Module:
Biological Foundations of Mental Health

Week 3
Synaptic transmission & neurotransmitter systems

Topic 3
Neurotransmission defects and mental health: Focus on schizophrenia – part 3 of 3

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Lecture transcript

Slide 3

So what is the involvement of other neurotransmitters in schizophrenia? If increases in dopamine are not present in all schizophrenia patients, then what else is going wrong at the level of neurotransmission? We have seen that treatment-resistant patients have elevated levels of the neurotransmitter glutamate in the frontal cortex. Atypical antipsychotic drugs also have a dual action at dopamine and serotonin receptors. Therefore, alterations in either of these neurotransmitter systems is likely to be implicated in schizophrenia.

This situation is likely more complex, still, since dopamine, glutamate, and GABA interact and regulate each other. So how does the glutamate hypothesis work, in terms of positive symptoms? In the first diagram, A, you can see that, in the normal brain, cortical projection neurons, indicated by 1, send glutamatergic projections from the frontal cortex to the dopaminergic neurons in the midbrain, where, we have already seen, is the origin of the mesolimbic pathway, indicated by 2. The activity of these cortical neurons is regulated by another type of neuron in the cortex which releases the inhibitory neurotransmitter, GABA, indicated by 3.

When this circuit is functioning normally, glutamate, GABA, and dopamine are in equilibrium. In schizophrenia, panel B, it is hypothesised that the glutamatergic cortical projection neurons, shown by the number 1, become overactive, due to a reduction in the activity of the GABA interneurons, shown by 2. This overactivity drives activation of the mesolimbic pathway, indicated by the number 3 in the figure, leading to high levels of dopamine in in the striatum and nucleus accumbens, indicated by the number 4, and the appearance of the positive symptoms of schizophrenia.

Therefore, imbalances in glutamate and GABA systems may also give rise to dopamine imbalance. This is supported, again, by evidence from studies with drugs that block N-methyl-D-aspartate receptors and thus lead to excess glutamate, such as ketamine, which causes the manifestation of positive symptoms in schizophrenia in healthy individuals and exacerbates positive symptoms in schizophrenia patients, providing clear evidence for the role of glutamate in schizophrenia symptomatology. Whilst this may explain the positive symptoms, how do alterations in glutamate explaining the negative symptoms of schizophrenia?

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Here we see, again, the glutamate-GABA-dopamine circuitry in the normal brain, on the left, in panel A, and the schizophrenia brain on the right, in panel B. How do alterations in neurotransmission in this circuit lead to the negative symptoms of schizophrenia? Here, a cortical glutamate neuron, a

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GABA interneuron and mesolimbic dopaminergic neurons interact in the same way as shown on the previous slide. In addition, we now highlight an additional synapse between GABA interneurons in the midbrain and dopaminergic neurons projecting back to the cortex, the mesocortical pathway.

Under normal conditions, these cells are all in equilibrium, such that sufficient dopamine reaches the cortex to allow normal social reward and cognitive functioning. In schizophrenia, we think that the overactive cortical projection neurons, following GABA deficiency in the cortex, leads to hyperactivation of GABA interneurons in the midbrain, which in turn block the activity and firing rate of dopaminergic mesocortical projections, which become inhibited and fire less. Thus, the mesocortical dopamine pathway becomes underactive and unable to supply adequate dopamine to the frontal cortex, leading to hypofrontality and the emergence of negative and cognitive symptoms.

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Here, then, we can see the complex polysynaptic nature of neurotransmitter actions in the brain functioning as part of large and complex neuronal circuits and ultimately networks, the activity in which defines behavioural outcomes. Whilst these are normally in balance, when neurotransmission becomes defective the outputs of these circuits and the information flow within them are fundamentally corrupted, leading to behavioural disturbances, as highlighted here, by example, in the positive and negative symptoms of schizophrenia, driven by alterations in dopamine, GABA, and glutamate neurotransmission, respectively.