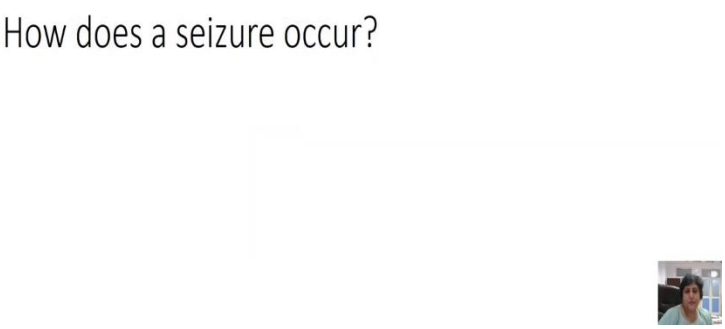
Introductory Neuroscience & Neuro-Instrumentation
Professor Latika Mohan
Professor and Head Physiology
AIIMS Rishikesh
Lecture - 53
Epilepsy: Epileptogenesis

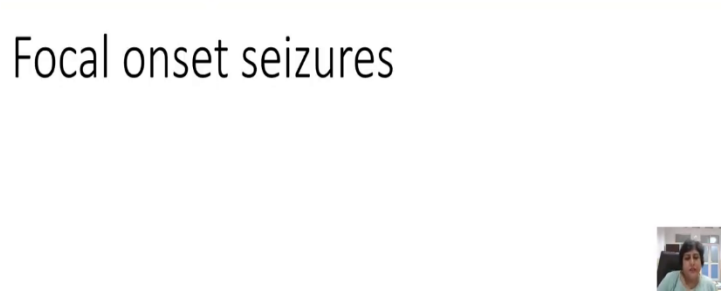
Welcome to the second lecture on Epilepsy. Today, with this lecture, I would like to focus on the process of Epileptogenesis. I am Professor Latika Mohan, Professor and Head of Physiology, AIIMS Rishikesh.

(Refer Slide Time: 00:35)



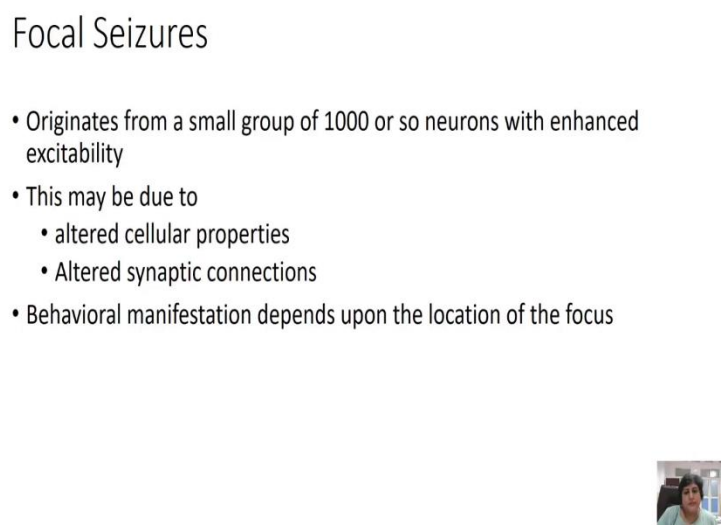
So, let us see how does a seizure occur?

(Refer Slide Time: 00:40)



We start with focal onset seizure seizures.

(Refer Slide Time: 00:43)



So focal seizures basically originate from a hyperexcitable group of neurons, a small group of neurons, maybe about 1000 or so; we cannot really predict what number but 1000 is, seems to be a reasonable number. And these neurons have enhanced excitability.

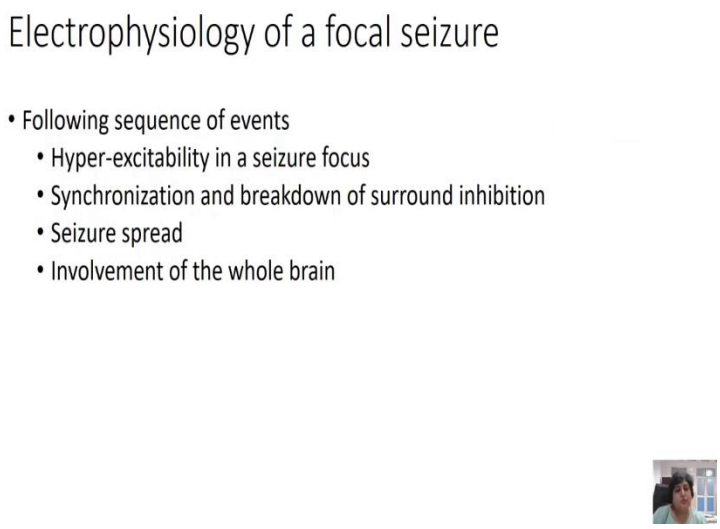
Now, this enhanced excitability may be due to certain altered cellular properties like the cell membrane channels, etc. may be more excitable, or they may be arranged in reentrant circuits,

special synaptic connections may be them, amongst these neurons. So they perpetuate their own excitability.

And where, what kind of clinical symptoms this focus is going to produce or lead to depends on where it lies. So the focus, if it is present in the frontal part of the brain, it may create thought disorders to start with.

If it is present on the occipital part of the brain which is near the center for vision, you might get the visual and hallucinations to start with; if it is in the temporal side, then maybe sounds which start with. And then, of course, the various other manifestations of epilepsy which occur.

(Refer Slide Time: 02:00)



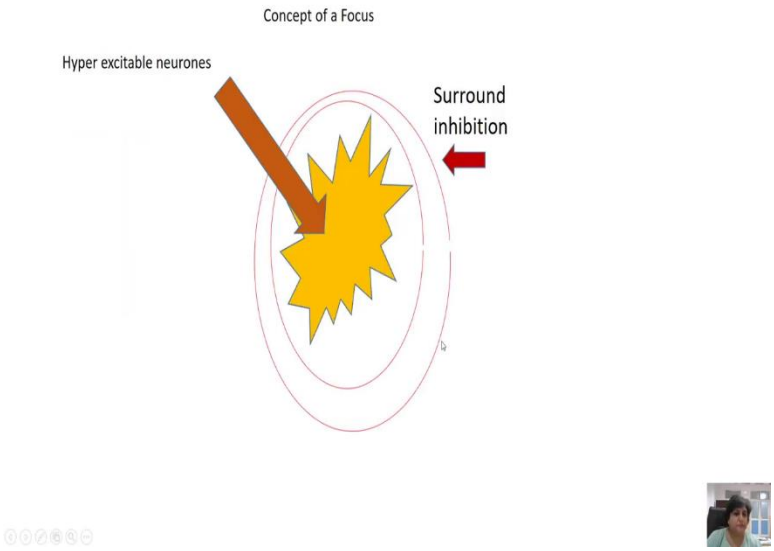
So how does a hyperexcitable focus lead to the development of a full-fledged seizure? So there is a sequence of events or a process that occurs, which is hypothesized. There is a group of neurons as I had already said, which is the hyperexcitable and it forms this focus.

Now, surrounding this, there is a surround inhibition which prevents from the focus from constantly producing epileptic seizures. So there is always a walling off or a surrounding inhibition which keeps this excitable area under control.

But there is some process which leads to the synchronization and breakdown of this surround inhibition. And that, in a kind of way, that hyperexcitability leaks out of the focal area and that causes the seizure to spread.

It moves down the normal tissue, the normal pathways, and involves the entire brain, and leads to a full-fledged seizure.

(Refer Slide Time: 03:03)

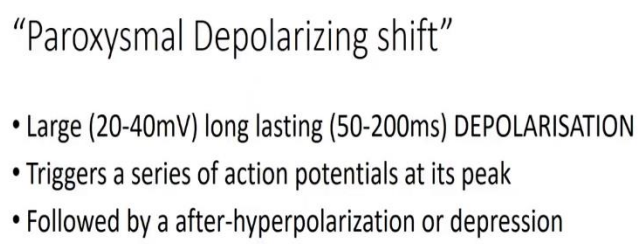


So something like this diagram, this is kind of a schematic diagram. In any area of the brain, there may be a small group of say, about 1000 neurons which are hyperexcitable because of their own properties, synaptic connections, or their channel or membrane properties.

And they get walled off by a, you know, a group of other neurons which are surrounding which may be secreting an inhibitory neurotransmitter like GABA. So the surround inhibition keeps this focus under control under normal circumstances.

But if the milieu is right, if the circumstances are right, sometimes this abnormal electrical activity tends to leak out of the surrounding inhibition and spread to the other tissues, leading to the seizure to happen.

(Refer Slide Time: 03:51)

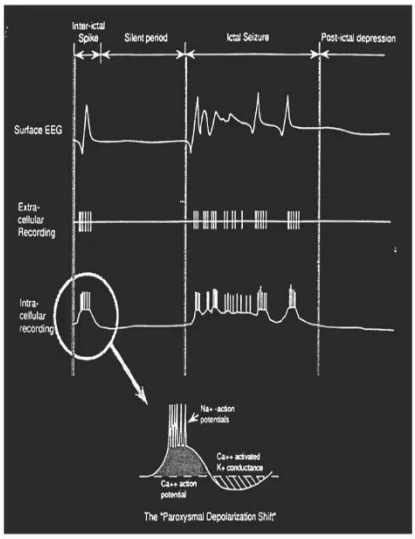


So what is this excitability or hyperexcitability that exists amongst these neurons? There is a peculiar kind of biophysics kind of electrical activity that goes on, which is a large long-lasting depolarization.

So a normal action potential is over in a couple of milliseconds, and it is about the same size otherwise. So this would be a large depolarization kind of drift of the resting membrane potential.

And at the peak of this drift of this resting membrane potential, there is a trigger of or a series of action potentials which happen. And after this action potentials are over, these hyper excite, there is after-hyperpolarization or in an increase in negativity or depression, after the episode is over.

(Refer Slide Time: 04:51)



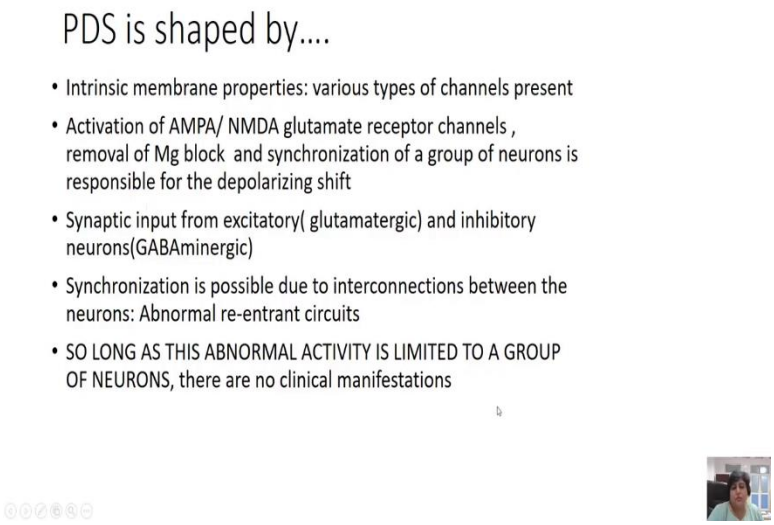
So this diagram would like would kind of explain what I have just been talking about. See, if you see the bottom of the diagram, you have this is the resting membrane potential, and it is undulating in a kind of a sin curve.

And that the peak of this depolarization, moves towards the positive side, there is a train of action potentials that occur. And this leads to eventually a calcium-activated increase potassium conductance which leads to a hyperpolarization, where there is a period where the membrane is not sensitive and is not able to give off any spike potentials.

So this particular configuration is what is seen as an intracellular recording. If you see it extra-cellularly, you would probably just pick up the action potentials. And if you see it in the surface EEG, it comes as a surface spike which is, so if a spike is seen or a sharp wave is seen in the EEG, it is basically meaning that underneath it there is some kind of activity of hyperexcitable neurons, which is going on.

Now, this may just be isolated in one area, walled off by that surrounding inhibition, or it may spread and create what is known as a seizure, where this gets into the rest of the tissues. And that is, once it gets into the rest of the tissues and spreads there is an area of kind of depression which happens makeup, which leads to the negative symptoms of the seizure.

(Refer Slide Time: 06:29)



So what basically characterizes this paroxysmal depolarizing shift? The intrinsic membrane properties, the properties of the neurons which are there in that, they have certain types of channels which are present in them, which predispose to this hyperexcitability.

Then there may be activation of certain very highly excitable, hyper-excitable receptor channels such as AMPA, NMDA, glutamate receptors, and the removal of magnesium block and synchronization of this group of neurons together.

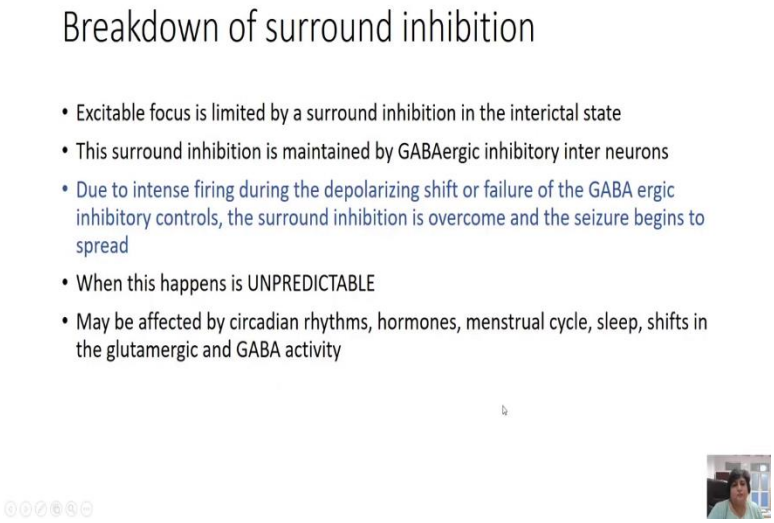
There may be increase synaptic input from various excitatory neurons which may feed into this group of neurons. And there may be the development of abnormal synaptic connections, interconnections between these neurons. So they kind of keep feeding into each other and causing more and more re-entry circuits, which hype up the excitability further.

So, so long as this kind of abnormally channeled properties of those neurons, and the interconnections, and this excitatory neurotransmitter feeding into it, it remains inside that local area only, there is no clinical manifestation.

A person may be having this all the time but he may not have any kind of abnormal symptoms. But the moment there is something that breaks downs the surrounding inhibition, which may be, you know, a change in the excitability of the entire cortex, it may be due to sleep deprivation, it may be due to increasing in temperature, it may be due to various other problems in the milieu;

interior of the body like alkalosis or acidosis or anything like that, when that is surrounding inhibition breaks down, then this increase excitability leaks through, it leaks through.

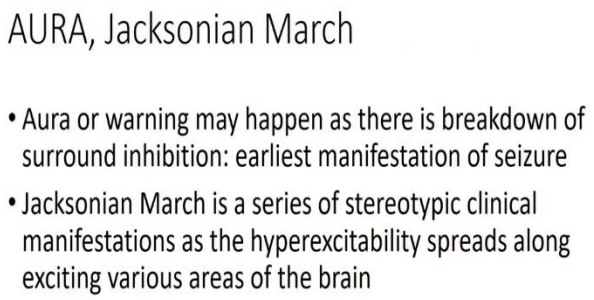
(Refer Slide Time: 08:23)



So this surround inhibition, it due to either the intense firing during depolarization shift of failure of the GABAergic inhibitory controls, when the surround inhibition is overcome, the seizure begans to, begins to spread. And when this happens, it is unpredictable.

So as I said, it is dependent upon hormones, menstrual cycle, sleep shifts in glutamatergic activity, GABA activity, the milieu interior, and so many other factors.

(Refer Slide Time: 08:57)



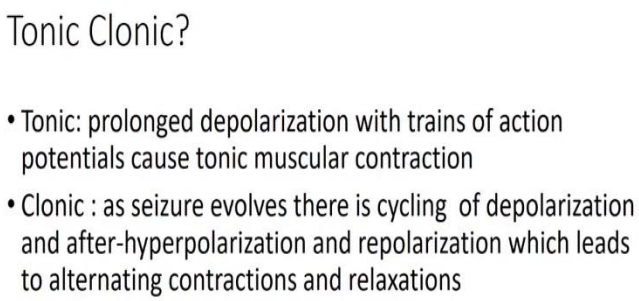
So when the surround inhibition starts to break down and the electrical activity that is hyper-active action potentials which are coming out of that focal area, when they spread, the first to be affected are the surrounding normal tissue. So there is this abnormal tissue in the middle and then there is this surrounding tissue which is normal.

So when the surrounding tissue gets excited, wherever that focus is, those kind of symptoms start to happen. So if it is in the temporal lobe, where there is a area for hearing, a person may start hearing some abnormal weird sounds and that may be heralding the beginning of the seizure.

Similarly, if it is in the visual cortex, the focus is in the visual cortex the aura may be in the form of seeing various lights and hallucinations. And generally, the seizure, if it is slow, as, with this electrical activity, abnormal is spreading in a slow fashion, they may be a series of stereotype clinical manifestations.

Just as the hand may be moving in a particular stereotype way or they may be smacking up the face facial muscles, the mouth may be opening and closing or blinking of the eyes depending on which area is getting excited, step by step, and that is what we call the Jacksonian March, and it is a typical feature of focal epilepsy.

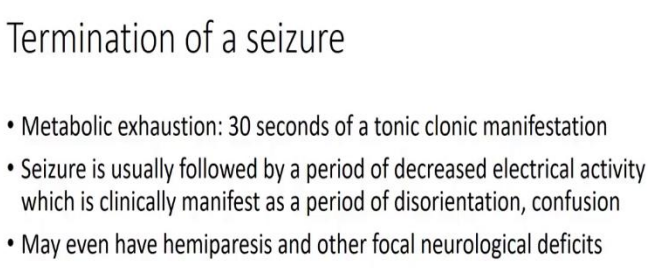
(Refer Slide Time: 10:21)



If the whole cortex gets overwhelmed, especially the motor areas, the entire musculature of the body goes into a tonic spasm. That is known as a tonic phase of the generalized seizure. So the acute muscular contraction, including the lergigan muscles also contract, it gives rise to a cry. They were also, that causes what is known as tonic phase of an epileptic fit or seizure.

And immediately after the tonic phase, everything relaxes, and then it may go into a kind of a multiple spasm and relaxation phase, which is known as the clinic, clonic phase of the seizure. And hence, we call it the tonic-clonic phase of the epileptic seizures.

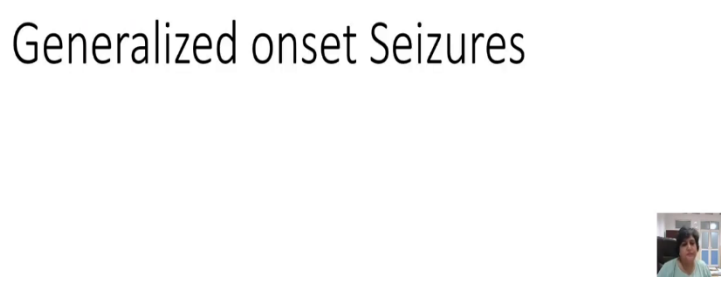
(Refer Slide Time: 11:08)



So termination of a seizure. There may be, after an intense phase of excitation like this, which may last for about 30 seconds, a complete exhaustion of all neurotransmitters takes place and there maybe, you know, there is a metabolic exhaustion of the ATP, there is everything gets exhausted in that in the brain.

And that leads to a kind of a phase or negative phase of loss of consciousness and a period of disorientation or confusion. And there may be even paralysis of one part of the body or some other you know blindness or something which resolves over a period of time. And this is known as this post-ictal, ictal meaning seizure, post-ictal confusion.

(Refer Slide Time: 12:02)



So generalized onset seizures. This is slightly different from what we just discussed about focal seizures.

(Refer Slide Time: 12:09)

Generalized seizure

- Sudden onset
- No aura
- Involve both hemispheres from the onset
- May or may not have post ictal confusion

In generalized onset seizures, there is a sudden catastrophic onset. So you do not see any aura, and there is no buildup. Generally, the cause of generalized seizures is a group of abnormal channels or which may be present towards the central portion of the brain.

So this may be located in the thalamus or some others, sub-thalamic, some subcortical nucleus. And this group of channels basically give gives the initial sort of trigger to the excitation. And so, it may involve both hemispheres from its very onset and it may not have any post (act), it is just a on-off kind of thing; post, there may not be any post-ictal confusion.

(Refer Slide Time: 12:54)

Generalized Seizures

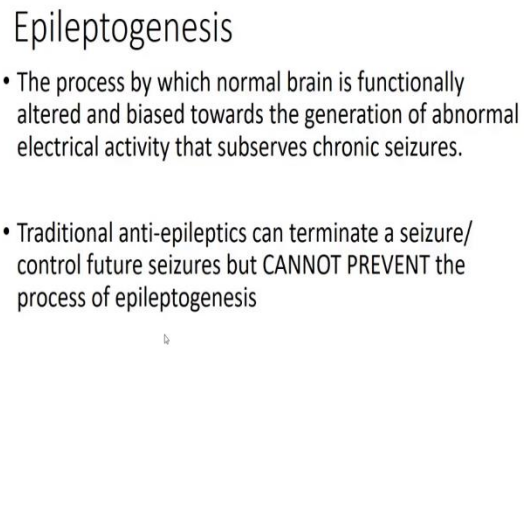
- Cortical hyperexcitability hypothesis
- Thalamic origin: centricephalic hypothesis
- Disruption of both hemispheres simultaneously
- Trigger in thalamic reticular nucleus, relay nuclei and perigeniculate nuclei
- Rapid synchronous activation of thalamocortical reciprocal loops
- Rapid spread: cortical hyperexcitability

So there are two main hypotheses. One is that whole cortex itself is hyperexcitable. So the seizure happens because of the cortical hyperexcitability for various regions, which may be related to neurotransmitters, channel properties, maybe related to the milieu of the cerebral spinal fluid and the extracellular fluid in the brain.

And the thalamic origin that means, there are certain triggering channels which are present the thalamus, which gives the initial trigger to the already hyperexcitable cortex and leads to this catastrophe bilateral sudden kind of a seizure that happens.

So both that the hemispheres are disrupted simultaneously. There is a rapid synchronous activation of all the normal pathways, and that is what leads to a generalized seizure.

(Refer Slide Time: 13:45)

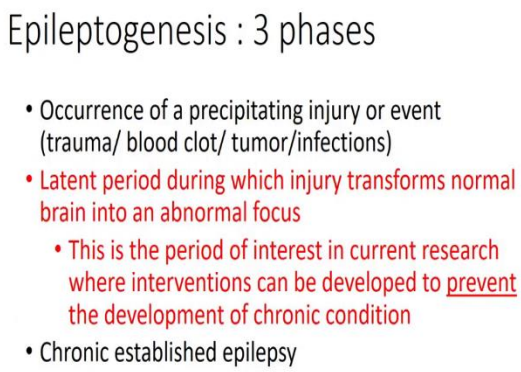


So let us try and figure out what is this epileptogenesis. Now, the process by which a normal brain is functionally altered and biased towards the generation of abnormal electrical activity, and that is what forms the basis of any chronic seizures or epilepsy.

So the traditional anti-epileptic drugs that we have got. They can terminate a seizure, or they can control future seizures and keep them, keep a person from having more seizures. But you cannot prevent the process of epileptogenesis.

That means, you are not, when you give an anti-epileptic medicines, you are not curing the patient, you are basically just keeping the epilepsy under control. And the moment that drug is stopped, again the problems will start.

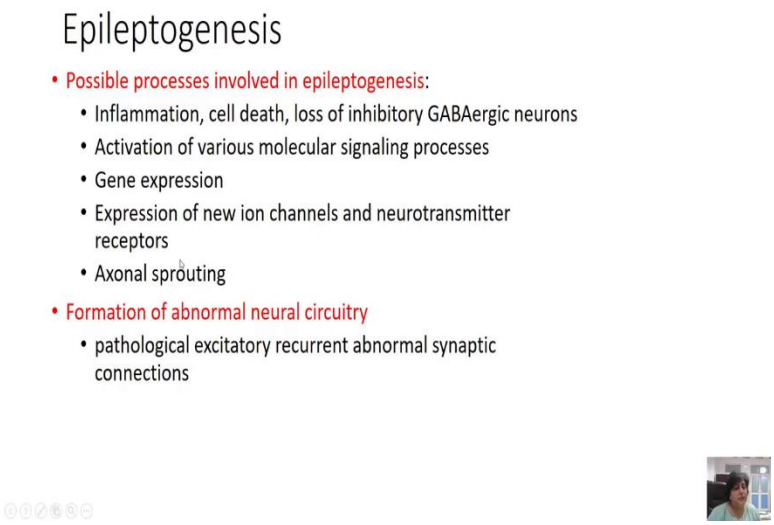
(Refer Slide Time: 14:29)



So what do you understand by epileptogenesis? It is in three phases. So there is an initial precipitating event or injury, which may damage the brain. It may be in the form of trauma, it may be a formation of a clot like in a stroke, it may be the development of a tumor or it may be an infection like cysticercosis. So these are basically the primary event which would lead to an abnormal focus from developing.

Then there is a latent period during which the injury transforms this normal tissue into an abnormal focus. And this is the period of interest of all current research where you can intervene and prevent that injured part of the brain from becoming a focus of abnormal electrical activity which would give rise to recurrent seizures. So this is where you can do something and prevent the state of epilepsy from developing at all.

(Refer Slide Time: 15:27)

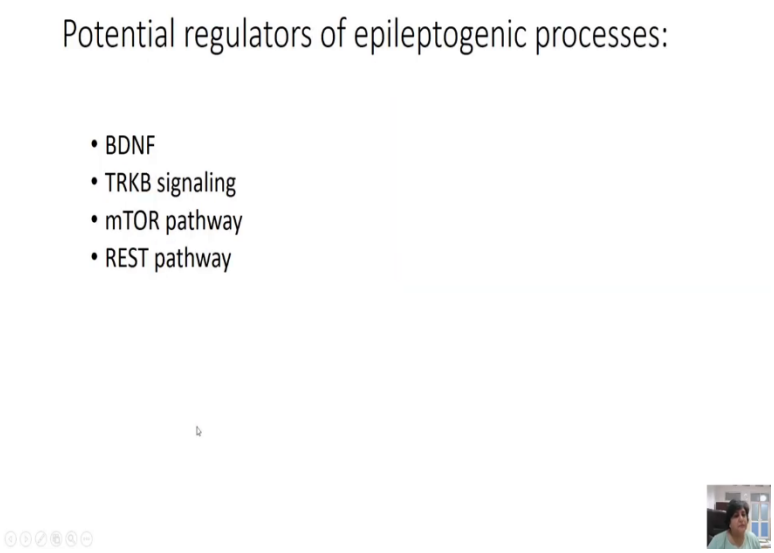


So what are the weighted processes in epileptogenesis? There is inflammation, there may be some cell death, loss of certain inhibitory neurons, and activation of certain molecular signaling processes which I will cover later.

Certain new genes may be expressed, maybe expression of certain ion channels which are more hyperexcitable, and they may be the form, this axonal sprouting that means, new connections being developed amongst the neurons.

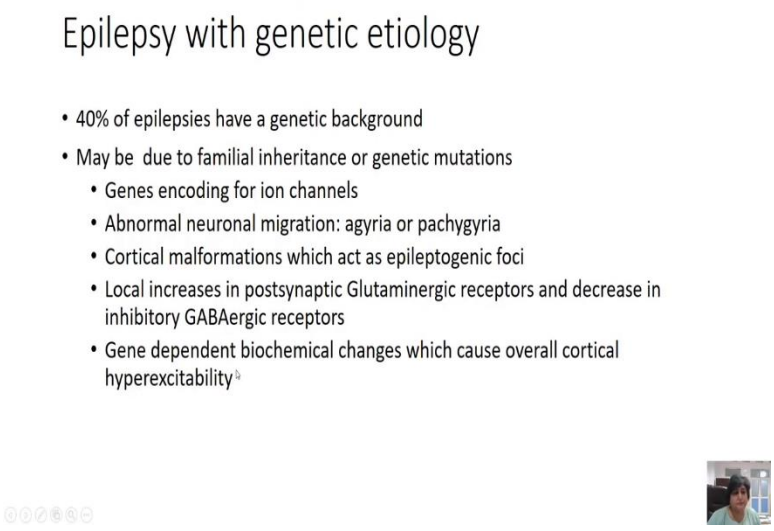
So especially, these new sort of circuits which that which are self-sustaining and excitable, which have formed pathological excitatory recurrent abnormal synaptic connections, which lead to developing that hyperexcitable group of neurons which are more excitable and they are able to sustain the excitability. And that is what is the formation of the epileptogenic focus.

(Refer Slide Time: 16:22)



The pathways which are under study right now regarding this other BNDF, TRKB signaling pathway, the mTOR pathway, and the REST pathway. These are under active research as possible ways by which this epileptogenesis happens.

(Refer Slide Time: 16:38)



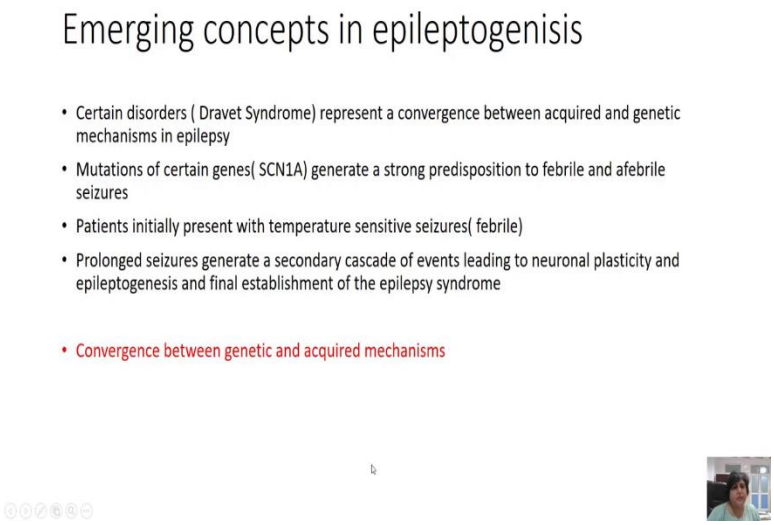
Now, certain epilepsies with genetic etiology. There are about 40% of these which have a genetic background. They may be due to a family inheritance or due to genetic mutation. So either they are inherited or it may be due to a specific mutation in that particular person.

They may be for genes that encode for certain ion channels, they may be genes which are assisting abnormal neural migration. So that means, maybe some area when the gyrus may not develop or they may be reduced development of certain gyria, various cortical malformations which may act as epileptogenic foci.

So basically, abnormal connections of the neurons or abnormal channels which are present in some of the cells; that is the bottom line as far as these are concerned. And there may be certain excessive excitatory circuits which are feeding onto them or there may be loss of inhibitory circuits.

And there is another variety with certain genes may cause biochemical changes, which overall influence cortical hyperexcitability. So these are the ones which are reeling to the genetic type of epilepsy.

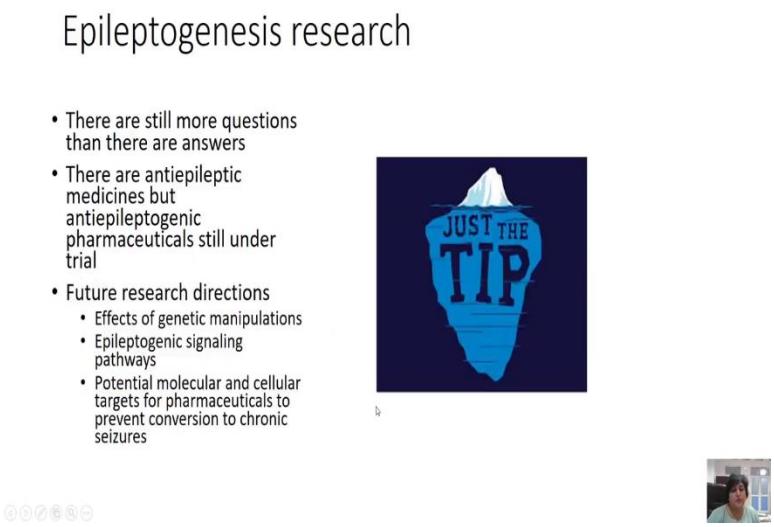
(Refer Slide Time: 17:51)



Another interesting concept which is coming up in epileptogenesis is that they may be actually a convergence of acquired and genetic mechanisms in epilepsy. So a person who has got a tendency to have epilepsy because of certain genetic problems, he, if he is put in the right kind of environment, say, because of temperature variations or repeated febrile seizures, the person will be able to express certain kinds of proteins or may be able to initiate a certain secondary cascade of events, which leads to establishment of epilepsy.

So there is a possibility of convergence of genetic and acquired mechanisms which may lead to epilepsy which need also further focus on.

(Refer Slide Time: 18:39)



So there are a lot of questions, more questions than there are answers in epilepsy. There are varying large number of anti-epileptic medicines which control the seizures, which prevent them from happening, but they do not remove the cause; the moment you stop the anti-epileptic medicines, again the person will start having the seizures.

But we have to look at how we can have anti-epileptogenesis and we can prevent the establishment of a seizure state in the person at all. And future research directions are towards more genetic manipulations, epileptogenic, epileptogenic signaling pathways, which I talked about, and potential molecular and cellular targets for various drugs to prevent conversion to chronic seizures and development of epilepsy.

(Refer Slide Time: 19:29)

Selected References

- E.M. and D.A. Coulter, Mechanisms of epileptogenesis: a convergence on neural circuit dysfunction. Nat Rev Neurosci, 2013;14:337À49
- Pitkänen A, Lukasiuk K. Mechanisms of epileptogenesis and potential treatment targets. Lancet Neurol. 2011;10:173–186.
- McNamara JO, Huang YZ, Leonard AS. Molecular signaling mechanisms underlying epileptogenesis. Sci STKE. 2006;2006:re12
- Kandel ER, Schwartz JH, Jessell TM, Siegelbaum SA , Hudspeth AJ Eds Princliples of Neural Science 5 ed 2000.
- Scheffer IE et al ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology.Epilepsia 2017 Apr;58(4):512-521.

Some of the references which I used to prepare the stock and some interesting further reading. Please do go through it to understand the topic in greater detail.

(Refer Slide Time: 19:42)

Thank you

Thank you.