Module:
Biological Foundations of Mental Health

Week 3
Synaptic transmission & neurotransmitter systems

Topic 3
Neurotransmission defects and mental health: Focus on schizophrenia – part 2 of 3

Dr Anthony Vernon
Lecturer in Neurobiology of Psychiatric and Neurodevelopmental disorders

Lecture transcript

Slide 3

Having learned something about the basic clinical features of schizophrenia, we will now go on to consider how deficits in neurotransmission underpin the symptoms of this disease. In this section, we will focus on the role of dopamine, considering the evidence for the dopamine hypothesis of schizophrenia. To do this, we first need to know something about dopamine neurochemistry.

Slide 4

On the slide is a cartoon of a dopamine-releasing neuron, illustrating the uptake, synthesis, storage, release, and re-uptake of dopamine. This basic information is necessary to understand some of the evidence that we will discuss in later slides for the role of dopamine in schizophrenia.

Dopamine itself is synthesised from the amino acid tyrosine, which enters the neuron by active transport. In the cytoplasm of a dopaminergic neuron, defined as a neuron that primarily synthesises and releases dopamine, tyrosine is first converted to dihydroxyphenylalanine, or DOPA, by an enzyme called tyrosine hydroxylase. This is the rate-limiting step for dopamine synthesis and is a useful marker of how much dopamine a cell is producing, and by proxy, releasing. And this will be important later on.

DOPA is converted to dopamine by L-amino acid decarboxylase also known as DOPA decarboxylase, and actively transported into synaptic vesicles through vesicular monoamine transporter 2. Following release, dopamine binds to postsynaptic dopamine receptors, which are divided into D1 and D2 subtypes. And please refer to earlier lectures by John Robbins.

Dopamine can also bind to presynaptic auto receptors that inhibit further dopamine release. Dopamine in the synaptic cleft is inactivated by active transport back into the presynaptic terminal by the dopamine transporter, or DAT, where it is degraded or stored again in vesicles. Degradation of dopamine occurs presynaptically via an enzyme known as monoamine oxidase, but a small percentage may also be degraded postsynaptically by Catechol-O-Methyl Transferase, or COMT.

Slide 5

Now we have some idea of how dopamine is made in a dopaminergic neuron, we next need to explore the neuronal pathways in the brain that utilise dopamine as a neurotransmitter. Dopamine is used by dopaminergic neurons in three primary pathways in the human brain, as shown on the slide.

Transcripts by 3Playmedia

These are the nigrostriatal pathway, which is critical for the control of movement, and projects from the substantia nigra to the striatum. The mesolimbic and mesocortical pathways, which project from the ventral tegmental area to the nucleus accumbens, amygdala, hippocampus, to the mesolimbic pathway, and the prefrontal cortex, the mesocortical pathway. And this pathway involved in both limbic and cognitive functions, such as memory, motivation and emotional response, reward and desire, and addiction.

The third pathway is the tuberoinfundibular pathway, which projects from the A8 dopaminergic nucleus via the hypothalamus to the pituitary gland. This is involved in hormonal regulation and secretion of the hormone prolactin. The mesolimbic and mesocortical pathways, as you see from their function and their topographical projections, are, therefore, well placed to contribute to the symptoms of schizophrenia.

So how does this occur?

Slide 6

To understand this, we now must introduce the dopamine hypothesis of schizophrenia. The basic premise of the dopamine hypothesis is that an increase in dopaminergic neurotransmission in the mesolimbic pathway leads to abnormally high levels of dopamine in the nucleus accumbens and the striatum, which are thought to underlie the positive symptoms of schizophrenia, as we've already heard about, including hallucinations.

As you can see on the slide, in panel A, we can see the mesolimbic pathway in a normal individual projecting from the VTA to the nucleus accumbens. In panel B, this is what is happening in the schizophrenic patient. Now we can see that this projection is overactive and there is a much higher amount of dopamine in the nucleus accumbens as compared to the normal control.

In contrast, a decrease in dopamine transmission-- shown in the second image-- in the mesocortical pathway leads to lower levels than normal of dopamine in the prefrontal cortex, and this is thought to explain the negative and cognitive symptoms of schizophrenia. So again, in the diagram, in panel A, we can see the situation in the normal brain where there is a normal equilibrium of dopamine neurotransmission from the VTA to the prefrontal cortex. And in panel B, we see that this pathway is reduced and there is less dopamine in these areas, leading to negative and cognitive symptoms.

Slide 7

If we accept the dopamine hypothesis, we have to first understand the evidence underlying it. What is the evidence for the dopamine hypothesis? Primarily, this comes from clinical observations and experiments with dopamine-releasing drugs combined with Positron Emission Tomography, or PET, a neuroimaging method used commonly in humans, but is also possible to do in animals.

Clinical observations in the 1950s, doctors treating schizophrenia patients serendipitously observed that certain drugs, such as chlorpromazine, the target of which was unknown at the time, decreased the positive symptoms of schizophrenia. This suggested that understanding how chlorpromazine had this action could provide insights into the neurobiology of schizophrenia. These drugs were thereforafter referred to as anti-psychotic drugs.

In 1963, Carlsson and Lindquist subsequently showed that anti-psychotic drugs increased the amount of dopamine metabolites in the cerebral spinal fluid of schizophrenia patients. They hypothesised that this may be something to do with the brain compensating for the blockade of a dopamine receptor in the brain, although at this stage, dopamine receptors have not yet been identified.

Subsequently, in the late 1980s, early 1990s, and into the 2000s, experiments in healthy people using PET who were given amphetamine showed that when amphetamine is given, dopamine release is

stimulated, and these patients displayed positive symptoms of schizophrenia, including hallucinations. More importantly, when schizophrenia patients were given amphetamine, their symptoms became much worse. Clear evidence that increasing dopamine neurotransmission induces schizophrenia-like symptoms in otherwise healthy people and increases the severity of symptoms in patients already with a diagnosis of schizophrenia.

Taken together, these clinical observations and experimental medicine studies with amphetamine were the first key pieces of evidence that led to the development of the dopamine hypothesis.

Slide 8

Although it is clear that changes in the amount of dopamine could be related to the positive symptoms of schizophrenia, it was unclear where this might happen in the brain. So to understand this, we can use PET, as we discussed in the previous slide, to look at how much dopamine is present in specific parts of the brain.

PET is a technique that allows the visualisation of specific proteins, such as an enzyme or neurotransmitter receptor with very high sensitivity, by combining a specific molecule that binds to these proteins with a radiolabel.

Figure A shows the cartoon of the dopamine neuron you saw earlier. To visualise dopamine production in the brain, we can use a radiolabeled analogue of dopamine, 18 fluorodopa, to visualise dopamine synthesis and storage pathways in a living person, because the synapse treats this as if it were normal dopamine.

18 fluorodopa is taken up into the presynaptic terminals, where it is metabolised by DOPA decarboxylase This can provide a proxy measure of the rate of dopamine synthesis, otherwise referred to as dopamine synthesis capacity, which we would expect to be higher if there is an increased rate of dopamine release in the patient we're studying.

An example of the image this generates is shown in figure B. The areas of high signal intensity, red to green, are the caudate and putamen, which contain the highest density of dopaminergic terminals.

Patients with schizophrenia have been repeatedly imaged using 18 fluorodopa PET and compared to healthy controls who do not have schizophrenia, or any other psychiatric disorder. These experiments show that schizophrenia patients, the red dots in the graph where each patient is represented by a dot, have a higher uptake value given by the rate constant KI on the y-axis of 18 F-DOPA in the striatum compared to the healthy controls indicated by the blue dots.

This increase in dopamine synthesis capacity correlates positively with the severity of patient positive symptoms. Several studies greater than 50 to date have replicated these findings in different groups of schizophrenia patients around the world, and this provides the most robust evidence of dopamine dysfunction in schizophrenia localised to the mesolimbic pathway.

Slide 9

Further evidence for the dopamine hypothesis comes from studies of anti-psychotic drugs and their binding to dopamine D2 receptors. As we've already heard, the finding that drugs like chlorpromazine block the positive symptoms of schizophrenia were serendipitous, but led to the coining of the term anti-psychotic drugs. The role of dopamine in schizophrenia was therefore strengthened by the identification of dopamine receptors in the brain, and the subsequent finding that all anti-psychotic drugs bind the dopamine D2 receptor.

Indeed, the efficacy of anti-psychotics, measured as a daily dose required for the treatment of positive symptoms of schizophrenia, is closely correlated to the potency or affinity with which a

particular anti-psychotic binds to the dopamine D2 receptor, as shown in figure A.

An exception to this, however, is clozapine, which has a low affinity for the D2 receptor, but is one of the most effective anti-psychotic drugs. The reason for this is currently unclear, but clozapine and other anti-psychotics do bind to a number of other neurotransmitter receptors in the brain. This tells us that changes in dopamine neurotransmission might not be the whole story behind the symptoms of schizophrenia, which we will revisit later in this topic.

Slide 10

Nevertheless, subsequent PET studies found that a specific percentage of dopamine D2 receptors must be blocked to achieve a good clinical response, defined as a reduction of positive symptoms. These studies suggest that 60% to 80% of dopamine D2 receptors must be blocked for the maximum therapeutic effect. This is shown in figure B.

Here on the x-axis is the percentage of occupied or blocked D2 receptors following anti-psychotic dosing. On the y-axis is the clinical improvement in positive symptoms from none to significant improvement. It can be seen clearly that as the percentage of dopamine D2 receptors blocked increases to the critical window, more patients, indicated by the green dots, show recovery of their symptoms.

We should note, however, that once the threshold of 80% dopamine D2 blockade is crossed, patients' positive symptoms may improve, but they begin to suffer side effects, as shown by the red dots. These are described as extrapyramidal symptoms and include dyskinesia and other movement disorders, such as akathisia. These reflect the action of anti-psychotics on dopamine D2 receptors in other dopamine pathways, such as the nigrostriatal pathway, which are responsible for the control movement.

This represents an elegant description of a drug therapeutic window, defined as the range of doses in which positive effects are seen without adverse side effects. As we can see, for anti-psychotics, this window is quite narrow, suggesting care must be taken in dosing.

Slide 11

If the dopamine hypothesis is correct, we might ask where the excess dopamine activity comes from. It might be that the patient produces too much dopamine, doesn't metabolise excess dopamine quickly enough, or has D2 receptors that have been modified so they respond differently to dopamine binding, principally being more sensitive to dopamine.

So how could this come about? The stress diathesis model was developed to explain this excess of dopamine in the schizophrenic brain. It suggests that an individual inherits several genes that encode for abnormal proteins, leading defective dopamine function in the mesolimbic pathway, rendering the pathway hyperactive and leading to the positive symptoms.

So what is the evidence for this model? The dopamine D2 receptor is one of the more significant hits in large scale studies of the genetics of schizophrenia. This genetic risk is paired with environmental stresses which further modify dopamine release. For example, stress during adolescence. Perhaps together, these can be enough to create the symptoms leading to a diagnosis of schizophrenia.

However, we must also consider what evidence does not support the dopamine hypothesis model, and here, it is important to realise that a significant proportion of schizophrenia patients do not respond to anti-psychotic drugs, and their positive symptoms do not improve. This might suggest that dopamine hyperactivity is only one of the causes of the onset of schizophrenia. But is there any evidence for this?

Transcripts by 3Playmedia

Slide 12

Reading slide (no audio)

Slide 13

Here, we consider this possibility by looking at levels of dopamine and response to anti-psychotic treatment to understand whether there may be subtypes of schizophrenia. As we have just discussed, in about 30% of cases, the positive symptoms of schizophrenia patients do not improve following treatment with anti-psychotic drugs. If this continues, despite switching drugs or changing the dose, these patients may be described as treatment-resistant. This is a very difficult clinical problem, as essentially, there are no effective treatments for these individuals.

One explanation for treatment resistance could be that the patients do not have the same abnormalities of dopamine neurotransmission as those who respond conventionally to anti-psychotic drugs. But is there any evidence to support this?

Using 18 fluoro PET scans, as we discussed earlier, recent studies have revealed that this may be the case. The graph in A on the slide shows that people who respond to treatment have an increased capacity to produce dopamine. In other words, a higher dopamine synthesis capacity in the striatum, as shown by the red dots. And these are referred to as treatment responders.

In contrast, people who are described as resistant to anti-psychotic treatment do not show an elevation in this dopamine synthesis capacity and are indistinguishable from healthy controls.

Studies in the same individuals using a different neuroimaging technique called Magnetic Resonance Spectroscopy have found that patients who respond to anti-psychotics have normal levels of glutamate in the frontal cortex, whereas patients who are resistant have higher amounts of cortical glutamate as compared to healthy controls and treatment responders. These data confirm that treatment-resistant patients may not have an abnormality in dopamine synthesis capacity, but may have defective glutamate neurotransmission instead. This suggests that other neurotransmitters, particularly glutamate, are important for schizophrenia symptoms, not just dopamine.

Clearly, there are also implications for the treatment of schizophrenia, and it is critical to be able to identify individuals who will or will not respond to anti-psychotic medication early such that other alternative drugs may be tried, including glutamatergic drugs that are currently in development.

Slide 14

The dopamine and glutamate evidence that you've looked at is the first biological in vivo data that demonstrates that there may be at least two subtypes of schizophrenia-- one based on dopamine and one that does not seem to involve the dopamine system. Although these data require replication in a larger cohort, they confirm what has been long suspected, that the symptoms of schizophrenia cannot solely be explained by the dopamine hypothesis.

Clinical evidence would support this, suggesting anti-psychotic drugs do not effectively treat the negative symptoms of schizophrenia. Therefore, there clearly are other transmitter systems involved, and in the next section, we will focus on a similarly influential theory of schizophrenia, the glutamate hypothesis.