Module:
Biological Foundations of Mental Health

Week 4
Biological basis of learning, memory and cognition

Topic 2
From the dynamic synapse to synaptopathies – Part 2 of 4

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Slide 3:
In this part of the lecture, we will now focus on the function of dendritic spines and discuss how the structure of dendritic spines is thought to be linked with the functional properties of synapses.

Slide 4:
Dendritic spines come in a myriad of shapes and sizes. The shape and size of a dendritic spine can tell you a lot about its function. Here, we have a serial electron microscopy reconstruction of a small part of dendrite from a hippocampal neuron. What you will hopefully be able to see is that dendritic spines can be large and small in size, and even long and short.

So, what is the consequence of having dendritic spines with different morphologies? Well, in this image, we can also see the size of the synaptic connection, which is shown in red. This nicely shows you that larger dendritic spines typically have larger synaptic connections, whereas smaller or thinner spines have much smaller synaptic connections.

Slide 5:
Dendritic spine shape is also intimately linked with its function. For example, in this study, the authors have labelled the dendrite of a neuron with green fluorescent protein, or GFP, to show the shape of the cell. They have also immunostained the cell for GluA1-containing AMPA receptors, as a proxy for measuring synaptic strength. More GluA1-containing AMPA receptors would indicate the stronger synapses.

Hopefully, what you can see is that larger spines – shown here by these red arrows – contain a lot of GluA1-containing AMPA receptors. Whilst, on the other hand, much smaller or thinner spines – shown here by the yellow arrows – have much smaller amounts of GluA1-containing AMPA receptors. What this tells us is that larger dendritic spines not only contain more GluA1-containing AMPA receptors but that they are more likely to have bigger responses to a glutamate or synaptic activity whereas thinner or smaller dendritic spines, that have less AMPA receptors, are likely to have smaller responses to glutamate or synaptic activity.

This was very nicely shown by a study carried out by Matsuzaki and colleagues in 2001. Here, the authors performed a very elegant study to show that larger dendritic spines have much stronger responses to glutamate whereas smaller dendritic spines have a smaller response to glutamate. In this study, the authors have recorded excitatory post-synaptic currents in hippocampal neurons. The hippocampal neurons are bathed in cage glutamate – that is, glutamate that is inactive unless you shine a particular wavelength of laser on it, allowing it to become active. The authors were able to uncage glutamate at very specific sites, such as directly over a dendritic spine – this means that you can activate only the AMPA receptors within a specific dendritic spine. Thus, the authors uncaged glutamate over dendritic spines with different sizes and, at the same time, recorded the excitatory postsynaptic current that it resulted.

In the left image, we can see four spines labelled 'A', 'B', 'C' and 'D' – all of which have different sizes. In the middle and right panels, we can see that the measured, post-synaptic current induced by the uncaging – in these images, yellow and red colours – indicate a larger response whereas darker and blue colours indicate a smaller post-synaptic current. What the authors found was that if they uncaged glutamate over the spine labelled 'A', that the current was much larger than if they uncaged glutamate over spines 'C' and 'D'. Taken together, these studies demonstrate that larger dendritic spines typically contain more AMPA receptors and generate larger excitatory post-synaptic currents as compared to dendritic spines with smaller size. Thus, indicating that dendritic spine structure is linked to synaptic function.

Slide 6:
So, do dendritic spines change shape in response to different stimuli? In short, yes, they can. As we discussed earlier, physiological stimuli – such as changes in synaptic activity – can change the number and strength of synaptic connections. This also leads to a change in dendritic spine size. For example, if we were to induce a long-term potentiation- or LTP-like stimulus, we can see that dendritic spines can actually increase in size. Conversely, if we were to induce a long-term depression- or LTD-like stimulus, we can see that dendritic spines actually shrink in size. The ability of dendritic spines to change size in response to stimulation is known as 'structural plasticity' and is thought that this process plays an essential role in the encoding of information.

Slide 7:
If structural plasticity does play a central role in the encoding of information – based on our understanding that larger dendritic spines have more AMPA receptors and, thus, make stronger synaptic connections – one would expect that following a LTP-like stimulus that not only would dendritic spines change in size but also the amount of AMPA receptors would also increase.

In 2006, Kopec and colleagues tested this idea. What they did was to monitor the amount of GluA1-containing AMPA receptors in dendritic spines, before and after the induction of LTP. Here, the authors induced LTP using a chemical approach and, thus, have labelled this 'chemically-induced long-term potentiation' or 'cLTP'. What the authors did was to monitor both the size of the dendritic spines, by measuring spine volume, as well as the amount of AMPA receptors within dendritic spines. This was done by making hippocampal neurons express a red fluorescent protein, to outline the morphology of the cell, and to express GluA1-containing AMPA receptors that would link to a special form of GFP, that only fluoresces when the receptor is expressed at the surface of synapses. What this means was that the authors could easily monitor the size of dendritic spines whilst simultaneously measuring the amount of synaptic and, thus, active AMPA receptors within dendritic spines.

The authors then monitored both the size of dendritic spines as well as the amount of AMPA receptors in dendritic spines 30 minutes before and up to 80 minutes after the induction of this chemical LTP. What the authors found was that, as expected, the induction of chemical LTP caused dendritic spines to increase in size.

This can be seen in the left-hand image. In addition, the authors found that the amount of GluA1 in dendritic spines also increased following the induction of chemical LTP. This can be seen in the middle panel where an increase in the amount of GluA1 within dendritic spines is shown by an increase in the amount of yellow and red colours. These data are summarised in the graph on the right and it shows that as spine size increases – shown by the red line – the amount of AMPA receptors also increases. Ultimately, what this tells us is that as dendritic spines change size in response to stimulation, the amount of AMPA receptor also changes. Thus, demonstrating that structural and functional plasticity are linked.

Slide 8:
So, to summarise, what we have shown here is that physiological stimuli – such as long-term potentiation (LTP) or long-term depression (LTD) – can not only change the number of dendritic spines but can also result in a change in the size of dendritic spines. This results in a concurrent change in the amount of AMPA receptors within these dendritic spines, which underlies the changes in synaptic strength that is observed. Thus, structural and functional plasticity are coordinated and can be changed, resulting in refinement of neuronal circuitry. This process is, therefore, thought to be essential for normal brain function.