Module:
Biological Foundations of Mental Health

Week 3
Synaptic transmission and neurotransmitter systems

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

Dr Jon Robbins
Reader in Neuroscience, Wolfson Centre for Age Related Diseases, King's College London

Slide 4:
My last neurotransmitter today is '5-HT' or '5-Hydroxytryptamine'. It's also called 'serotonin' and it's another monoamine or, indeed, it's, more specifically, an indolamine. Like dopamine, it has a very restricted distribution. As you can see, there's one major nucleus that contains the cell bodies of these neurons, which is the 'raphe'. And these project almost to everywhere in the brain. So, the cell bodies are all located in one part of the brain, but the projections go all over the brain. It's also found in quite high concentrations in the enteric nervous system, but we won't be discussing that now.

Slide 5:
As with dopamine, there are three steps to its synthesis. You've got 'tryptophan' taken into the diet. 'Tryptophan hydroxylase' is the rate limiting enzyme which converts it to 5-Hydroxytryptophan. 'DOPA decarboxylase' then finally converts it to the 5-HT, which is the active neurotransmitter.

Slide 6:
The second 'S' – storage. Again, a very similar picture to the one we saw before. We've got the same transporters – 'VMAT1' and 'VMAT2' – which transport 5-HT into the vesicles, again requiring hydrogen ions to be pumped out in exchange.

Slide 7:
The release is calcium dependent, mainly on the axon terminal bouton but, interestingly, it can be co-released with other neuropeptides, such as 'somatostatin' or 'substance P'.

Slide 8:
Receptors fall into the two classifications, as before. You have the ligand-gated ionotropic receptor, which is the '5-HT_3' receptor, and that's the only example of a 5-HT receptor that is a ligand-gated ion channel. This is a mixed cation channel, so it allows sodium and calcium into the cell and a little bit of potassium out.

The big list of G-protein coupled receptors, which are shown here, indicate a list of at least six families – '1', '2', '4', '5', '6' and '7'. And these are subdivided by what G-proteins that they couple to, as we saw before. So, for example, the '5-HT1' receptor family are mainly coupled to the G-proteins 'Gi' and 'Go' and, more than likely, found on the presynaptic nerve terminal. Whereas, the '5-HT2' family couples to a different set of G-proteins – 'Gq' and 'G11' – which are usually postsynaptic. I will point out that the '5-HT5B' receptor, although found active in animals, is a pseudogene in humans – so it does not actually get expressed.

Slide 9:
Reuptake – again, as before, diffusion of the 5-HT away from the synaptic cleft leads to its re-uptake by a particular protein called the 'serotonin transporter' or 'SERT', for short. Again, chloride and two sodium ions are co-transported with it to get it back into the presynaptic terminal.

Slide 10:
Degradation – the first 'D'. 5-HT is converted by monoamine oxidase into '5-hydroxyindolealdehyde'. And then the second enzyme, 'aldehyde hydrogenase', converts it into '5-HIAA', which is the common metabolite that monitors 5-HT.

Slide 11:
Then we come to drugs and disease. Important drugs – 'L-tryptophan' is an important precursor for the synthesis of 5-HT. It's often used as a drug in depression. An example of a drug that works on the receptors for 5-HT is 'sumatriptan', which is used for migraine treatment. There are also competitive antagonists, such as 'ondansetron' and 'ketanserin'. Reuptake of 5-HT can be blocked very specifically by 'citalopram', which is a serotonin selective re-uptake inhibitor used for depression, as is 'imipramine' and the monoamine oxidase inhibitor, 'phenelzine'. You'll hear more about these drugs as the module and course goes on.

Slide 12:
5-HT has quite a large list of recreational drugs: amphetamines and its derivatives – particularly MDMA (or ecstasy, as it's commonly known); LSD, a very famous one, works on this system and so does 'mescaline' and 'psilocybin'. And psilocybin comes from magic mushrooms. Important diseases associated with 5-HT are depression, anxiety and hallucinations. As you can see, a number of the recreational drugs can produce those effects. So, therefore, 5-HT is probably important in mood, the sleep/wake cycle and appetite.

Slide 13:
Now we go to the fact sheet for 5-HT or serotonin. Again, down the left-hand side, as before, are the six letters. And I fill in, here, the particular important bits, which include 'tryptophan hydroxylase' as the synthetic enzyme, 'vesicular' storage, 'calcium dependent' release at the 'terminal'. And then we have examples of the receptors that it works on, the re-uptake system 'serotonin transporter', and the important enzymes involved in its degradation – 'monoamine oxidase' and 'COMT'.

On the right-hand side, we see a list of drugs which 'L-tryptophan' is used clinically, so is 'ondansetron' and 'sumatriptan'. And, again, we can identify which drugs are clinically used by colouring them green, whereas the others are useful compounds for studying the 5-HT system and maybe not used in humans.

Slide 16:
So, I've just given you four important neurotransmitters in the brain, but they're only four of the 30 you may come across. I've given you a list, here, of others that are important and you are likely to come across in this

course, including ‘acetylcholine’, ‘ATP’ – ‘adenosine triphosphate’ – ‘bradykinin’, ‘glycine’, ‘histamine’, a whole range of neuropeptides – a couple of which I’ve already mentioned – ‘nitric oxide’ and ‘noradrenaline’.

What I would suggest, as you go through the course, is make your own fact sheets as you find out about these neurotransmitters. And this will really help you build up your knowledge and get you a good understanding of the important roles of these molecules in the central nervous system.