Module:
Biological Foundations of Mental Health

Week 4
Biological basis of learning, memory and cognition

Topic 2
From the dynamic synapse to synaptopathies – Part 3 of 4

Dr Deepak Srivastava
Senior Lecturer, Basic and Clinical Neuroscience, King's College London

Slide 3:
In this section, we will investigate the evidence indicating that abnormal dendritic spine function may be linked with a range of mental illnesses.

Slide 4:
In the last two sections, we have focused on the role of dendritic spines in the healthy brain. Now, I would like to explore the potential contribution of dendritic spine dysfunction in disease.

There is now increasing evidence that dendrites and dendritic spine morphology may be affected in a range of brain disorders. For example, here we have a cartoon of the dendritic arbour as seen in normal neurons and those seen in disorders such as autism spectrum disorders (ASD) or schizophrenia. As you can see that in a range of different disorders, the overall dendritic arbour seems to be simplified as compared to that seen in a normal neuron or healthy neuron.

Similarly, in studies where researchers have examined the post-mortem brains of individuals with different mental health issues, such as autism or schizophrenia, we can see that there is an abnormal number of dendritic spines compared to healthy or controlled individuals. For example, in patients with autism, you can see that there seems to be an increase in the number of dendritic spines, compared to healthy or controlled patients. Conversely, if we look at the number of dendritic spines of neurons found in the brains of patients with schizophrenia, you can see that there seems to be a reduction in the number of dendritic spines as compared to healthy individuals.

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This has led to the overall idea that aberrant dendritic architecture or abnormal dendritic spine density could result in altered neuronal network or circuitry and, thus, wiring – which could, ultimately, result in cognitive deficits that are seen in brain disorders, such autism spectrum disorders and schizophrenia. However, a major issue with relying in post mortem studies, to help identify underlying causes of disease, is that we do not know whether the observed deficits, such as impaired dendritic arbours or altered dendritic spine numbers, are a

cause of the disease or have been caused by the disease progression. Indeed, the post-mortem tissues have been taken from individuals at the end of their life and after they have likely suffered from the disease for a long time. As such, a number of factors – such as chronic exposure to drugs – may have influenced the observed phenotypes.

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So, what evidence is there that dysfunction of dendritic spines may contribute to disease?

Well, if we look at typical neurodevelopment, we can see that dendritic growth and dendritic spine morphogenesis and, thus, synapse formation occurs early on in life. If we examine when specific disease symptoms occur, we can see that they coincide with critical periods of synapse formation. For example, symptoms associated with autism spectrum disorders emerge during early childhood, a period when there is increased spine and synapse formation. Current research indicates that an increase in the number of dendritic spines, occurring early on in this disorder, may contribute to the symptoms.

Symptoms associated with schizophrenia, on the other hand, typically emerge around adolescence or early adulthood. This also coincides with a period when there is a refinement of synaptic connections. This is typified by pruning of synaptic connections. One theory is that an increase in synapse elimination during this period may contribute to the emergence of schizophrenic symptoms.

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However, perhaps the most compelling evidence that dendritic spine dysfunction may play an important role in the emergence of disease, lies in recent large-scale studies investigating the underlying genetic causes for neurodevelopmental and psychiatric disorders.

These studies have identified a large number of de novo protein coding mutations. That is, genetic variance that would cause a change in the sequence of specific proteins that are associated with risk of developing diseases – these include disorders such as intellectual disability, epilepsy and autism spectrum disorders, all of which have an early onset, as well as disorders like schizophrenia and bipolar disorder, which have a late onset.

Interestingly, if we compare these de novo protein coding variants with the proteome of human post-synaptic density – or the 'PST' – as a proxy for what proteins are present at synapses, we find that there is a large overlap. What this strongly indicates is that many of the de novo protein coding mutations associated with various neurodevelopmental and psychiatric disorders occur in proteins that are found at synapses. This strongly supports the idea that dysfunction at synapses and, in turn, dendritic spines play an important role in the emergence of disease.

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Indeed, if we examine which genes have been implicated with disease in more detail, we can start to see that many of these genes, not only encode for proteins that localise to dendritic spines, but also have critical roles in dendritic spine formation, maintenance and remodelling.

In this image, we can see several classes of synaptic proteins, all of which have been implicated with disease. These include adhesion proteins, scaffold proteins and glutamate receptors, all of which we have discussed earlier in this lecture as having critical roles in the basic function of dendritic spines. In addition to this, we also find a number of signalling molecules as well as voltage-gated calcium channels as being implicated.

These examples help to build a picture indicating that alterations in the function of some or many of these proteins, could easily result in dysfunction of dendritic spines and, thus, impact synaptic communication and connectivity. Right now, there is a lot of work that is going on, trying to understand how these aberrant structures occur and, moreover, if it is possible to reverse or stop these deficits from occurring. And it is with this that we hope we will be able to treat different mental illnesses.