Module:
Biological Foundations of Mental Health

Week 4
Biological basis of learning, memory & cognition

Topic 1
Learning, memory and synaptic plasticity – Part 2 of 4

Professor Peter Giese
Department of Basic and Clinical Neuroscience

Lecture transcript

Slide 3

Welcome to the second part of our lecture on synaptic plasticity and memory. So in the second part, we will focus in more detail on the phenomenon of long-term potentiation. We will discuss some molecular mechanisms that underlie the induction, the consolidation, and the maintenance of long-term potentiation. So you will learn about key molecular processes that underlie these processes.

Slide 4

Just to remind you, so long-term potentiation when we discuss it, focuses on glutamatergic synaptic transmission. Glutamatergic synaptic transmission, obviously, uses glutamate as neurotransmitter. And on the postsynaptic side there are two glutamate receptors that are of relevance, the AMPA receptors and the NMDA receptors.

So the AMPA receptors, they bind glutamate, and then they are opened. Once opened, they allow sodium ions to influx with postsynaptic membrane, whereby depolarising with postsynaptic membrane. Now these receptors are the main carriers of glutamatergic transmission.

We have, in addition to these AMPA receptors the NMDA receptors. The NMDA receptors are more complicated, because these receptors require, not only glutamate for their opening, they also require a postsynaptic depolarisation to be opened. So they require two coinciding events, glutamate release from a presynaptic determiner and a postsynaptic depolarisation.

This is because they are blocked by magnesium ions, which are indicated here by this grey circuit. So the magnesium ions block the pore, and this block of the pore can only be removed by depolarisation. Now interestingly, once NMDA receptors are activated, they allow calcium ions to enter the postsynapse.

So calcium, as you know, very important second messengers. So the second messengers can trigger a number of different signalling cascades. Most prominently, calcium can bind to calmodulin which is in high doses in postsynapse. And calcium calmodulin activates a number of different kinases.

And so these kinases can then modify how the synapse works. So one way of modifying with synapse is, for example, by phosphorylating AMPA receptors. So phosphorylation of the AMPA receptors could increase the conductivity of these receptors.

Transcripts by 3Playmedia

So thereby, you get now for a given amount of glutamate release more neurotransmission. You get basically be more depolarisation. So neurotransmission is enhanced, because you get more ions fluxing in.

Another way aware of and enhancing synoptic transmission at the postsynapse is by increasing numbers of AMPA receptors. So this can be achieved by basically incorporating or providing more AMPA receptors through these vesicles. So there in the postsynapse, there are endosomes that contain AMPA receptors. And these endosomes can be fused with the membrane so you get more AMPA receptors.

There are also AMPA receptors that are outside the postsynaptic zone. And they can be diffused into a postsynaptic zone. So thereby, you enhance the density of AMPA receptors. Now increasing the density of AMPA receptors is another means of enhancing synaptic transmission, because now you can activate per glutamate release more AMPA receptors. And thereby, you get more depolarisation, so more synaptic transmission.

It's also conceivable that actually synaptic transmission can be enhanced at the presynaptic site so that you get more glutamate release. Now to enhance synaptic transmission at the presynaptic site, however, is a little bit more complicated, because long-term potentiation is actually induced at the postsynaptic site. So you need to get a signal across from the postsynapse back to the presynapse to modify a presynaptic neurotransmitter release.

And so-called retrograde signalling, basically. And for example, diffusable gases such as nitric oxide could be such a retrograde signal. So you could produce nitric oxide, where it diffuses from the postsynapes to the presynapse and thereby, induces signalling to enhance neurotransmitter release.

Ultimately, once signalling cascade is activated, there are some aspects of the signalling cascade may also change gene expression in the nucleus or at the synapse, some translation of mRNA, where it is located at the synapse. And so you can get the synthesis of new proteins. And these new proteins are really important for very long lasting forms of long-term potentiation, as we will see.

So this cartoon will basically indicate to you how synaptic transmission can be enhanced and what has to happen when LTPs induced. So the NMDA receptor is critical for it. And most people think these days that the AMPA receptor trafficking into the postsynaptic density is the key mechanism for long-term-- the induction of long-term potentiation.

Slide 5

This slide basically shows you this in a little bit more detail. So now we have here the NMPA receptors in purple that allow calcium to flux into the postsynapse. Calcium binds to calmodulin. And then calcium calmodulin can activate a prominent kinase, that is CaMK kinase 2, calcium calmodulin-dependent kinase 2, a very complicated enzyme that consists of 12 subunits. And six subunits are indicated here as a hexagon. And the kinase can phosphylorate itself. And that's indicated by the P. And then once phosphylorated itself, it can phosphylorate AMPA receptors. The AMPA receptors are shown in kind of like pinkish. And so we can see that this phosphyloration of the AMPA receptors enhances for conductivity of these receptors. But also some receptors can be trafficked into a postsynaptic density, which is shown like dark brown. And so you can increase the density of the AMPA receptors. And so CaMK kinase 2 seems to be a critical enzyme for all these processes for induction of long-term potentiation.

Slide 6

Long-term potentiation lasts a long period of time, which is the definition of long-term of potentiation. However, there are different types of long-term potentiation in terms of duration. And some types of long-term potentiation that lasts really very long called Late LTP or L-LTP. Eric Kandel, Nobel Laureate

has introduced the term.

We would like to use it, late LTP. And the operational definition is that these forms of LTP require protein synthesis in gene transcription to be very long lasting. So after the induction of such LTPs, new proteins need to be synthesised. And these new proteins contribute then to the long lasting nature of the LTP.

To get such LTP, one needs even stronger stimulation when traditional LTP. So what I showed in part one is with 100 word stimulation is sufficient to induce long term potentiation. However, it would induce only the so-called early LTP with declines within a few hours. But to induce late LTP, you need three times, for example, 100 Hertz stimulation to activate gene expression and protein synthesis, to get these very long-lasting forms of LTP.

Slide 7

The question arises is, basically, how could that work, because if one has to synthesise a new protein, first of all, one has to transcribe new genes in the nucleus, and when synthesising new protein, let's say in the cell soma, then how can these proteins be delivered, specifically, to the synapses that are important, should have LTP? So how do you keep the input specificity involving the nucleus of a neuron?

So this cartoon tries to indicate this, so let's just focus on panel A first. So what we see here is a synapse, just shown with a post synapses with experience is a very strong tetanisation, like with three times 100 hertz stimulation that produces L-LTP. And in the middle of this slide, we see the soma of the neuron, which is very far away from the synapse. And in the soma, we have a nucleus shown by this bowl, basically. The nucleus has all the genomic DNA that needs to be transcribed. And an mRNA is indicated here, is the blue wave. And once the mRNA is translated, we get this protein. And the protein diffuses all over the place.

What is happening is the strong tetanisation at the synapse, produces a signal from the synapse to the nucleus to induce gene expression. We do not understand the signal very well, but there are some ideas that, for example-- importins are very important molecules for that. So once the signal it reaches the nucleus, we get gene expression. Then, we get mRNA translation and protein synthesis.

For newly synthesised proteins, diffuse back into the dendrites and could ultimately affect all synapses. However, these proteins can't be taken up by the synapses. It can only be taken up by the tetanised synapses. And the reason for that is that the strong tetanisation induced the molecular change, which we call tag setting. So it sets some kind of tag, but it's unable to capture the plasticity-related protein, PRP. So with newly synthesised proteins, we also call PRP.

And so, basically, taking up the PRP's then allows the LTP to be developed into late phase LTP. So whereby, you keep, basically, synapse specificity, because only the strongly tetanised synapses can take up the PRPs and neighbouring synapses can't do so.

This is actually very interesting, because this process has also associative properties, it was indicated in panel B. So if it happens when a strong tetanisation caught inside in time for weak tetanisation at another synapse, and this weak tetanisation gives us, now, an early LTP, but not a late LTP, then the weak tetanisation is still sufficient to induce, also, a tag setting. And when these newly tagged synapses can take up some of the PRPs, so that the early LTP can be transformed into late LTP.

Only because the weak tetanisation coincided in time with a strong tetanisation, we now transform early LTP into late phase LTP. On its own, weak tetanisation would give us only early LTP. So here, we have another mechanism, how a neuron can make associations.

Slide 8

Finally, I would like to address the issue of maintenance. So the induction of LTP-- it required NMDA receptors, CaM kinase, to when we talked about the consolidation of LTP that requires protein synthesis that have to be taken up only by the activated synapses. And now, all these processes have occurred. The question is how do you maintain this process? In particular, how do you maintain the high density of AMPA receptors to, basically, keep LTP?

Now, it has been suggested that this is mediated by local translation of a kinase that is called PKM zeta, protein kinase m zeta. It's a protein kinase C isoform. And this protein kinase C isoform lacks a regulatory domain, so most kinases have a regulatory domain that inhibit the catalytic domain. And the catalytic domain is important to phosphorylate substrates. Now, lacking the regulatory domain and having only catalytic domain means with PKM zeta is actually active over time, once it is produced.

So the idea here is that the stimulated synapses have mRNA that encode PKM zeta. And this mRNA translation is normally repressed. However, when LTP is induced-- and particular late phase LTP is induced-- then this repression is relieved. And now, the PKM zeta and mRNA can be translated.

So we get PKM zeta protein, a kinase that is active over time. This kinase keeps on promoting the AMPA receptor density, so it promotes trafficking of AMPA receptors. And therefore, the kinase is active over the time. And it's a nice mechanism to maintain high density of AMPA receptors.

Now of course, such a mechanism lasts only so long as PKM zeta is around. And as you know, each protein in the body is turned over within a few hours or, at most, within a day or so. And so to keep long term potentiation for a lifetime, say, how would that work? And so the idea is that once PKM zeta is turned over, it's replaced by newly synthesised PKM zeta, because PKM zeta can stimulate its own synthesis. So the mRNA is there and can be translated further to produce more PKM zeta proteins.

So at synapses, that basically, maintain LTP where it should be PKM zeta that is active all the time. That would be the engine that maintains the high density of AMPA receptors and, thereby, the enhancement of synaptic transmission.

Slide 9

So in this part, we have touched on the principles, the molecular principles, of LTP induction that requires NMDA receptor activation and allowing calcium entry into the synapse, MK2 activation, AMPA receptor trafficking, and the LTP consolidation. So we can consolidate early LTP into late phase LTP by synthesis of new proteins. These new proteins are taken up. We do not know exactly what these new proteins are. And research is still undergoing to understand what these proteins are, and why are they so important for late phase LTP.

And finally, we talked about the LTP maintenance, in particular about PKM zeta-- a kinase that is locally-produced at the synapses and is persistently active and persistently increases, or keeps the increased density of AMPA receptors.

In our next part, we will be talking about memory, because now, we would like to establish whether long term potentiation actually is really important for memory or not. So it has interesting properties, but we need to find out, is it important?

Transcripts by 3Playmedia