Module:
Biological Foundations of Mental Health

Week 3
Synaptic transmission & neurotransmitter systems

Topic 3
Neurotransmission defects and mental health: Focus on schizophrenia – part 1 of 3

Dr Anthony Vernon
Lecturer in Neurobiology of Psychiatric and Neurodevelopmental disorders

Lecture transcript

Slide 4

Well hello, and welcome to this subtopic, which focuses on schizophrenia as an example of how neurotransmission deficits can cause mental health disorders. And the aim this subtopic is to give you an appreciation that defects in neurotransmission are associated with several mental health problems. You will do this mainly through looking at how impairment of dopamine signalling in the brain is implicated in schizophrenia. And you will also consider glutamate as a factor in schizophrenia.

Slide 5

In order to fully understand this subtopic, you first need to be familiar with the fundamentals of neurotransmission. Neurotransmission is a fundamental brain process by which information encoded in the form of an action potential is communicated from one neuron to another within a given anatomical pathway and ultimately a neuronal network. Electrical information is received at the pre-synaptic neuronal terminal, and this is converted to chemical information through electrically stimulated neurotransmitter release which is driven by calcium influx into the pre-synaptic terminal.

The released neurotransmitter then diffuses across the synaptic cleft and binds to an effector on the pre-synaptic membrane. This can either be a membrane-bound receptor protein or an enzyme and so on and so forth. The receptor becomes activated, which will activate second messenger pathways, for example, ionic flux, and depolarisation of the post-synaptic membrane. This converts the chemical information encoded by the neurotransmitter back into electrical information in the shape of action potentials, and in this way, information is propagated from one nerve cell to another.

Slide 6

So what happens when neurotransmission goes wrong? Neurotransmitters, as we have seen, are essential for the transfer of electrical information between neurons within a functional brain network. So it may be said that neurotransmitters modulates the flow and rate of information transfer within a network, effectively gating synaptic plasticity. As a consequence, this process is subject to very tight regulation at several levels. In terms of neurotransmitter release, it's controlled from the pre-synaptic terminal by autoreceptors. Neurotransmitter sites of action are subject to regulation-- for example, post-synaptic membrane receptors-- the number can be increased or decreased on the membrane.

The neurotransmitter itself may be degraded either in the synaptic cleft by an enzyme-- an example of which would be acetylcholine, by uptake into the pre-synaptic terminal-- for example, through a

Transcripts by 3Playmedia

transporter, or into surrounding glial cells. And finally, neurotransmitter synthesis and storage can be dynamically regulated by enzymes in the pre-synaptic terminal. And these multiple levels of regulation essentially ensure the correct fidelity of synaptic signalling. Ergo, when this equilibrium is altered, the final consequence is a disruption of the normal patterns of synaptic signalling. These will reverberate through neuronal networks, which ultimately manifests as a behavioural consequence.

Slide 7

We'll now move on to look at specific psychiatric disorder, schizophrenia, and how this is associated with neurotransmitters and deficits in neurotransmission. But to do that, first we need some basic facts about schizophrenia.

So what is schizophrenia? Schizophrenia is a severe psychiatric disorder characterised by major disturbances in thought, emotion, and behaviour.

How common is it? It is relatively common. Schizophrenia affects approximately 1% of the UK population.

When does it begin? The onset of schizophrenia is typically in late adolescence or in early adulthood.

How is it diagnosed? There is no diagnostic pathology for schizophrenia and diagnosis is currently based on clusters of symptoms. These are described as positive, negative, and cognitive, and we'll look at these in more detail in a moment.

How does schizophrenia relate to other psychiatric disorders? In common with other psychiatric disorders such as bipolar disorder or major depression, schizophrenia patients display cognitive impairments, but in contrast, schizophrenia is characterised by psychotic episodes consisting of both positive and negative symptoms. We will now consider these symptoms in more detail.

Slide 8

The symptoms of schizophrenia can be grouped into three classes as you've just heard-- positive, negative, cognitive. Positive symptoms are described as additional features that are not ordinarily present. These include delusions, hallucinations that maybe auditory or visual, and thought disorder. Delusions occur and 90% of patients and represent an idiosyncratic belief or impression which is maintained despite being contradicted by reality or rational argument-- for example, I'm being watched by an alien force.

Hallucinations are generally auditory-- for example, hearing voices-- and occur in 70% of patients. Patients may feel as though these voices come from the outside and they often think they're being criticised by them. Hallucinations may also, however, been visual or related to smell, taste, or touch.

Thought disorder may show up as disordered speech, including rapid changes of subject, the use of invented words, or in an appropriate emotional response to other people in a particular situation.

Negative symptoms in contrast refer to a loss or reduction in a normal function. Examples include-- alogia, the function of being reduced speech; affective flattening, which means a lack of emotional facial expression; avolition, meaning a diminished ability to begin and sustain an activity which is related to motivation; anhedonia, meaning you no longer find pleasure in something you used to enjoy; and asociality, meaning social withdrawal.

Cognitive symptoms refer to specific impairments in certain cognitive domains and affect the patient's general quality of life and ability to hold down a job. These include working memory, spatial memory, the ability to pay attention, and executive functions which may be defined as planning and decision making. The combination of these symptoms make it difficult for patients to interact with

other people and may severely affect their work depending on the severity of each domain.

Slide 9

Schizophrenia itself can take several courses over a patient's lifetime. The graphs on the slide show possible life courses following a diagnosis of schizophrenia. The x-axis represents time and the y-axis symptom severity. Patients may fall into one of at least four broad categories.

Number one, Group 1-- a single episode of psychosis which recovers with no lasting impairment, which corresponds to about 20% of the total number of schizophrenia patients. Group 2-- show repeated episodes of psychosis-- also referred to as relapse-remit-- with no lasting impairment, accounting for approximately 35% of patients. Group 3-- show repeated episodes of psychosis without full recovery to pre-symptomatic levels of functioning. The proportion is about 8%. In Group 4, the most serious, show repeated episodes of psychosis which increase in severity and are associated with no recovery to pre-symptomatic levels. This is about 35% of all cases on average.

Slide 10

What then are the causes of schizophrenia? Epidemiological studies clearly highlight the combination of environmental factors, but there is also evidence from genetic studies that suggest genetic risk is a serious component of schizophrenia risk. In reality, it is the interaction between these environmental factors and genetic factors that determine the clinical outcome in terms of symptom severity, long-term outcome, and the life course that we just heard about.

Some examples of environmental factors include obstetric complications; pre-term birth; hypoxia; exposure to infection or inflammation, either in utero or in early post-natal life; exposure to social stress, particularly during adolescence-- particularly childhood trauma is a common risk factor; and drug use, particularly addictive drugs such as cannabis, particularly during vulnerable periods of brain development have been associated with an increased risk of psychosis in the adulthood.

On the genetic side, schizophrenia is clearly highly heritable, but the genetics are complex and they break down into rare variants that have large effect and are highly penetrant. And examples of this include the DISC1 gene and deletions of the gene known as neurexin-1, although there are others. More common are variants of small effect, which together interact. And this is often referred to as the polygenic score, meaning the number of these small mutations that you have in your genome. And together, as we said at the beginning, it is the interaction of these environmental factors and the genetic risk factors that define the clinical outcome.

Transcripts by 3Playmedia