Module:
Biological Foundations of Mental Health

Week 4
Biological basis of learning, memory & cognition

Topic 1
Learning, memory and synaptic plasticity – Part 1 of 4

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Lecture transcript

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Hello. I'm called Peter Giese. I'm a professor of Neurobiology of Mental Health at King's College London. I'm very, very interested in how the brain stores and forms memory. Ever since I was a child, I was really interested in that question. And so I've developed into a researcher and about 23 years ago, I started to work actively in this area of research. I joined King's College London about 10 years ago. And today I would like to share with you some kind of like of a key principles that are important for understanding learning and memory basically.

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So the first lecture will be actually on the topic of synaptic plasticity. So it turns out that actually neurons are connected by synapses. And these synapses are terribly complicated actually. They can change their properties over time and this change in properties actually is called synaptic plasticity.

And synaptic plasticity is thought to be very, very important for learning and memory. So we will discuss within these lectures. So in the first part, we will address the topic basically, what is synaptic plasticity. We will talk about the phenomenon of synaptic plasticity and then we will focus in particular on properties of a particular type of synaptic plasticity that is called long term potentiation, or briefly LTP.

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Let's start with the definition of synaptic plasticity. So synaptic plasticity is basically a history dependent change in synaptic transmission. So synaptic transmission can change in different ways as you can imagine. So it could increase or it could decrease. And the change in synaptic transmission could be short-lasting or long-lasting.

Accordingly, we distinguish therefore between a potentiation or a depression of synaptic transmission. And we qualify over time course as short or long lasting. So we could have a long-term potentiation, that is LTP, what I briefly introduced. Or we could have long-term depression, that is LTD as we are calling for that. Or we could have short-term potentiation or short-term depression.

So as you can imagine, such changes in synaptic transmission may very well be suited to store information of the brain. Basically the inputs have triggered then a change in synaptic transmission and that has changed. And that's a very good mechanism possibly to store information. Now for the

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sake of simplicity, we will discuss only plasticity of excitatory synaptic transmission.

The main excitatory neurotransmitter in the brain is glutamate. So we will talk about plasticity and glutamatergic synapses. There is of course also plasticity at inhibitory synapses. For example, GABAergic synapses, this is beyond the topic of this lecture series.

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Now most forms of synaptic plasticity have been studied in the hippocampus. So this slide here shows you the rodent hippocampus. So if a rodent brain has a neocortex where it is not very much foliated in comparison to human cortex, so it's rather smooth and flat. And underneath you see like a cashew nut here lining the hippocampus rather big in relation to neocortex in rodents.

And when you make a slice through the hippocampus, you see this beautiful anatomy. So you see basically the so-called tri circuitry. So what you see are granule cells in the dentate gyrus with granule cells are innervated by the so-called perforant path, which is PP in this diagram. The perforant path comes from entorhinal cortex.

When the perforant path innovates with granules cells. Which have as axons with so-called mossy fibres, MF in this diagram, and for mossy fibres innervate C3 pyramidal neurons. These are pyramidal neurons because the neurons have a shape like a pyramid.

So we see C3 pyramidal neurons send their axons for so-called Schaffer collaterals on to C1 neurons. These are C1 pyramidal neurons. Now synaptic plasticity has been basically studied between C3 and C1 neurons mostly. First of all because of its beautiful, simple anatomy. But secondly and very importantly, the hippocampus is fundamentally important for learning and memory. There's this famous case of patient H.M. Patient H.M. suffered from severe epilepsy and when the '50s surgeons decided to remove the focus of the epilepsy in this patient H.M.

And what they did is they lesioned this here brain area that produced the epilepsy and that brain area was included the hippocampus. So the lesion treatment worked for the treatment of epilepsy, but it left the patient with severe memory impairment. And since then basically people have started to realise that the hippocampus is particularly important for learning and memory.

It's particularly important for the types of memory we are aware of, so-called declarative memory. For example, you may know who's the Prime Minister in your country or you may know who is Boris Becker, my favourite tennis star. So kind of such memories depend on the hippocampus. So now there was great motivation to study synaptic plasticity in the hippocampus because its importance for learning and memory and also because of its simple neural anatomy.

Now how do you study synaptic plasticity in the hippocampus? Well you have to use electric stimulation electrode. So the stimulation electrode can give you the electric impulses that evoke action potentials on axons. So a stimulation electrode is placed onto the Schaffer collaterals to produce action potentials, which propagate down the axon to ultimately induce neurotransmitter release. And then you need a recording electrode to measure synaptic potentials. So therefore what you can do here, you can repeatedly stimulate and record the synaptic potentials or synaptic currents.

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Now when you do this you may discover different forms of synaptic plasticity as we have classified in-principle at the beginning. So for example, in the left panel you see an example for short-term potentiation, or the acronym is STP. So what is shown here or what is plotted here over time, the excitatory postsynaptic potential, or EPSP. So the EPSP is a measure of synaptic transmission of excitatory synaptic transmission. So when you stimulate once in a while you get this dot basically--

this black dot.

So stimulating once in a while gives you a constant synaptic transmission at 100% level. But then if you provide a high frequency stimulation, which is indicated by the green arrow here. Then after the high frequency stimulation, now stimulating once in a while shows you more synaptic transmission in the increased EPSP. And in this case we increased the EPSP, the increase last only for a short period of time. So over time it declines and it goes back to the so-called baseline.

So this phenomena is called short-term potentiation. Normally it lasts for about 30 minutes and it depends, as I said, on a high frequency stimulation. So as if this synapse remembers that it had experienced a high frequency stimulation. The next, in the middle, is long-term potentiation, another form of synaptic plasticity. And the difference now if you compare the curves, is that this type of potentiation lasts longer and it actually has initially a transient increase. This is the transient increase because actually in this case, we have some short-term potentiation that precedes long-term potentiation. So the short-term potentiation declines over time and then you see synaptic transmission remains at a higher level.

So this is long-term potentiation and therefore long-term potentiation should be measured once short-term potentiation has declined. Let's say after 30 minutes. Long-term potentiation can last in the hippocampus slices for several hours and in vivo, people have suggested it may last even for up to a year when you use electric stimulations.

The difference for evoking long-term potentiation versus short-term potentiation is that a higher frequency stimulation is required. This is indicated here by the green arrow that is thicker. So you need more use of the synapse and that gives you more synaptic transmission. The final example is a form of depression, long-term depression. In this particular instance the stimulation is of very low frequency, indicated by this thin green arrow. And it leads to a depression of synaptic transmission that lasts for a long period of time.

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Now we will focus more on the phenomena of long-term potentiation because when it was discovered, people thought that this could be a very intriguing mechanism to store information in the brain. Because it's a long lasting phenomenon and up to the discovery of long-term potentiation, all forms of synaptic plasticity that were known were short lasting. And it's not clear how a short lasting plasticity could really store memory for years, for example. But long-term potentiation may have the ability to store information for such long periods. So therefore we would like to discuss this phenomenon more clearly.

So this graph shows you again what I showed before just with a little bit more details. So the time scale is more detailed and what you see here, is for example, a typical 100 Hertz stimulation is used to induce long-term potentiation. 100 Hertz means 100 stimuli in one second. So Hertz is per second. Now this stimulation induces long-term potentiation. So some processes are induced, shown here in green, to get long-term potentiation. And not only long-term potentiation but also short-term potentiation, which when declines-- you can see the decline where the long-term potentiation can be nicely measured about 30 minutes after the stimulation. And then once long-term potentiation has been established some processes are needed to maintain the phenomenon. So there is kind of like a maintenance issue and one would like to know what are the mechanisms that underlie the maintenance of long-term potentiation and what are the mechanisms underlying the induction of long-term potentiation.

This slide also shows you-- basically indicates to you with two blue arrows, what basically the face of short-term potentiation with declines within 30 minutes and there's an even a shorter one, called post-tetanic potentiation, or briefly PTP, that declines even quicker.

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Long-term potentiation as I mentioned, has a property that is long lasting. So it's a long-lasting enhancement of synaptic transmission. That is very exciting because long lasting mechanisms may be important for storing memory but it has also other properties that make it a very interesting mechanism. So it is input specific. That means that it is specific to the activated synapses only. It doesn't affect neighbouring synapses. There is the principle of cooperativity. That means that you need a threshold stimulation to induce long-term potentiation. That is important so that not any signal can produce long-term potentiation. Only signals of relevance should induce long-term potentiation.

And finally we have a phenomenon called associativity. And that associativity applies to long-term potentiation at two different synapses. So if one synapse undergoes a weak stimulation where is not sufficient in itself to produce long-term potentiation. When this stimulation can be converted into an LTP inducing stimulation when a neighbouring synapse experiences LTP induction.

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I will illustrate this now as we show you the principles of long-term potentiation. In this case we're doing an electrophysiological experiments. So we are recording a synaptic transmission from pyramidal neurons and we are using two different stimulation electrodes, S1 and S2. Stimulating with S1 stimulates a set of synapses that is different when stimulating with S2. So below this cartoon, you see that we are recording the EPSPs, the excitatory postsynaptic potentials, that are a measure for synaptic transmission. Or more precisely here we talk about field excitatory postsynaptic potentials, or the FEPSPs.

So the top graph really shows we're recording results after stimulating with S1. And the bottom graph shows your recording result after stimulating with S2. And we have again our time bar. So what we see we first record the first 30 minutes. We record synaptic transmission after stimulating with S1 and S2. And this is-- if you see the EPSP stays more or less constant here it is around zero, it's just basically what is plotted here that is for percent change. You could call it also 100%. It's a way how you present the data.

So synaptic transmission is basically constant. With S1 we produce now a high frequency stimulation indicated by the open arrow. And with high frequency stimulation it's not sufficient to induce LTP. It produces only some kind of STP. So you see after the stimulation, an increase in synaptic transmission where it declines quickly back to the baseline. So that indicates to you the principle of cooperativity. So this stimulation did not reach the threshold to induce LTP.

When this stimulation was given nothing happened at the S2 pathway where the S2 stimulation was used so synaptic transmission at that pathway is not affected. At one hour, we now give for with the S2 stimulation, a very strong stimulation indicated by the closed arrow. And so the closed arrow shows you now production of LTP. So now you get an increase in synaptic transmission where it is first transient. So we have PTP and STP followed up by LTP that's longer lasting and stable. That LTP is input specific because it occurs only in the S2 pathway and not in the S1 pathway at the same time. So the neighbouring synapses did not increase synaptic transmission, so we have an input specific phenomenon.

At one and a half hours, we produce again in pathway S2 a very strong stimulation that gives us even more LTP. So now we have even a further increase in synaptic transmission that is long lasting. That is because LTP in this case was not saturated. While this stimulation occurs, S1 pathway experiences a sub-threshold weaker stimulation indicated by the open arrow. This weaker stimulation was not sufficient to induce LTP at half an hour time at the S1 pathway. However, now that this stimulation is coinciding with the strong stimulation at S2, we can obtain LTP. This indicates a principle of associativity. So the association of a weak stimulation with a strong stimulation led to the production of LTP.

And this is a very interesting property because it reminds us of conditioning-- Pavlovian conditioning. So even Pavlov, that made these famous experiments with dogs, where he could basically show them and then he could condition the dog to a bell so when a bell did ring, well the dog could learn that food may be coming and then the dog would salivate to the bell. So this is since when we all know about Pavlovian conditioning and it's the principle of associative learning. So we learn a lot of information by making associations. And LTD induction of LTP has now also associative properties. And so making it very interesting as a mechanism for learning and memory.

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So that concludes our first part. So we have introduced you now into the phenomenon of long-term potentiation. And in the next series we will talk more about this phenomenon in detail-- about its underlying molecular mechanisms and its role in learning and memory.