Module:
Biological Foundations of Mental Health

Week 3
Synaptic transmission and neurotransmitter systems

Topic 2:
Neurotransmitters, receptors and pathways – Part 3 of 4

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Slide 4:
Now we come on to my third example neurotransmitter – 'dopamine'. This is a monoamine. And you can see it's located in specific areas in the central nervous system. It has a more restricted distribution. For example, important pathways – the nigrostriatal pathway is dopaminergic and this one is particularly associated with Parkinson's disease; the mesocortical pathway is also dopaminergic and that is associated with schizophrenia. So, you can see the distribution of cells that release dopamine are much more restricted than you see for glutamate and for GABA.

Slide 5:
My first S for this neurotransmitter is synthesis again. And this is a three step process where tyrosine is taken in by the diet and the rate limiting enzyme that converts this to DOPA is tyrosine hydroxylase. DOPA is converted to dopamine by dopamine decarboxylase.

Slide 6:
Storage, as before, occurs in vesicles. And these vesicles are very acidic, as before, because they also have the proton pump. And there are two types of vesicular monoamine transporters, called 'VMAT1' and 'VMAT2'. And these can be cell type specific. Some dopaminergic neurons have one and, some, two. So, you can see this is a consistent event occurring commonly with many neurotransmitters.

Slide 7:
Dopamine is released. And, here, there's some variation. It is calcium dependent, as normal. It occurs at the end terminal, as normal. But you also get a release that's called 'en passant'. And that's where you have small release sites that occur all the way down the axon, as shown on this slide. And these varicosities can release dopamine all the way down, as the axon travels through tissue, as well as dopamine being released at the terminal end, as normal.

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Slide 8:
Dopamine receptors all of one type. They're all G-protein coupled – or 'metabotropic' – class type. There are no ligand-gated ion channels for dopamine. They can be, again, subdivided into 'D1-like' and 'D2-like'. The 'D1-like' family are 'D1' and 'D5'. And they're coupled to their G-protein, 'Gs'. Whereas the 'D2-like' family, include 'D2', 'D3', and 'D4'. And they're coupled to G-proteins – 'Gi' and 'Go'.

Slide 9:
Like before, once released, dopamine can be re-uptaken back into the neuron. And that's by something called 'DAT' – 'dopamine active transporter'. And that's co-transported with one chloride ion and two sodium ions.

Slide 10:
The degradative pathway, the first D, is complicated. Dopamine can be degradated through a lot of steps to reach the common, final product, which is usually homovanillic acid.

As you can see from this slide, you can go straight down-- where dopamine is first converted by monoamine oxidase-- and then an intermediate is converted into dihydroxyphenylacetic acid by catechol-O-methyltransferase.

Conversely, dopamine can be converted by catechol-O-methyltransferase into three 3-methoxydopamine and then, by MAO, down to homovanillic acid. So there are a number of biochemical pathways that can lead to the breakdown of dopamine.

Slide 11:
For our drugs and disease section, an important drug, 'levodopa', used to treat Parkinson's disease is a precursor for dopamine and, therefore, increases the amount of dopamine in peoples' brains who have lost a component of it. A number of important drugs work on the storage of dopamine. And these work by blocking the vesicular transporter. And these drugs are 'reserpine' and 'methamphetamine'.

Drugs that interfere with release – 'amantadine' is a good example. And then some of the drugs that work on the receptors – full agonists – include dopamine itself, a compound called 'apomorphine' and 'bromocriptine'. Competitive antagonists which are clinically used – 'haloperidol' and 'chlorpromazine' are also available. Reuptake of dopamine – a number of drugs work here – cocaine, for one, 'bupropion' and 'methylphenidate' – which is also called 'Ritalin' – work at this point.

And then there are a number of important drugs that interfere with the degradation of dopamine – the monoamine oxidase inhibitors, 'phenelzine' and 'selegiline', and the COMT inhibitors, 'entacapone' and 'tolcapone'.

Slide 12:
Then we can talk a bit about the recreational drugs that interfere with the dopaminergic system and there are some very famous, or infamous, ones here – cocaine, amphetamines and a rather unusual compound called 'bromocriptine', which can be found in the fungal contamination of grain and adds an important historical contribution to some of the psychosis that occurred when abnormal fungal were growing on the wheat used to make bread in the Middle Ages.

The famous disease association with dopamine is Parkinson's disease, but also schizophrenia – as you'll find out later in the modules – also hormonal disturbances and drug dependence all involve the dopamine neurotransmitter system. What's its role in the brain? Well, it's possibly involved with reward systems, it's

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certainly involved in motor control and it possibly has an important role in thought processes and definitely in pituitary control of hormones.

Slide 13:
The fact sheet, as before – we've got our six letters down the left-hand side. And, for dopamine, the synthetic enzyme is 'tyrosine hydroxylase'. The storage is by 'vesicular process'.

Again, we've got 'calcium dependent terminal' and, this time, 'en passant' release. Dopamine receptors, all G-protein coupled receptors of five subtypes. The re-uptake protein is called 'DAT'. And there are a number of enzymes involved in its degradation – 'monoamine oxidase' and 'catechol-O-methyltransferase'.

Many more drugs of clinical use are identified here – 'L-DOPA', which affects syntheses, 'amantadine', which can cause neurotransmitter release. And then a number of drugs, such as 'apomorphine', 'haloperidol' and 'chlorpromazine' – some of which are used for schizophrenia treatment. I've already indicated that 'methylphenidate' is used for some mental problems. And then there are some compounds that are used as adjuncts with L-DOPA and can be used to help treat Parkinson's disease.

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