Module:
Biological Foundations of Mental Health

Week 3
Synaptic transmission and neurotransmitter systems

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

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Slide 4:
The next neurotransmitter I'm going to talk about is another important one. It's called 'gamma aminobutyric acid'. That's rather a mouthful, so we'll usually call it 'GABA'. Again, it's an amino acid. It's widely distributed in the central nervous system and it's at about 30 per cent of the synapses in the brain. There's very little in the peripheral nervous system and this is probably the most important inhibitory neurotransmitter in the central nervous system.

Slide 5:
GABA is synthesised from glutamate – which is the first 'S' – by an enzyme called 'glutamic acid decarboxylase'. So, its synthesis is relatively straightforward.

Slide 6:
It is stored, like glutamate, in vesicles, but the transporter that moves it into these vesicles is called 'vesicular GABA transporter', or 'vGABAT'. Again, the vesicles also have a proton pump that fill them up with hydrogen ions which they use to exchange for the GABA neurotransmitter. And this is a common occurrence for vesicles. So, that's the second 'S' – storage.

Slide 7:
The first 'R' is release. And, again, this will be a common occurrence. Again, it's a calcium dependent vesicular release for GABA and this mainly occurs at the axon end terminal bouton.

Slide 8:
Receptors, once again, can be subdivided into two major classes. The ionotropic receptors, which are called the 'GABA-A' receptor, which is actually, in this case, an ion channel for chloride ions rather than the sodium and calcium. So, it allows negative ions into the cells. The metabotropic glutamate receptors associated with GABA are the 'GABA-B' receptors and they are coupled to the G-proteins, 'Gi' and 'Go'.

Slide 9:
Like glutamate, GABA is released into the synaptic cleft. Once it's done its job of binding to the receptors, it can then be transported back, once again, into neurons and into glial cells – particularly astrocytes. The transporter protein that moves it into neurons is called the 'GAT1' or the 'Neuronal GABA Transporter'. And the one that transports it into glia is appropriately named the 'Glial GABA transporter', 'GAT3'.

Slide 10:
Degradation occurs by an important enzyme called 'GABA transaminase'. And this occurs mostly in glial cells, such as astrocytes. a-Oxoglutarate is converted to glutamate and, at the same time, GABA is converted to an inactive compound called 'succinic semialdehyde'.

Slide 11:
Finally, we talk about subset 'D', the last one, which includes drugs. And, here, I've shown drugs under the terms of receptors. And some famous drugs – that are used not clinically, necessarily – that act on the GABA A receptor are 'muscimol', which is an agonist and activates the receptor, 'bicuculine', which is a competitive antagonist, and 'picrotoxin', which is a GABA receptor channel blocker. Some of the clinically useful drugs that act on the GABA A receptor are the benzodiazepines, ethanol and many general anaesthetics – as these are all positive allosteric modulators of the GABA A receptor.

For the GABA B receptor, 'baclofen' is an agonist and 'saclofen' is a competitive antagonist. Good examples of drugs that interfere with GABA re-uptake is 'tiagabine', which blocks GAT or the GABA transporter. And another drug, which is 'vigabatrin', blocks the important enzyme, GABA transaminase. So, there's a number of places where you can interfere with the GABA synaptic transmission.

Slide 12:
The last 'D', here, is disease. I've indicated some recreational drugs – of which barbiturates are a good example – that act on GABA A receptors. The diseases you might be expected to find associated with GABA are epilepsy, anxiety, and insomnia. GABA has a major function in the central nervous system particularly associated with inhibitory actions of the brain.

Slide 13:
I'll now move onto my fact sheet for GABA. Again, it's in the same style as I've shown you before. Down the left are the six letters and what I've identified is the important aspect for each of these for GABA.

So, the synthetic enzyme is 'GAD', the storage is 'vesicular', the release is 'calcium dependent at the terminal', and the receptors can be subdivided into 'ionotropic GABA A receptors' and 'metabotropic GABA B receptors'. Reuptake is by GABA transporter and degradation is by the enzyme 'GABA transaminase'.

On the right, clinically used drugs indicated in green are 'muscimol' and 'bicuculline' – for the GABA A receptor – and the clinically used drugs that act here are benzodiazepines and anaesthetics. For the GABA B receptor, 'baclofen' is used clinically and 'saclofen' is a synthetic compound that is used for investigation action of receptors. As I previously mentioned, 'tiagabine' blocks the GABA transporter and 'vigabatrine' blocks the enzyme that breaks down GABA. So, these drugs are used clinically.