Module:
Biological foundations of mental health

Week 1
Introduction to brain anatomy

Topic 1
Overview of CNS development – Part 3 of 3

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Lecture transcript

Slide 2
Examples of human disorders which can be caused by defective developmental processes are autistic spectrum disorder, schizophrenia, childhood onset epilepsy, and X-linked mental retardation. In this section, we will highlight certain developmental aspects of ASD and schizophrenia. Understanding the developmental processes I have described in this subtopic is extremely important, as this can give insight into neurodevelopmental disorders in humans.

Large-scale human genetic screenings and experiments in animal models have started to uncover some of the principles that underlie these disorders. We now know some of the genes that are mutated in humans with these disorders. Developmental neuroscientists are trying to understand the mechanisms that underlie the changes caused by these mutations.

It's emerged in recent years in particular that dendrite and synapse development are often affected by these gene mutations. Many aspects of development can be perturbed to lead to such disorders, such as axon growth, guidance, neuronal migration, synapse formation, and function.

Slide 3
Autistic spectrum disorder, ASD, is an umbrella term for a disorder which can take on multiple forms and have multiple causes. Nevertheless, it is clear that ASD is a neurodevelopmental disorder and that some forms of ASD are genetically based.

In humans, it has been shown that mutations in several genes including neuroligin-4 are linked to autistic spectrum disorder. Neuroligin-4 is involved in synapse development. Studies using mice, which are deficient in the neuroligin-4 gene, called knockout mice, have shown that markers of inhibitory synapses are reduced in some areas of the hippocampus, pointing to a developmental defect.

In the figure, you can see the white staining representing immunofluorescence for two markers of inhibitory synapses-- gephyrin and a GABA A receptor subunit. Compared to the wild-type panels to the left, there's a reduction in the staining in the neuroligin for KO, or knockout, mouse. In addition, neuroligin for knockout mice showed behavioural changes reminiscent of ASD.

It's perhaps surprising that it's been possible to model some of the behavioural aspects of ASD in mice using assays of, for example, social interaction or vocalisation. These experiments have shown that neuroligin for knockout mice showed impairments in social interaction and communication, as well as repetitive behaviours and interests. Some of these features are characteristic of humans with ASD. Whereas the process of synaptogenesis and its link to behaviour is extremely complex, these

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studies give us hope that ASD can be modelled using the mouse as an experimental system.

Slide 4
As well as changes in the numbers of synapses, there may be changes in the structural features of dendrites and dendritic spines which are key to synapse formation. There is a large amount of evidence now to show that the numbers, shape, and development of dendritic spines change in some individuals with schizophrenia or ASD including X-linked mental retardation, Fragile-X, which has features of ASD. The number of dendritic spines is reduced in the dorsolateral prefrontal cortex of some schizophrenia subjects.

You can see this in the figure where the black line with the blobs on it represents a dendrite and the dendritic spines in a normal subject. In the two schizophrenia subjects shown, you can see that the number of dendritic spines looks to be reduced. This may reflect defects in either the process of dendrite development and/or pruning.

Mice lacking the Fragile-X mental retardation protein have more immature, thin spines, and there is evidence for a similar change in humans with Fragile-X. You can see this in the figure comparing a dendrite from the wild-type animal with a mouse used as a model for Fragile-X and lacking the FMRP protein.

Knowledge about the genes and proteins which are involved in dendritic spine development and testing their role using animal models will be key to understanding the link between spine development, function, and mental health. It's worth bearing in mind, however, that there are a large variety of studies on issues such as dendritic spine development, density, and maturation. Some of the results from these studies are conflicting, and much further work will be required before we can draw general conclusions from this work.

Slide 5
We can conclude that understanding development in detail can unlock many of the secrets of the way the nervous system is built and how it later functions. Research in developmental neuroscience will help us understand neurodevelopmental disorders and mental health and vice versa, Many of the techniques currently being used and under development will play an essential role in the next decades in unravelling these principles. For example, live imaging in vivo using the mouse and zebrafish can now tell us much about the dynamic events that occur during dendrite development, pruning, and plasticity.

Behavioural tests in the mouse are also beginning to give us insight into the effect of particular genes and proteins on behaviour at the organism level. Genetic screens in humans can then reveal the genes whose function can be tested in animals, while genes shown to be important in development through basic science studies can be screened in the human population. This interplay will be the foundation of future discoveries in development and mental health.

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