Module:
Biological foundations of mental health

Week 1
Introduction to brain anatomy

Topic 1
Overview of CNS development – Part 2 of 3

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Lecture transcript

Slide 2
Now we will consider neural development as it applies to the individual cell level. During development, individual cells go through a process of differentiation. We can broadly think of development as a process where cells progress from a 'multipotent' population, capable of producing a range of cellular derivatives, to cells of particular, specialised identities, or 'fates'.

The embryologist, Waddington, nicely represented this as a ball rolling down a hill-- the epigenetic landscape-- and then rolling into one of a number of channels. Which channel the ball ends up in is not random, however. It depends on a number of events which take place in development, especially external influences and interactions between groups of cells, which instruct cells on their next developmental step.

The process of neural induction is an example of this, in which the neural plate is influenced by the mesoderm to develop into the nervous system. We can thus see cell differentiation as a decision tree, which will eventually lead to cells assuming one of a number of fates.

Slide 3
There are various different aspects of neuronal differentiation. One is the appearance, or morphology, of individual cells, shown here using the examples of a Purkinje neuron and a pyramidal neuron. The Purkinje neuron resides in the cerebellum and has an extremely elaborate dendritic tree, whereas the pyramidal neuron resides in the cerebral cortex and is less elaborate, with an apical dendrite and some branches.

Both neurons have an axon which extends downwards in the diagram, exiting the cerebellum or cortex to project to other parts of the brain. Other aspects of neuronal differentiation are the gene expression profile, neurotransmitter type, and connectivity to other neurons in the nervous system. Together, all of these features make up the individual characteristic of differentiated neuronal types.

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Now I will explain the developmental steps which lead to differentiation in more detail. These steps are neurogenesis, during which cell division occurs to generate neurons; cell migration, when young neurons migrate away from the ventricular zone; axonogenesis, when the neuron starts to develop processes, including an axon which grows out towards targets; synaptogensis, when axons make contact with their target neurons or other structures; cell death or pruning, when regressive events often occur, leading to the formation of the mature neuron.

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The neural tube is divided into a ventricular zone, adjacent to the ventricle, which contains the cerebrospinal fluid, and a mantle zone, adjacent to the pial surface covered by the meninges. Radial glial cells are elongated cells with a long process or endfoot on each surface. These are the progenitor cells of the nervous system.

Radial glial cells undergo cell divisions repeatedly to expand the progenitor cell population, and some of these divisions give rise to a neuron shown by the shaded cell in the cartoon. The cell divisions themselves, of the cell body, occur adjacent to the ventricular surface of the neurepithelium.

Once the neuron is generated in such a cell division, it will migrate along the radial glial cell, using it as a guide towards the mantle zone. There, further differentiation of the neuron will take place, including extension of an axon.

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Neurons frequently have to migrate long distances towards their final position in the developing nervous system. There are two main types of migration-- radial migration and tangential migration. We have already dealt with one type of migration in the previous section using the example of the spinal cord, in which progenitors of cells migrate radially from the inside to the outside of the neural tube to generate neurons.

This type of radial migration also occurs in the telencephalon, or forebrain, and is shown here in a transverse section of the developing telencephalon in a mouse, which will later form the cerebral hemispheres. Cells which migrate radially, along radial glia, give rise predominantly to the neurons with long axons that project to other regions of the nervous system, and that use the neurotransmitter glutamate, called excitatory projection neurons.

The other type of migration which occurs in the telencephalon is called a tangential migration, in which neurons migrate orthogonal to the radial axis. Neuronal progenitors migrate from the ventral telencephalon into the dorsal telencephalon, the developing cerebral cortex, and intermingle with the neurons which have undergone radial migrations. These neurons, which have migrated tangentially, give rise to neurons with short axons, which use the neurotransmitter GABA, called inhibitory interneurons.

Our third example of a neuronal migration concerns cells that split off from the ectoderm while neurulation is underway. These are the neural crest cells. Shown in a transverse section of the developing spinal cord, neural crest cells migrate away from the forming neural tube to form elements of the peripheral nervous system. In particular, these are the dorsal root ganglia and sympathetic ganglia in the trunk, and the cranial ganglia of the head.

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As neurons move into the mantle zone and start to differentiate, they start to develop an axon. This process of axonogenesis can be beautifully visualised in hippocampal neurons growing in vitro, as shown by this example from the lab of Gary Banker. Here you see the different identified stages of axonogenesis and neural development at the single cell level.

At Stage 1, neurons are initially round blobs. At Stage 2, neurons look radially symmetrical, with several neurites, or processes. At Stage 3, one of these neurites becomes selected as an axon in a process of symmetry breaking. This axon will go on to grow out and extend towards its targets.

At Stage 4, the axon continues to grow and the dendrites start to grow out from the cell body. At Stage 5, the dendritic tree becomes more elaborate with small protrusions, or dendritic spines, forming on the dendrites. In vitro, the neurons can be seen to form a network.

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Development of the axon and the dendrites proceed in parallel. Growing axons are guided by molecules in their environment to their targets. Axons eventually make contact with their targets, whether that is a neuron, as in this case, a gland, or a muscle. In the case of neuron-neuron synapses, these are most frequently made on dendrites, and in fact, the dendritic spines.

Synapses are sometimes made on the neuronal cell body itself-- axosomatic-- or on an axon-- axoaxonic. Just to make this clear, in the diagram, the synapse is formed by the growing tip of the neuron to the left on the neuron on the right. Thus, the neuron to the left is the presynaptic part, and the neuron to the right, the postsynaptic part.

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Once the growth cone has reached its target cell, synapse formation is initiated between the presynaptic axon and the postsynaptic dendrite, soma, or axon.

There are many stages to synaptogenesis. Various molecules, including cell adhesion molecules, contact dependent, and diffusible molecules play a role in synapse formation. Neuroligins and neurexins are families of transmembrane proteins that are expressed by the postsynaptic and the presynaptic neuron, respectively, and that are important in the process of synaptogenesis. They bind the pre- and postsynaptic parts of the synapse together, and serve as a focus for other proteins to cluster together to form the synapse.

Different members of the neuroligin group are enriched in excitatory and inhibitory synapses, and are involved in specifying these different synaptic types. Molecules such as cadherins and SynCAMs help to consolidate synapse formation. The neurexins and neuroligins then help to recruit specialised groups of proteins into the presynaptic active zones, containing the neurotransmitter vesicles in the presynaptic terminal.

They also coordinate the assembly of the postsynaptic densities, which contains so-called scaffolding proteins and neurotransmitter receptors. Overall, the process of synaptogenesis is a very complex and coordinated process.

Slide 10
The nervous system forms not only by growth and elaboration of axons and dendrites, but also by sculpting of neuronal architecture and by cell death. Cell death is a surprisingly common phenomenon in the nervous system. It's estimated that around 50 per cent of motor neurons, for example, die during later development.

These regressive events may thus involve either the elimination of whole cells, or parts of cells, axons, synapses, or dendrites. In the examples shown of the developing cortex from humans, the complexity of the brain can initially be seen to increase, in terms of the density and numbers of neurons, up to two years of age, with increasing synapse formation.

From four years to six years, however, a process of synapse pruning and consolidation takes place, and some decrease in the complexity of the brain landscape occurs. Pruning can occur to axons and to dendrites, which disintegrate and the debris is then cleared away. Cell death and pruning may eliminate unwanted neurons or connections, match numbers of pre- and postsynaptic cells, and ensure that synaptic transmission and circuit function is optimised.

It's not completely clear why these events occur, but it may be to ensure that there are matching numbers of pre- and postsynaptic cells. In addition, the removal of any aberrant or unwanted connections may occur, and the fidelity of connections in terms of structure and function may be improved.

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