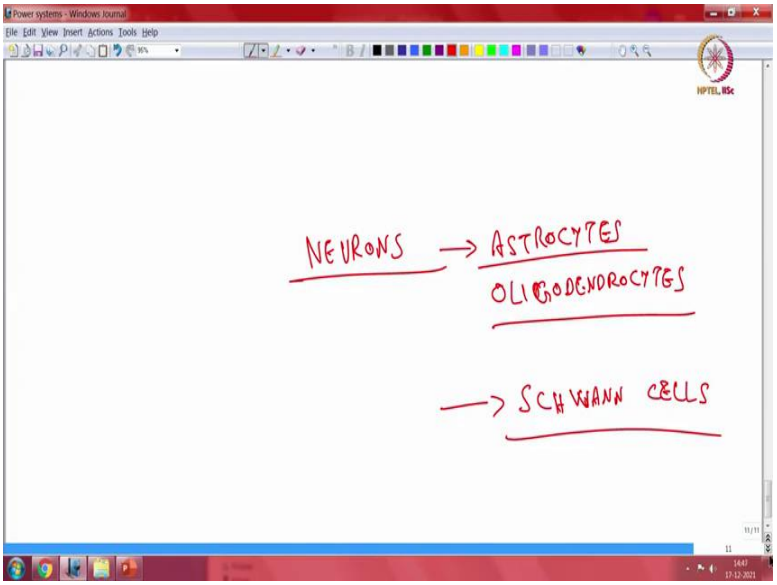

So, long time back I had told you that neurons do not function in isolation. So, neurons are surrounded by astrocytes. Then oligodendrocytes, in the peripheral nervous system you also got the schwann cells. So, there are various supporting cells and these cells as I told you they just do not function as you know they do not function as barricades, or you know they are just not around they have a lot of important functions to be taken care of and the functions include mopping operations.

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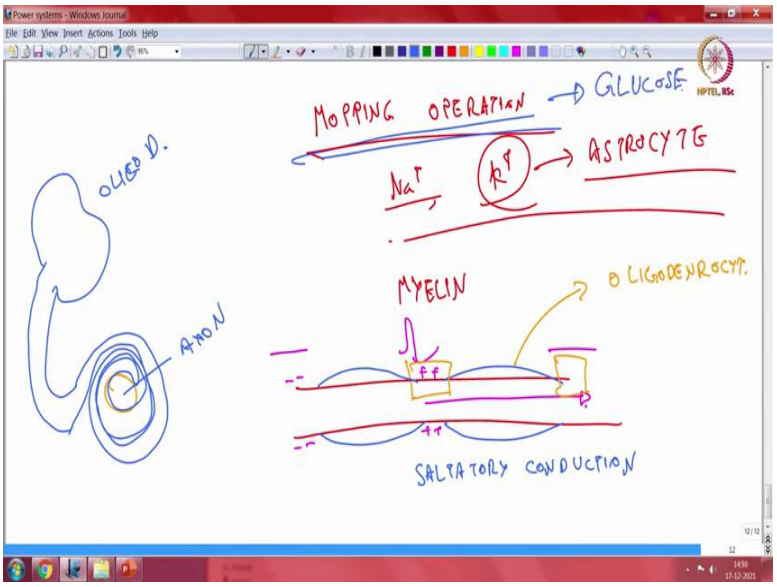

So, in spite of you know the strict regulation by the pump by the gradients and things like that you still can have excesses of sodium and more commonly potassium. So, potassium is apparently something which is very difficult to regulate and that is controlled by this astrocyte metabolism.

So, astrocytes sweep up excess potassium within the local environment of the cell so as to provide optimal functioning environment for the neuronal cell to function. So, that is one of the things. Now the other place where they perform is the generation of myelin.

So, I have told you that axons are covered by myelin and that is how I explain the phenomenon of saltatory conduction. Saltatory conduction is that you have local changes happening in a very small place where there is a signal and there are signals which are there and then the signal is transmitted from one node of ranvier. So, this is a node of ranvier to another node of ranvier. So, that helps in faster transmission of ionic current across larger spans of the cell body.

Now, myelin in turn is generated by the oligodendrocyte which actually curves. So, you have the axon in the center and the myelin producing cell produces a double layer of this one to the axon; sorry to the dendrocyte. Oligo D and this is the axon. So, they wrap.

Now, these are functions, and these cells though may not be generating action potential, though may not be actually participating in signal processing they are fundamentally responsible for the correct functioning of the nervous system. As such they are an integral part of the system.

The reason why I am telling that is, mopping operation does not happen in sync with the action potential. So, it is out of sync, it is out of phase of with respect to the neuronal function, but the mopping potential consumes glucose. So, you have glucose uptake not only related to the function, but also out of phase and happening due to the astrocytes.

And generally, these actions are what are captured through FMRI images and PET images and things like that. That is positron emission tomography in which you label the glucose and send it across. So, I think I should specify that. So, you would look at metabolic functioning through FMRI which is bold sequence versus fast acquisition.

So, these are fast MRI acquisitions and are dependent on oxygen utilization. So, oxygen utilization is not a direct reflection of neuronal. So, it is basically the energy consumption. So, it infers that the neuron in question I am using it in singular terms neuron in question has high function high rate of function which is one of the functions is generation of action potentials. So, it is not a direct measure.

So, unlike electrical activity when you measure bold FMRI, you are looking at the reflection of neuronal cell activity and which is reflected in oxygen consumption locally. So, you can actually determine how much flow is happening in small areas of the brain and that is what is captured to FMRI.

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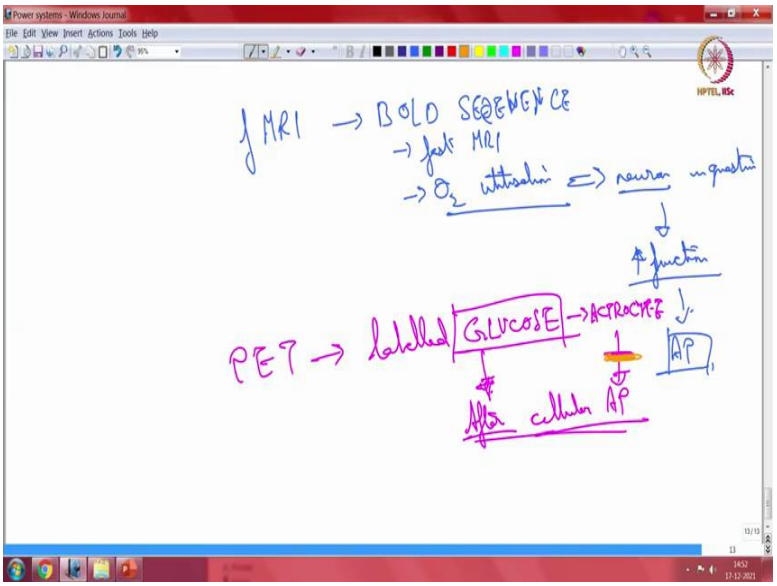

Now, if you look at PET. Looking at labeled glucose and again labeled glucose is basically looking at an after activity. So, after cellular action potential. So, it is after this action potentials are generated what happens in terms of recovery and is when maximum glucose gets consumed, and it also is reflection reflective of astrocyte activity which is not connected to action potential.

So, those are the things which you need to know. So, when we say that we are looking at FMRI images and at PET images; we service electrical investigation in terms of EG, cog, depth any kind of electrodes, the fundamental differences are these.

So, electrical is the true activity of the neuron also of the astrocyte; because astrocytes also have membrane potentials and because of this potassium stuff they do change, but they do not change like an action potential. The potential changes are more gradual and more spread out in time.

So, when you look at electrical activities you look at large part of the electrical activities contributed by direct neuronal function. Whereas, when we look at FMRI or PET imaging we are looking at looking at trace of activity. Trace in the sense that there is increased energy consumption, there is increased energy consumption as reflected in oxygen or glucose consumption and that in turn is reflected by the imaging modality.

So, you are looking at small phase differences between action versus energy consumption and that was actually the purpose of highlighting the glycolysis pathway, the TCA pathway, the electron transport chain and all that. So, they are all intricately connected. So, what is necessary is for people who work with this kind of imaging to have an idea that these are the mechanisms which are underlying the processes.

And when you find some signal which are not able to you know correlate. Say suppose you are saying that you have some issue with your EG signal and your bold, you should not look at it in the same frame both of them have different principles of signal acquisition. Bold in terms of oxygen consumption and EG in terms of electrical activity or glucose activity in terms of PET.

So, what aspect of neuronal function which you are looking are completely different. They have phase relationships to the original signal and that is something which I think you need to remember when you are analyzing especially cross modality data you know EG versus bold versus this one.

Because when you get very good quality signals these discrepancies become obvious, they do not make any difference when you have very broad areas being evaluated either with any of these modalities. But as you go finer and finer your signal acquisition techniques are more refined, your SNRs are better, these things become prominent.

Because there are bound to be differences between each of these methods of investigation and remember these are functional investigations. When we are looking at structural investigations like imaging techniques to functional imaging, there is a lot of difference again. As I told you one of the important things is it is fast you know you need to have a very high signal acquisition rate to ensure that at least match the output of the brain in some fashion.

So, electrical signals of course, you have, but still there are issues in bandwidth and spatial resolution. Bold has it is own problems and I think there have been controversies on the statistical methodology used in bold, but of course, it is very difficult to get the data true.

Because you need to have somebody in a scanner during some activity to be happening and it is not a very easy thing to do. So, roles of these investigative modalities are

evolved in various fashions due to several constraints EEG is easy to acquire that is difficult to acquire bold is somewhat halfway, but you know each of it has it is own constraints benefits each provide different kinds of data.

You should look at it more like complementary data no single data stream is a true reflection of the cellular activity, they all give an insight into cellular activity or functional activity and it is our job or a machine algorithms job to look at the true nature of the function and interpret correctly from that ok.

Thank you.