Module:
Biological Foundations of Mental Health

Week 3
Synaptic transmission and neurotransmitter systems

Topic 2:
Neurotransmitters, receptors and pathways – Part 1 of 4

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Lecture transcript

Slide 3

Slide 4:
Hello, my name's Jon Robbins. I'm a neuroscientist at King's College London. This Subtopic 2 is going to be on neurotransmitter systems. And you will have learned already that the neurons interact with each other by releasing neurotransmitters. You will have already heard about the synapse, in Subtopic 1, where this occurs.

I have simplified this system into something I call the 2S, 3R, 2D system. The first 'S' stands for 'synthesis', the second – 'storage'. The first 'R' is 'release', the second – 'receptors', the third – 're-uptake'. For 'D' – 'D' stands for 'degradation' and the final 'D' stands for 'drugs' that are targeted on the system and 'diseases' that involve it.

Slide 5:
The synapse, as you already know, is made up of two sections – the presynaptic terminal and the postsynaptic region. In between is the synaptic cleft. Synthesis occurs in the presynaptic terminal, along with storage, and re-uptake, and degradation. The neurotransmitter is released into the synaptic cleft and can work on a number of receptors which can be found both postsynaptically and presynaptically.

Slide 6:
The first neurotransmitter I'm going to talk about is a very important one – it's called 'glutamate' or 'glutamic acid'. It's an amino acid widely distributed in the central nervous system and it occurs at about 70 per cent of all synapses. There's very little glutamate in the peripheral nervous system. Indeed, glutamate is the most important excitatory neurotransmitter in the central nervous system.

Slide 7:
The first 'S' in my system is 'synthesis'. So, this is how the neurotransmitter is manufactured, as required in the neuron. In fact, for glutamate, the synthesis occurs in two sorts of cells – on the left, in glial cells, and on the right, in a neuron. In glial cells, oxoglutarate is converted into glutamate by GABA transaminase. And on the right, in neurons, glutamine is turned into glutamate by glutaminase.

Slide 8:
The manufactured glutamate is stored in organelles called vesicles. The method by which glutamate gets into these vesicles is by a special protein, called a 'transporter'. And this is particularly called a vesicular glutamate transporter. There are at least three types of vesicular glutamate transporter known and they all have this function of pumping glutamate into the vesicle. To get the glutamate in, hydrogen ions are pumped out. And this allows a concentration of glutamate in the vesicle to reach quite high concentrations – up to 20 millimolar. The high level of hydrogen ions found in vesicles that make them acidic and is used to pump in the glutamate is produced by a proton pump, which converts the energy of ATP into the higher concentration of hydrogen ions in the vesicle, which can then be exchanged for neurotransmitter. So, that is our storage part.

Slide 9:
Neurotransmitters, as you already know, are released by the nerve terminal at the axon terminal bouton. And these are released in a calcium dependent process. Calcium is required to both move and fuse the vesicles with the membrane to allow the neurotransmitter into the synaptic cleft.

Slide 10:
Once in the synaptic cleft, the neurotransmitter – in this case, glutamate – can act on the receptors. Glutamate has two major families of receptors – one family called 'ionotropic glutamate receptor', or 'iGluR's, and these are ion channels activated by glutamate. Pharmacologically, they could be subdivided into NMDA, AMPA, and kainate types. They're all cation channels. And, mostly, they allow in sodium and out a little bit of potassium. However, the NMDA type cation channel also allows in significant quantities of calcium ions, which will be important later on in the module.

Conversely, there's another group of receptors that glutamate can act on and that's the 'metabotropic glutamate receptors', or 'mGluR's. These are G-protein coupled receptors in the class 'C'. Again, these can be subdivided into 'Group One', 'Group Two' and 'Group Three'. Group One contains the mGluR 'one' and 'five'. And these couple to particular G-proteins called 'Gq' and 'G11'. Group Two include metabotropic glutamate receptors 'two' and 'three'. And these couple to different G-proteins, 'Go' and 'Gi'. And then the final group – Group Three – include the metabotropic glutamate receptor 'four' and numbers 'six' to 'eight'. And these, again, all couple to the G-proteins, 'Go' and 'Gi'.

Slide 11:
Once the neurotransmitter is released and acted on its receptors, then it can be re-uptaken back either into the neuron – as it shows on the left of this slide – or, indeed, back into glia – in this case, astrocytes, on the right hand of the slide. As we know, glutamate released into the synaptic cleft, can then diffuse. There are special transporters – proteins – that specifically take up glutamate back into the neuron. And they're known as excitatory amino acid transporters. And they can return the glutamate back into the presynaptic terminal of the neuron, where it can be repackaged into vesicles and reused.

Conversely, it can be taken up by the glial cells – in this case, astrocytes – and, here, it's converted into glutamine by glutamine synthase. The glutamine can then be transported out of the astrocyte and into the

neuron by the glutamine transporter, 'GlnT'. And that can then be synthesised back into glutamate by glutaminase. So, you can see there's quite a complex process of removing glutamate from the synaptic cleft and recycling it.

Slide 12:
So, the first 'D' is 'degradation'. Glutamate is quickly removed from synaptic cleft by the excitatory amino acid transporters and recycled. In astrocytes, it's converted to glutamine by glutamine synthase. And the glutamine is transferred back to the neuron, where it's converted back to glutamate by glutaminase. And again, this can be reused.

Slide 13:
The final 'D' covers two areas for this particular neurotransmitter. It indicates, firstly, the 'drugs' that act at this synapse. And these are examples for glutamate, shown on this slide. The receptors at which these drugs react are the NMDA receptor and the classic example of a drug that does this is 'ketamine'. This is a dissociative anaesthetic and a channel blocker at this receptor. 'Memantine' is a competitive antagonist at this receptor. And, furthermore, another recently discovered and approved drug that acts on AMPA receptors is 'perampanel'. And that's a competitive antagonist. So, you can see- you can map the drugs that act on the synapse to this system.

Slide 14:
The second subset 'D' here is the 'disease'. And, first of all, we know that some diseases are caused by the recreational uses of drugs – drug addiction and dependency. And that's what I've put under recreational drugs, in the top left part of this slide. Some famous drugs, such as PCP and ketamine, are used as recreational drugs that act on the glutamate system in the brain. There are also some diseases particularly associated with a glutamatergic system. And that is epilepsy, because the control of the excitability of the brain is partly under the control of the glutamate system. In terms of function, glutamate is critical to pretty much all CNS functions.

Slide 15:
Once we have gone through all the particulars for that neurotransmitter, we can produce something called a 'fact sheet'. And this is shown on the slide now. Notice the neurotransmitter is glutamate – so that's what we've just done.

And down on the left-hand side, I've given the individual letters – 'S', 'S', 'R', 'R', 'R' and 'D'. And against these, you can put in the specific enzymes, ion channels, receptors etc that are associated with each part for this neurotransmitter.

And on the right-hand side, you can indicate any drugs that you know of that act at these particular places. And you can subset the drugs, if you like, as I've done here. I've indicated, in green, drugs that are clinically used today.

So, for glutamate, the first 'S' is glutaminase. And that's one of the important enzymes that make it. The second 'S' – 'storage' – we know the storage is vesicular.

The first 'R' is calcium dependent release at the terminal, so that's release. And then the receptors we know about for glutamate are split into two major families – ionotropic, which include NMDA, AMPA and kainate, and then the eight subtypes of metabotropic glutamate receptors, which are G-protein coupled. Reuptake is by the excitatory amino acid transporter – EAAT. And degradation is by glutamine synthase.

On the right, I've indicated two drugs which are clinically useful – ketamine is used, as I said, as a dissociative anaesthetic and perampanel, which is used in some forms of CNS disorders.