Neuroscience of Human Movement
Department of Multidisciplinary
Indian Institute of Technology, Madras

Lecture - 74
Parkinson's Disease – Rate Model, Pathophysiology

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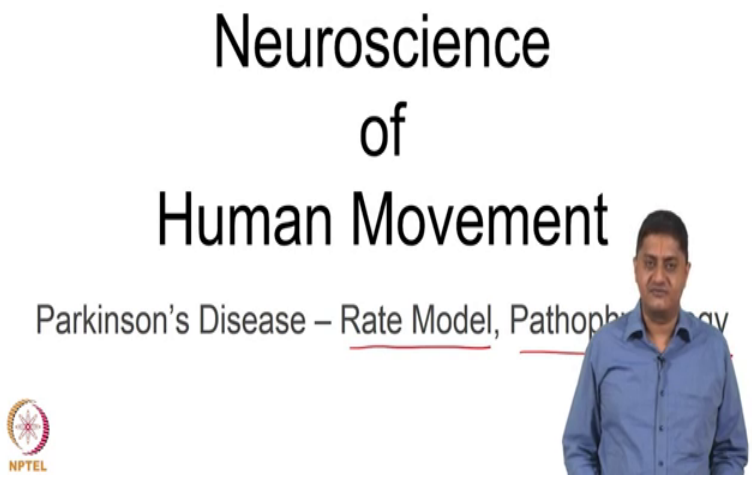

Welcome to this class on neuroscience of human movement. So, in this class we will discuss specific disorder of basal ganglia that is Parkinson's disease. One particular model of Parkinson's disease and whatever little pathophysiology of Parkinson's disease that we know about.

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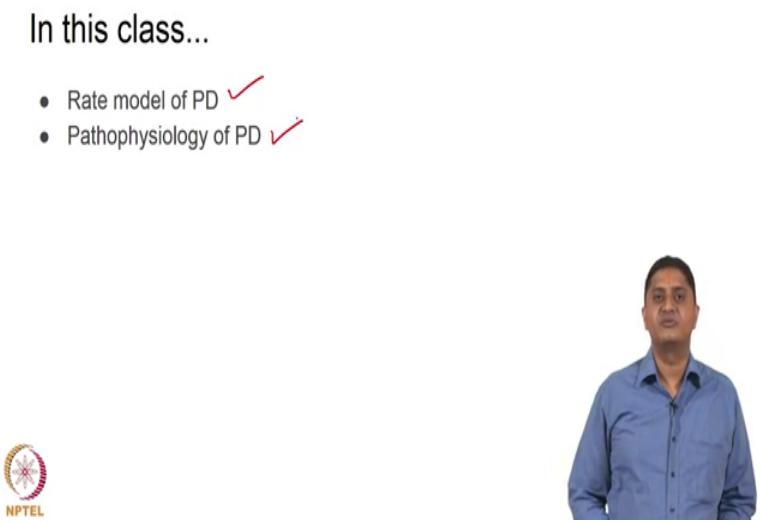

So, in this class we will discuss the rate model of Parkinson's disease and pathophysiology of Parkinson's disease.

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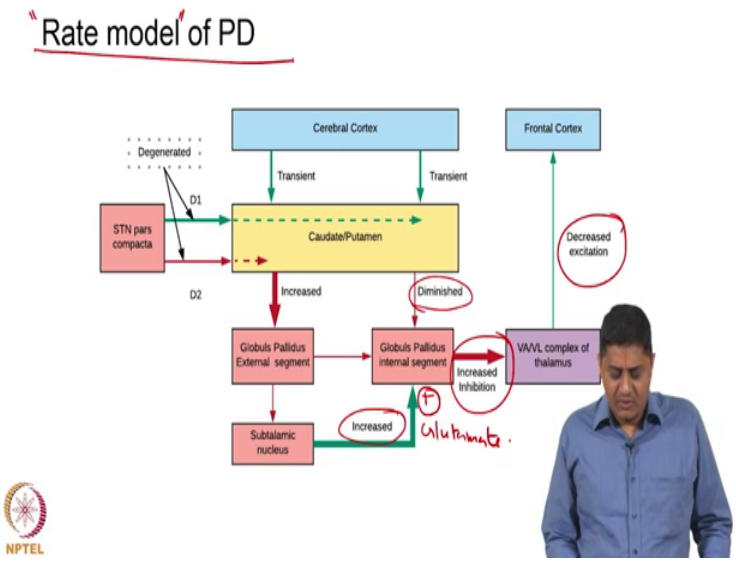

So, essentially we discussed; so, in the last class we discussed the importance of MPTP treated animals in understanding the pathophysiology of Parkinson's disease. Huge consequence of animal models in understanding Parkinson's disease have actually come from studies of MPTP treated permits right. So, what has happened in these cases is that

an artificial degeneration of the dopaminergic pathways is caused due to the effect of MPTP on and the substantia nigra pars compacta.

What was then found was that this led essentially to an increased inhibition at the thalamocortical level at the output level here, at the output level essentially what was found was an increase in inhibition ; an increase in the excitation going from the subtalamic nucleus to the GPI.

Let us remember that this is and excitatory pathway right. Let us remember that the subtalamic nucleus Globus pallidus internal pathway is excitatory right. It is neurotransmitter is glutamate, turns out that the activity of the direct pathway is diminished or reduced, because of this reason there is a net inhibition at the VA VL thalamus essential leading to a reduced amount of excitation at the cortex right. So, this was found or essentially what we mean by increased diminished reduced is the firing rate of the neurones in these circuitry right. So, the firing rate is increased not the number of neurons. So, this have then come to be called have the famous or the so called rate model of Parkinson's disease.

Fortunately, this model is able to explain the whole lot of data on patients; however, this model has it is limitations though. So, there are several cases where this model cannot explain specific pathophysiology.

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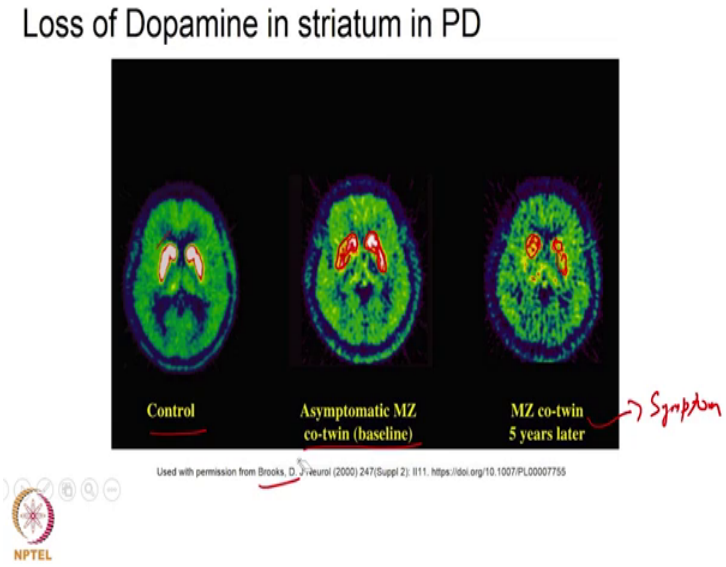

So, here is data from imaging that shows in a control subject the uptake of you know document in putamen. Whereas, in particular asymptomatic twin whose other twin is having Parkinson's disease. That is reduced uptake of dopamine and putamen. 5 years later this particular patient develop symptoms this particular patient has symptoms and you find very little you know activation of the putamen right due to this, when this is when compared with this control right.

So, essentially the control the activity is much higher. This is actually data from groups and colleagues right.

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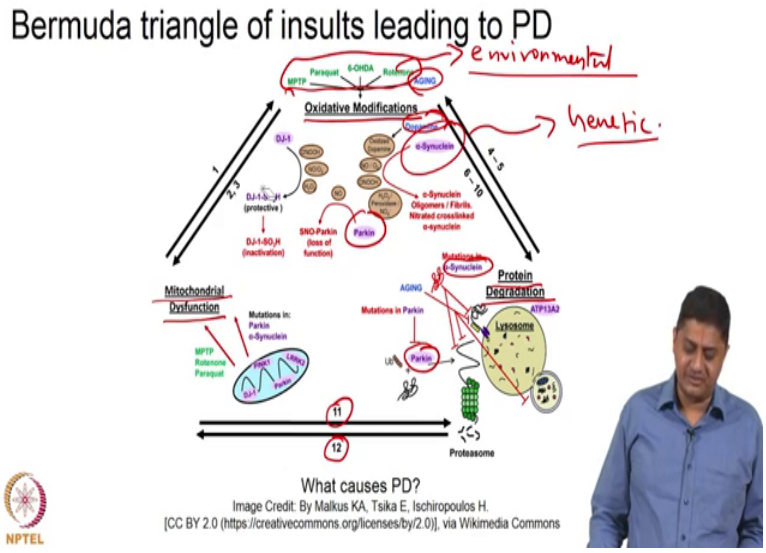

Essentially what happens in Parkinson's disease? What are the various things that happen in Parkinson's disease? Well, at least there are 3 specific reasons. One is oxidative dysfunction or oxidative modification. Second is mitochondrial dysfunction, and third is protein degradation.

So, note all these 3 are interconnected with each other. So, you see is there are specific reasons why one is connected with 2 as an oxidative modifications in mitochondrial dysfunction are connected in a 2-way street. And mitochondrial dysfunction in protein degradation, are also connected and protein degradation and oxidative modification are also connected right.

Essentially some of these causes for example, MPTP those that are in green for example, are actually environmental causes. Some of these causes such as those in purple here are actually genetic, and those that are in blue are specific to the particular organism right. Actually, what is going on is an interaction between all these separate factors leading to specific symptoms that are now diagnosed as Parkinson's disease. It is not that each particular thing causes by itself. There is an interaction between these particular causes. Together they cause the outcome which is diseases or the pathology right.

Some of these things are very well understood. Each of this refers to a specific phenomenon that has been understood right. 1 2 3 to 12 each of this is a phenomenon that has been relatively understood well understood. However, the interaction between this and what are the exact details are still remaining to be understood. So, there are still a lot of scope for improvement of our understanding of this particular disorder alright.

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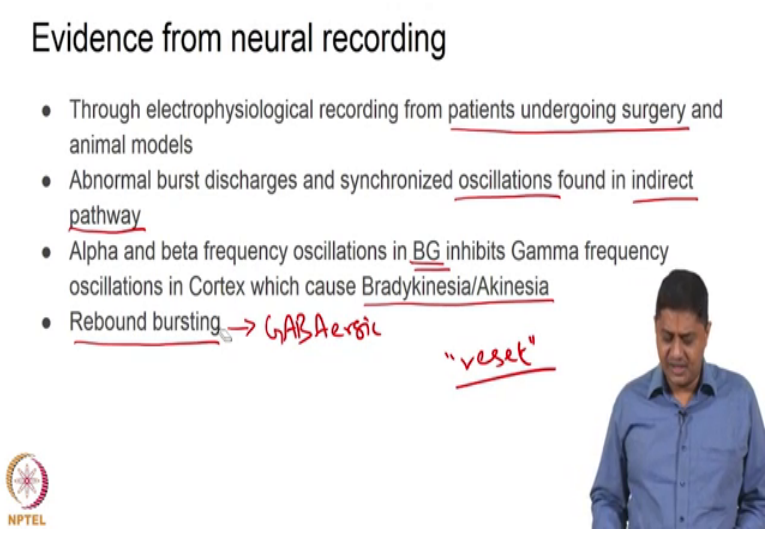

That kind of understanding usually results from recording of neurons from specific regions in the basal ganglia right, in this case. So, electrophysiology recording from patients undergoing surgery and from animal models; what has been found is that the particular cases that could not be explained by the rate model are explained by oscillations, that either synchronized or not synchronized right.

So, specific oscillations or synchronization between oscillations in different regions in the indirect pathway are believed to be at least one more source of information that could

help us understand the pathology better right. In particular alpha and beta frequency oscillations in the basal ganglia inhibits the higher gamma frequency oscillation in the cortex. So, it is this inhibition that causes bradykinesia, slowness and akinesia lack of movement. What is also believed to be true is this phenomenon of rebound bursting that is caused due to extensive GABAergic activity right. Within the basal ganglia activity especially between the input and output most of the connections are GABAergic various spiny neurons has GABAergic other interneurons are GABAergic, except the nerons from subtalamic nucleus, which is glutamatergic most other outputs are GABAergic right.

So, this interplay between GABAergic neurons somehow cause a reset a sort of a reset that probably affects the motor circuit. This phenomenon is called as a rebound bursting. I am leaving the details for you to read, but this is called as a reborn bursting.

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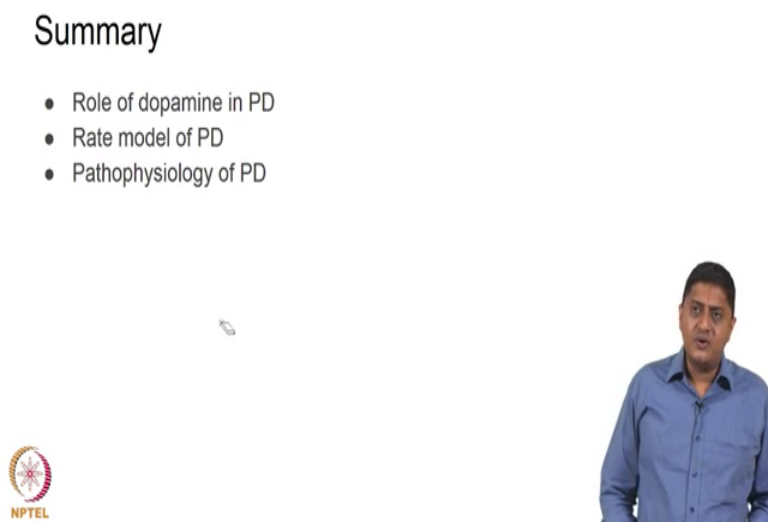

So, in summary what we have seen is the important role of dopamine in Parkinson's disease; essentially, the rate model of Parkinson's disease in the absence of dopamine what happens is that, the indirect pathway becomes more active or in the direct pathway becomes less active, essentially leading to an increased inhibition at the thalamocortical level right and the pathophysiology of Parkinson's disease right.

So, we discuss the pathophysiology, that there are at least 3 different, but interacting causes, these are oxidative modifications and mitochondrial dysfunction and protein

dysfunction. So, these 3 things interact with each other to result in the group of symptoms that is called as Parkinson's disease. A lot more remains to be understood.

So, unless and until we understand the pathophysiology clearly therapeutic approaches are difficult to develop right. So, a lot more remains to be understood the exact molecular mechanisms of many of these things are still elusive. As to why for example, alpha synuclein continuous to build right, what are the specific causes of that, what are the chain of events that lead to the build-up of this right. And all such things are continued to be mysteries. So, we need to continue to work on this to understand. So, with this we come to the end of this lecture.

Thank you very much for your attention.