Animal Physiology
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Lecture - 15

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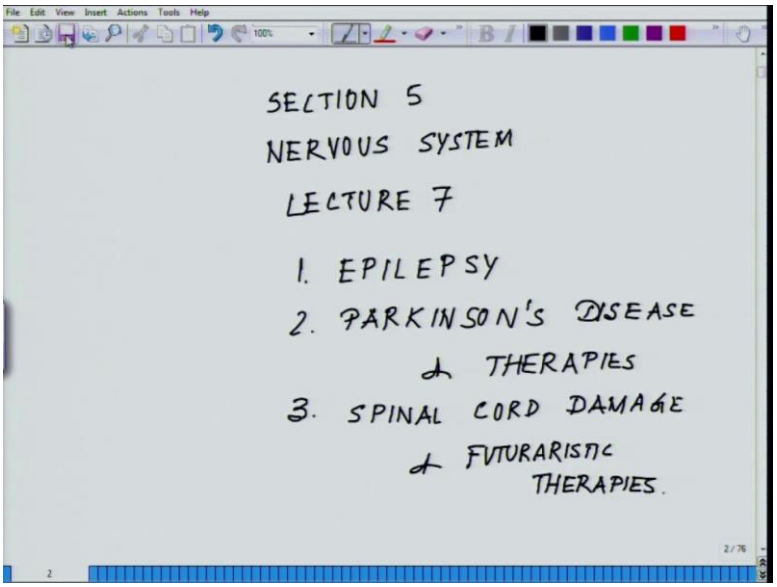

Welcome back to the lectures on animal physiology in the NPTEL. We are in section 5 in the nervous system. Today is the lecture seventh. As of now in a nervous system, if I just have to have a recap, we have started with the structure of neurons. We have talked about the supporting cells, the glial cells, and structure and function. We talked about myelination. And then we talked about the overall architecture of the nervous system, a central nervous system, peripheral nervous system.

Then we talked about the reflex circuits, talked about the higher brain functions like memory and learning. We talked about the two learning models, long term potentiation, long term depression, one of which is based on hebbian learning model, and then regarding alzheimers disease and dementia. Today, what we will start is we will talk about few other diseases of the central nervous system, which has helped us to learn a whole lot about the way the nervous system functions.

It is very interesting that most of these informations, what has been gathered in last 100 years are mostly have evolved from clinical 1940s, when this part of the hippocampus

was removed from the epilepsy patient, that leads to the loss of memory like this person never acquired any further memory. That set the tone to understand hippocampus and the energy storage mechanisms followed in the hippocampus for next almost now 70 years. It is still continuing and it is continuing at the molecular level with an enormous understanding and intense applications of electrophysiological techniques into it.

Whereas, that was the beginning of long term potentiation which was in 1970s. Followed by 1970 to 1980s, when the long term depression model, it was given by Masao Ito. And afterward people like Teres Sigonski in Sok institute and few are the people, who have done significant of work. In India, in national center of biological sciences, professor Sumintro Chaterji, he is doing a lot of work (( )) and some really ground breaking works have been done all over the world to understand, how our emotional memories are being stored and are being carried forward. In that process, while explaining the long term depression, we highlighted the fact that there are neurons whose threshold to respond, reduces because of long term depression. Just as opposite to the long term potentiation phenomena whose threshold increases. Here, the neurons thresholds decreases, because most likely, it has a different kind of neurotransmitters profile, and on its membrane, the channels densities may be, totally different, as compared to the neurons in the other regions of the brain. With this, let us talk about one or few of the diseases. We will be talking briefly about epilepsy, again, relevant to hippocampus. We will talk about Parkinson's disease and therapies.

Then, we will be talking about spinal cord damage and futuristic therapies. These are the aspects what we will be dealing in these three topics. We will try to do in this lecture or in subsequent lecture. We will wind up these all or at least, my objective is that you people should be aware about the state of art across the world, where we are. That will help you go through any kind of research papers or the findings, and should be able to see that how far we are progressed.

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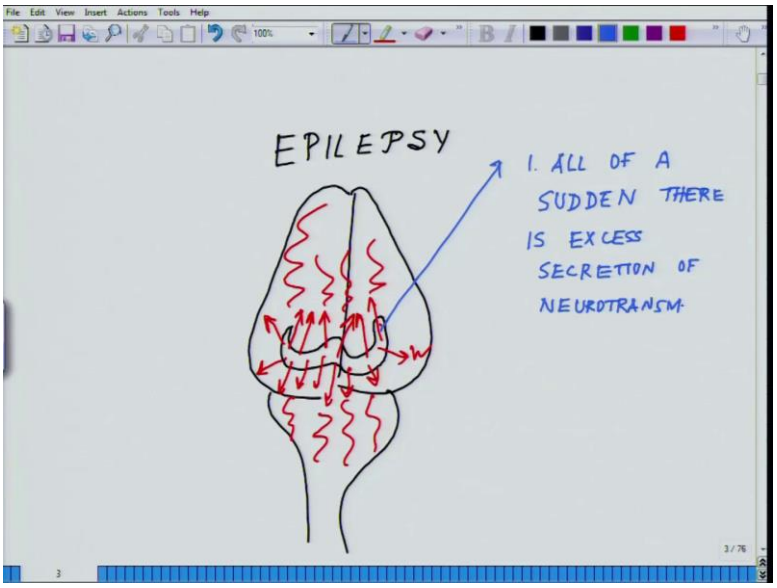

Coming to epilepsy, the first one deal with, what really is epilepsy? In the last class I explained you, that epileptic patients, all of a sudden gets about, is kind of when the first symptom, I do not know how many of you have seen an epileptic patient, like, they are like this, likewise. Then faint down like, the whole body starts shivering and then they fell down. You will see sometime, from their mouth, some kind of saliva started coming, they are not aware. Just after sometime, they are all fine; they just got up; they feel very tired, but then they have no idea; what happened few minutes back. Because, that part of the event, at that time T is totally washed out. They have no idea. How that happens? It is something all of a sudden; think of crossing on a road.

All of a sudden, the vehicles start coming from all sides and they colloid. There is a huge bang and then everything becomes quite. Obviously, you remove the debris and again, the traffic starts moving. So, there is something very similar to that, what happens in epilepsy. There is a hyper activity in the hippocampal region of the brain. It is something like this. If this is the structure of the brain and here, you have the hippocampal region. All of a sudden, there is an uncontrolled hyper activity here. So, what happens immediately, is due to this hyper activity, sudden hyper activity, the impulses are being transmitted all over the place; all the connected circuits.

As I have told you, all the circuits are connected. All of a sudden, all the coordination of the body is lost; you just have no proper signal as if, there is a collision on a four way

crossing. That collision could be because of; what are the possible processes out here? It could be because of all of a sudden, if you break out the problem at the cellular level, all of a sudden, there is excess secretion of neurotransmitter, sorry for the glitch, there are some errors in the system.

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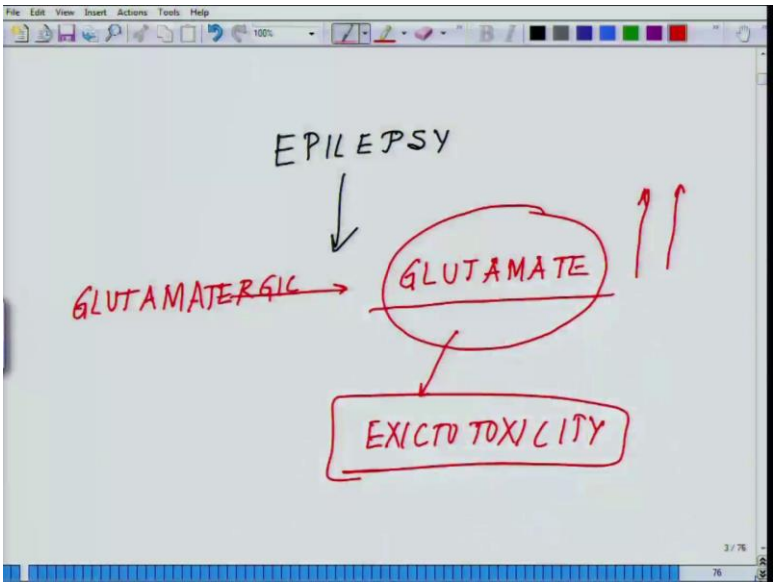

So, there may be excess secretion of neurotransmitters and control secretion of neurotransmitters. Most of these neurotransmitters, which involve or which are believed to be involved, are glutamate, as I have already mentioned that.

This is basically, most of the hippocampal region are consisting of glutometalogic neuron. This glutometalogic neuron, all of a sudden secretes a lot of glutomate. The problem with glutomate is that; gluomate may lead to exictotoxicity. This is another problem with glutamate, because it has to be removed from it. There is a baseline after which, a body or a brain can tolerate, but beyond that it becomes stuck. That leads to further complications. So, one of them may be, glutomate or some way or the other, there is another aspect to it.

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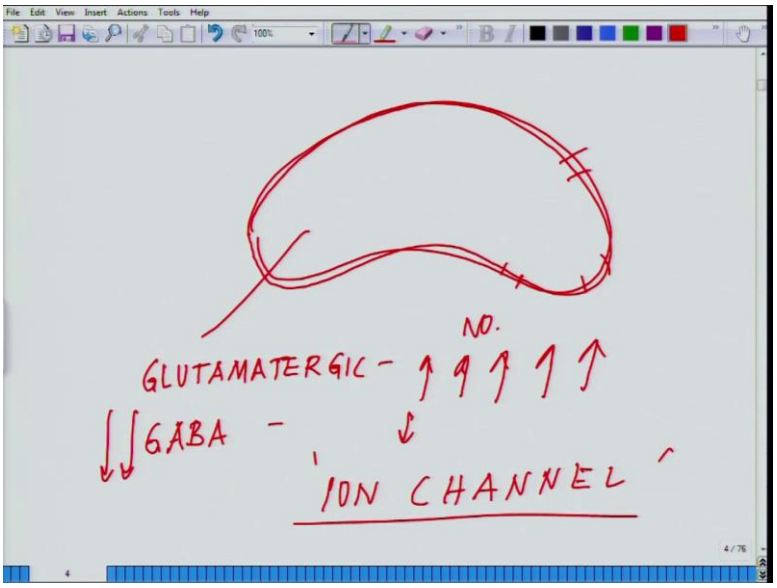

While talking about the hippocampal region, I told you that within the hippocampal region, you have glutometargic, gabargic; gaba secreting neuron, glutometric secreting neuron. There is a balance between the numbers. There is a proportion in numbers. So, maybe, there are brains which have developmental issues, or developing in different ways; there, number of the gaba may be much lesser. So, gaba which is an innovator in neuron, which allows some of the chloride and all these kind of ions, to move through, that may be less. That may lead to hyper activity and excess activity of the glutometargic neurons. So, whatsoever be the situation, it must have to deal with the neurotransmitters and the ion channels or there may be, some mutated ion channels, which are formed; the one which are conducting all, may be, an ion channel problem.

At the level, if you look at it from very simple chemistry perspective or biochemical perspective, it will boil down to either, neurotransmitters or ion channels. Now, if you go with the reference to the first chapter or the second chapter, what we covered in the membrane physiology, they are all membrane related phenomena. That is why, there is intense amount of funds across the world, in the best of the best places like, National institute of health or in UK, there is enormous grant which are given to understand the membrane channels; structure and functions. Because, these membrane channels are the ones which ensures, what is entering inside this cell and what is going out, and that is the hot target for all the drugs, to bind and carry out all the downstream functioning or

executing their pharmacologic effect. With this brief idea about epilepsy, we will move on to the next pathological condition, which is Parkinson's disease and its therapies.

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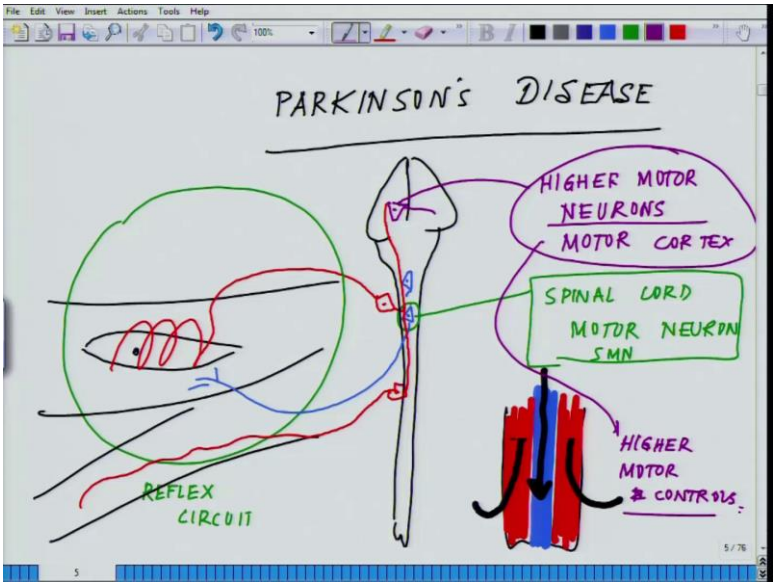

Parkinson's disease and its therapies; what exactly is Parkinson's disease? In order to understand Parkinson's disease, we have to rebuild the circuit. But, before we build the circuit, let me tell you the problems of Parkinson's patient faces. Parkinson's patients cannot move his or her, the motor controls are compromised. In other words, they cannot move their hands or their legs or several other parts of the body; do not move. What exactly that means? Whenever, we see a patient of Parkinson's, now if you recollect the circuit of neuromuscular junction, what is happening? There is a sensory muscle which goes all the way to this spinal cord, and from there, part of this goes to the brain. From the brain, if it is not a reflex circuit, of course, there are two options; either, it is a reflex circuit, it goes to the spinal cord and from spinal cord, it comes back.

Just for a recap. This is the brain and this is the spinal cord. This is the target tissue and these are the sensory neurons. These are going to body out here, and if it is a reflex circuit, then these motor neurons, which are sitting on the spinal cord, they come back and tell you. So, this is the classic reflect circuit, what we have already talked about. Now, there is a second circuit, which needs higher motor controls. The motor neurons can be divided into two parts; one which I have already mentioned here. These are called spinal cord motor neurons. Their cell bodies are sitting on the spinal cord.

Their process is to go out to all the target issues. These are sometime called SMN also; spinal cord motor neuron. They are all sitting, all along this ventral route. If you remember, when I talked to you, about the dorsal and the ventral route, just again for a recap. So, the centre is the ventral route out here, and on both sides, is the dorsal route, whether the sensory route or the ascending path way is being, you say, this is an ascending or the dorsal route. This is ascending, because I told you, all the informations are carried like this, to the brain on this. This is motor where, the signals are being brought back from the brain or directly from the spinal cord, like this so the ascending and descending paths.

Coming back to where I was, there are other circuits where, basically, a signal from, say for example, here a sensory signal from, let us draw another situation. This is sensory ending which is moving all the way. Here is the ganglia. From here, along the ascending path way, the signal is moving to the brain, say for example, here it reaches the motor cortex, and just for again recaptualting some of the mylination thing, these neurons which are sitting partly outside this central nervous system, are myelinated with schwann cells and the ones, which are the part of it, which is sitting inside the spinal cord, is mylinated with oligodentocites. Now, from the motor cortex, it synapses on another set of motor neurons, for example, it is on motor cortex. These neurons are called higher motor neurons. These higher motor neurons are present in the motor cortex of the brain Motor cortex is the region of the brain, which regulates the higher motor control or coordinate the higher motor control. How it does so? One second, higher motor controls.

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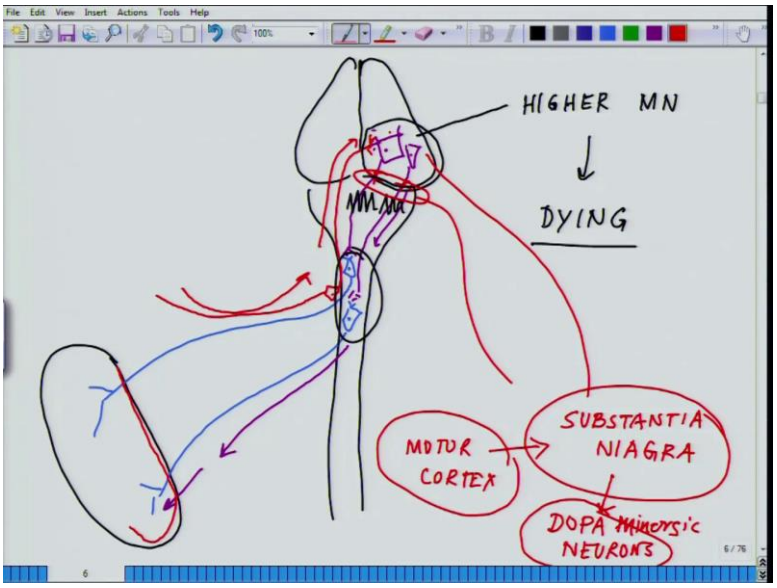

The way it works is from the brain, from the region of motor cortex, which are sitting somewhere out here; series of 1000s of motor neurons. They send the signal to the lower motor neurons. Here, in the blue, you have the lower motor neurons and ventral cord. That is where, the neurons sitting here, synapsing. These signals are then being sent to the target tissue. Here, you have the target tissue, fine. So, the way signal is moving is, here, is the sensory input going all the way to the brain; either, via inter neuron or directly, by synapsing on the higher motor neuron; the signals are being transmitted; signal moves like this all the way to the brain.

From here, the signal starts coming down, likewise. It reaches the target tissue. So, in that process, what happens? Signal reaches here. The higher motor neuron commands and this command is being executed by these neurons. Imagine a situation, when selectively, some of these higher motor neurons, which are present here, starts dying. Just putting it higher MN, they start dying. If this happens, next thing what will happen is this; the signal or the electrical impulses, which are supposed to be transmitted along this line, will be compromised; they would not be sent.

So, under that situation, option is that this person is no more receiving the higher motor inputs, and this may leave to unable for this person, to move his hand or her legs or all other body parts. This is the classic symptom of Parkinson's disease, and the series of neurons, which start dying at the motor cortex are specially, in a region of the brain

called substantia niagra. This is the region of the motor cortex, in the motor cortex, which is responsible for coordinating the motor control. The specific set of neurons which start dying are called dopaminergic neurons.

Now, if you people go back and see the classification of neurotransmitters, you will see there is a series; one class of neurons or neurotransmitters; Serotomine; Dopamine; all the amines; it is that class of neuron. There are a population of neurons whose, it is like this.

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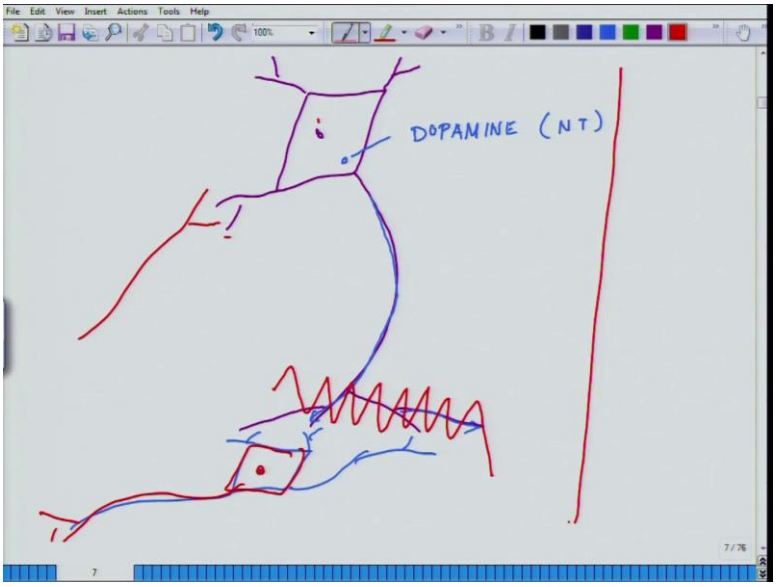

So, these higher motor neurons, on receiving input from the sensory neurons, secrets dopamine. This dopamine is synthesized here. These cells are specialized to synthesize dopamine and this dopamine acts as the neurotransmitters; NTs. These dopamines travel all along here, or make synthesized out here. These ones form synapse on the lower motor neurons out here through dopamine.

It is the dopamine, which is transmitted from here. Now, there is no more dopamine; dopamine, dopa minergic neurons are no more there. They start dying and under that situation, it is not getting any further signal. This is the classic case of Parkinson's diseases. What are the difference between a Parkinson's patient and an Alzheimer's patient?

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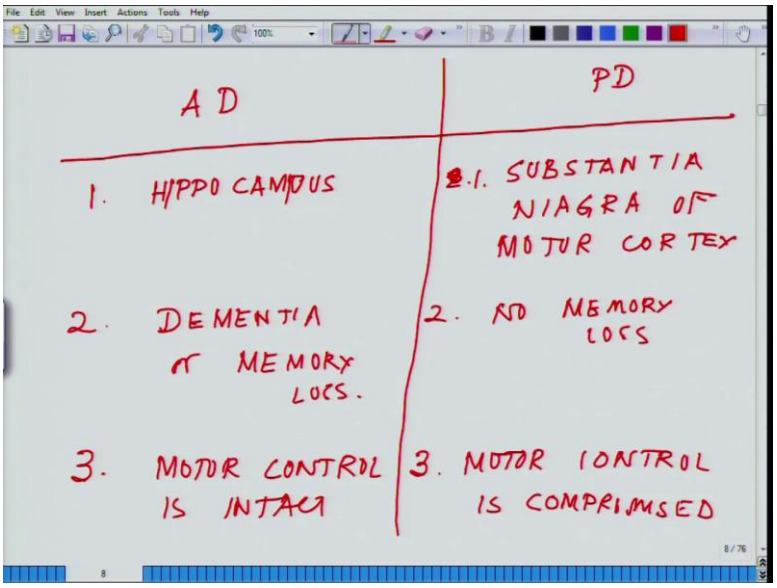

AD; Alzheimer disease and PD; Parkinson disease. In Alzheimer disease, the majorly effected region is the hippocampus, whereas, in the case of Parkinson disease, it is substantia niagra of motor cortex, first difference. The second difference is it leads to dementia or memory loss, conscious memory loss dementia or memory loss, whereas, in the case of Parkinson, no memory loss. Whereas, in the case of Alzheimer disease, motor control is intact; there is no problem in the motor control. Here, motor control is compromised. These are the very fundamental difference of these two different kinds of diseases, which happens in a brain.

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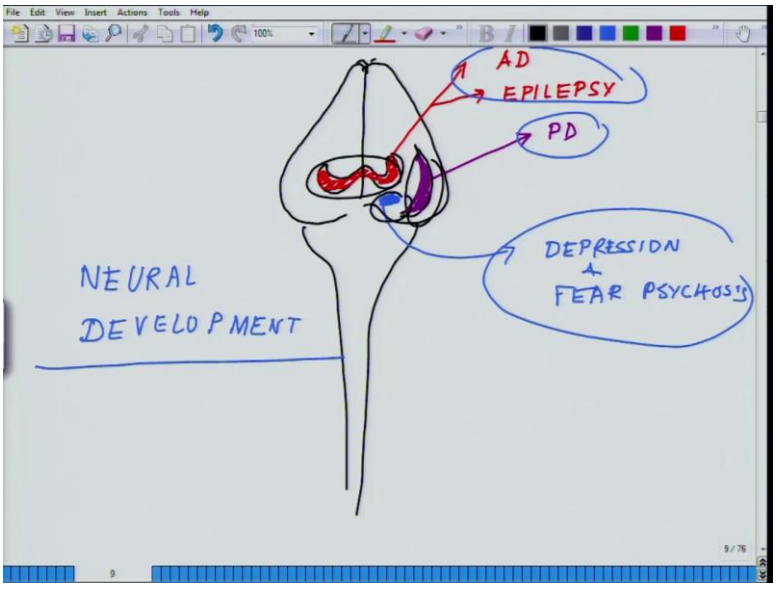

If you look at it, what I wish to highlight here, is that whenever, you think of a brain thinking, there is mass of neuron all over the face, but if you just think little bit in-depth, you think of it, a disease which is happening here. I mean, for example, this is the region of the motor cortex, which is all the substantia niagra and all other regions of the brain. Say for example, let us talk about a disease in amedilla. This is your hippocampus. So, it is the same mass of neurons, but the way they succumb to disease, is totally different. Say for example, if this one, it has two diseases we have discussed; Alzheimer disease and Epilepsy. This is a totally different kind of way it works. Talking about motor cortex, we talked about Parkinson's disease. Talking about amedilla, there are depression and fear psychosis.

So, if you look at these neurons; is there a central way, we can put them? Of course, they all have one common thing; there are all electrically active, but they have different kinds of neurotransmitter profiles; at the molecular level, at the level of their membranes, they are totally different. They are like, substantial niagra neurons; they secrete Dopamine, which is being transmitted to the lower motor neurons and then the signals are being executed. In the case of hippocampus, you have the glutometargic neuron; they secrete glutamate and this glutamate is being, helps in communicating with other neurons. We have the amegdilla; they have a lot of serotominargic neuron. They secrete Serotomine.

Basically, it is the same brain, but the fate of different neurons are totally different. What is the most fundamental question, one of very fundamental questions in neural development? How the nervous system developed, is how a neuron decides, that it will become glutometargic, that it will secrete glutamate or it will become dopametargic, it will secrete dopamine; how it decides to become collinargic, that it will secret acetyl choline; how it decides to becomes gabargic; it secrets gaba or serotony; serotonynargic. Because, this question has to be answered in the years to come. Why is it so? Because, now by this time, it is clear to you people, that all these different zones are dictated by different set of neurons.

Now, when we are ushering into the era of regenerative medicine and tissue engineering, where people are pulling out different kinds of stem cells, which has the putting shield to become any fields. For example, from the brain, you pick up a set of stem cells and you wanted to look for a therapy. How will you do? It is something like this.

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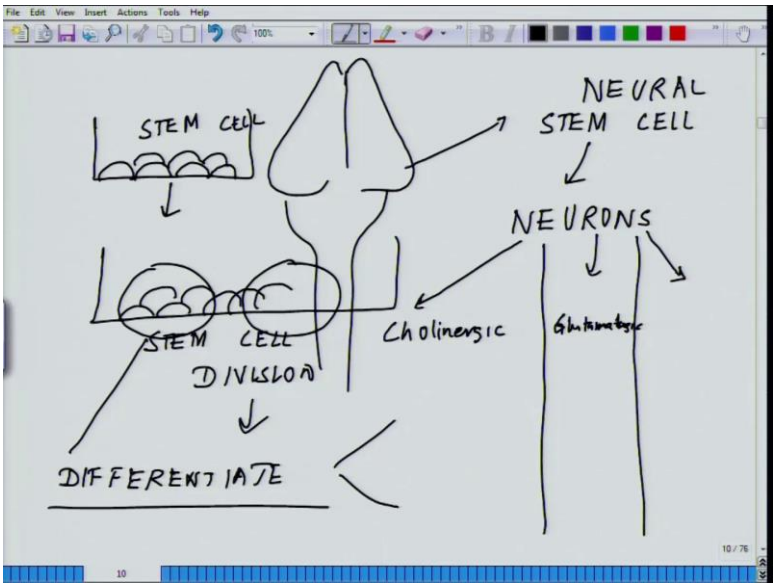

Say for example, if this is the brain and you know a part of the brain or any part of the tissue, which could be transformed into, say for example, some stem cells are coming out or let us call them as neural stem cells. So, these cells will form neurons; if they are given the proper conditions, they will form neurons.

Now, what will decide that these neurons could become; do you have a control mechanism, or do we? As human race have control mechanisms to tell; that under these conditions, these will become say, cholinergic; under these conditions, they will become say, glutametargic or under these conditions, if I grow them under this condition in a dish, what you do essentially, is that you take a stem cell population like this, then next thing, these are the stem cell population, and next thing you do, you grow these stem cells; you divide. Make these stem cells to divide; stem cell division and next thing you do. The dream therapies are like this. The next thing you do, you pull out a specific population out of it, like this. Then you differentiate them. Differentiating them means, you decide what kind of they feed, they will have; the first question is, could I make from a stem cell population, a motor neuron? Could I make a pyramidal neuron of the hippocampus? Could I make neuron of substantial niagra kind?

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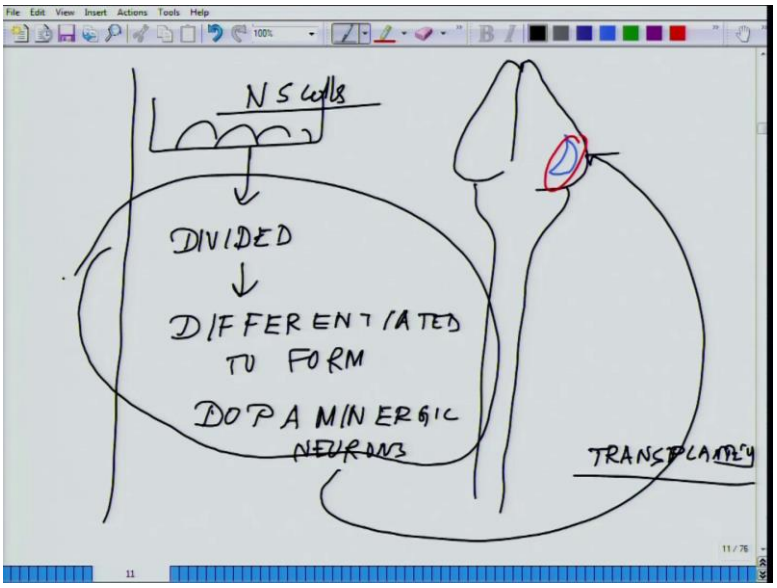

Say for example, here is a patient. In future, in a distant future, this is where our therapies will be. So, if I say for example, a person suffers from Parkinson's disease. This is the zone where, the neurons are dying. Now, what will happen? Distant future is that I know these are these kind of stem cells; neural stem cells in a cease. These neurons neural stem cells will be divided in the lab and then they will be differentiated to form dopaminergic neuron; the one which secretes dopaminergic neuron. Then these dopaminergic neurons will be transplanted back to that part of the brain, where they are dying out; transplantation.

With the hope, that these dopaminergic neuron; newly transplanted dopaminergic neuron, will form the same connectivity. So, that is another whole different ball game. This is at least, what is being dreamt of as the futuristic therapies for a mankind. If one day, and this is going to happen. So, for the generations now, the challenge lies here. We all now have well characterized stem cells from different parts of the body. These cells, it could be even skin cells.

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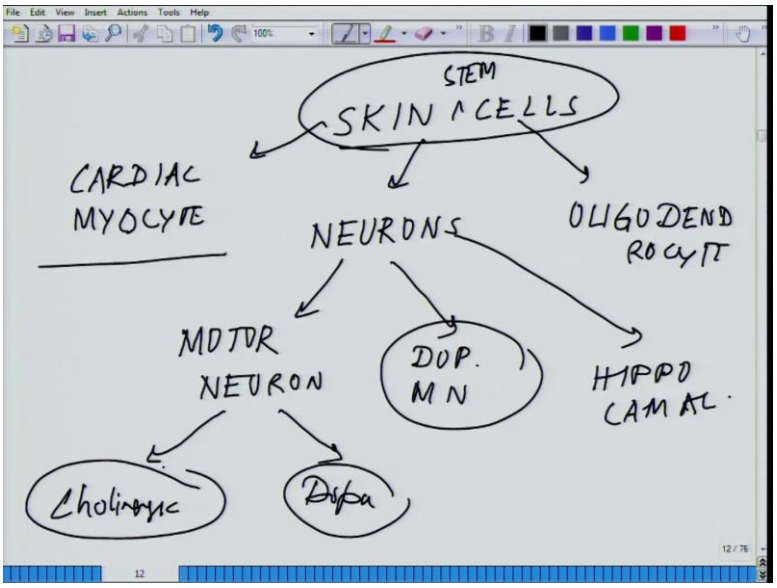

Skin cells, you know, you could have skin cells and you can make neurons from them. From skin cells you are making neurons. Now, these neurons have to be transformed into say, a motor neuron; could you do that? Or, I say I want to make from these skin cells, say, oligodendrocyte; could I make that? Or, while I am talking about, could I make, say for example, a cardiac myocytes, since we have already studied about it; cardiac myocytes. Could I make that? Because skin cells are most easily accessible; skin stem cells or may be, some skin cells or could I make say dopaminergic motor neuron? I just put dop as dopa; dopaminergic, or could I make hippocampal neuron?

Even if I could make them, could I decide that this will become cholinergic or this will become dopaminergic? So, these are the challenges for next few generations, that how far we can control the fate of a cell and then comes the next challenging part, what I was trying to highlight in the previous slide.

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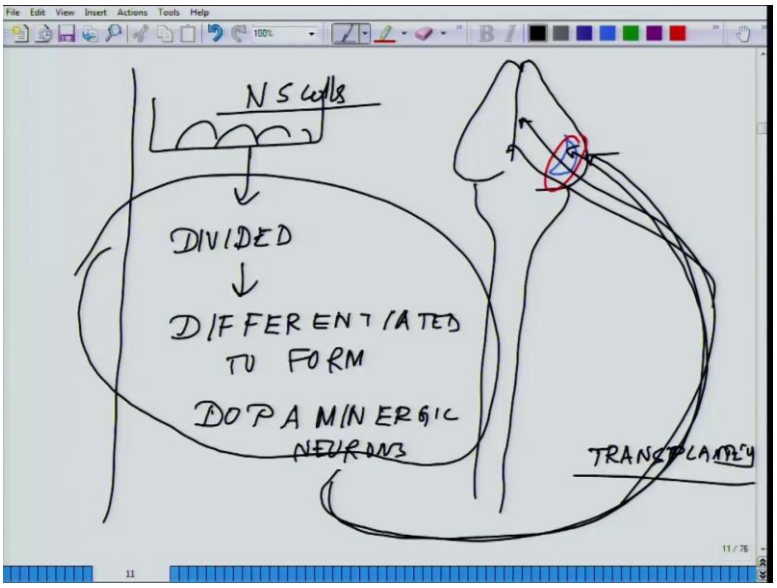

Transplanting it back to the brain or specific different parts wherever, it is needed and ensure, that they form the circuits. This will be, these kinds of experiments in future, will surely help us to look at neuroscience, from a totally different perspective. I mean next 100 years for neuroscience is going to be one of the most brilliant times, because where, all these things will be tried out, in some form. Now, already things are being tried out in small animals and rodents; all these things are being tried out. When this will come to human, is a different question. I mean, it is just the matter of time; it is going to happen; it is just the matter of time, when it is going to happen. But currently, what are the possibilities for persons, who are suffering from Parkinson's disease? For those, who are suffering from Parkinson's disease, one of the therapies is called L-Dopa; L-Dopa therapy. What is L-Dopa therapy?

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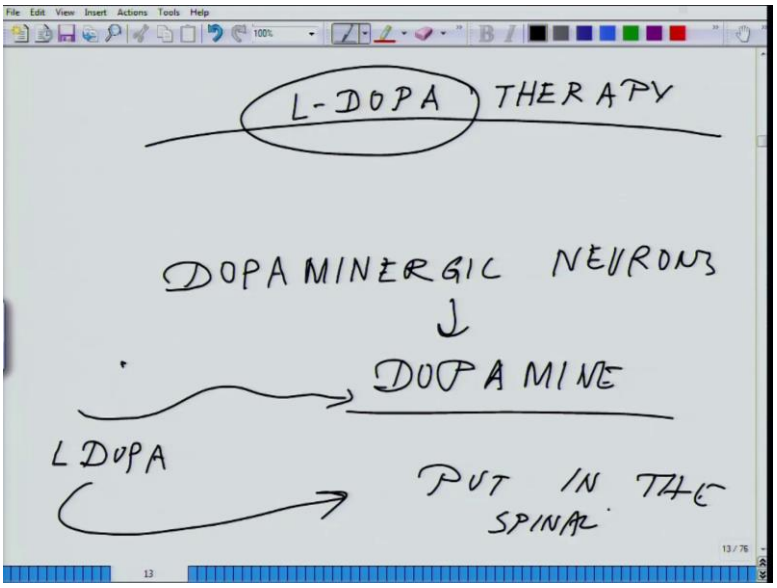

This is basically, I told you that, it is the dopaminergic neuron which are dying. Dopaminergic neuron secretes dopamine, which is the neurotransmitter. In the lab, there is an analog of dopamine, which has been synthesized called L-Dopa. L- Dopa is put in the spinal cord in a slow releasing manner. That is the L-Dopa therapy where, L-Dopa is being injected into the system. That is the only possible therapy currently existing for the Parkinson's disease patient. There is no other therapy currently successful.

While summarizing what all we have covered, we started with epilepsy. We talked about the role of excitatory neurotransmitter; glutamate, and all of a sudden, an uncontrolled activity of glutametargic neurons present in the hippocampus, which leads to hiper activity of the hippocampus and thereby, leading to temporary uncontrolled non-coordinated fate of the system; one. Second, we talked about the Parkinson's disease and in that process, we talked about death of the neurons of the higher motor neurons of substantial niagra, and their death leading to not sending signal to the lower motor neurons, which are cholinergic in nature. If you look at the neurotransmitter profile, the higher motor neurons from motor cortex substantial niagra, they are communicating with a lower motor neuron with dopamine. Whereas, the lower motor, neurons which are sitting on the ventral horn or the ventral root or the descending route of the spinal cord are communicating with their target tissue; it is acetylcholine. So, there are two different neurotransmitters, which are involved in this process, just for your interest, except in the case of drosophila, the small fly where, you have the nerve muscle connection, and most

of the nerve to muscle neurotransmitter involved is acetylcholine, except in drosophila, where it uses glutamate.

Except in drosophila, rest of all of them uses acetylcholine. So, there are two different neurotransmitters, which are regulating the whole motor control path way. Now, if one component of it is starts dying, which is the substantia niagra or the higher motor neuron, and that leads to something like, a Parkinson's disease situation, and we talked about the therapy.

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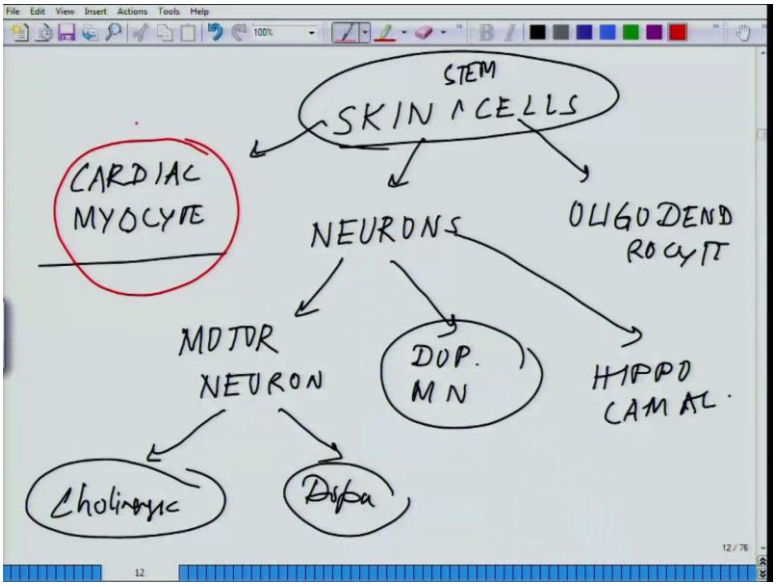

Then, we briefly talked about the regenerative medicine, where in future probably, what will happen or what we dream, that mankind dreams of happening is that, there will be neural stem cells. These will be divided and differentiated to form different kind of neuron dopaminergic; this could be cholinergic, I mean, secreting acetylcholine; it could be gabaergic, or secreting gaba; or even glutamatergic. Those could be transplanted for say, Alzheimer's patient or patients with a Parkinson's or epilepsy or anywhere, there is. Same for situations in others like, in the cardiac myocyte or cardiac damage and all these things. So, what we will do in our next class is, we will talk about another disease which is Amiotropic lateralischlorosis and spinal cord injury, because; then we will be talking about the diseases of the lower motor neurons and how they affect us.

Thanks a lot.