a closer look – how anti-epileptic drugs work

Our ‘a closer look’ series of factsheets looks at some subjects in greater technical detail. Here we look at anti-epileptic drugs (AEDs) – how they work, what they do, and what they don’t do.

For most people with epilepsy, treatment for their seizures includes anti-epileptic drugs (AEDs). But what do these drugs do?

**what they do and what they don’t do**

AEDs do not cure epilepsy or treat the reason why epilepsy has started. They are taken to try and stop the symptoms of epilepsy – the seizures. They aim to stop seizures from happening. Except for emergency medication, most AEDs do not stop a seizure once it has started.

**how AEDs get to the brain**

To work, drugs need to get from where you take them to where they start to work. They need a route to get there and then they need a waste-removal system to get rid of them afterwards.

**The route of administration**

There are various ways medications are taken – by mouth, by injection (into the vein, muscle, or just under the skin), or by suppository (into the bottom). AEDs are usually taken orally (by mouth), and in the form of tablets, capsules, liquids, and syrups.

**Absorption in the stomach**

Once swallowed, AEDs go to the stomach. Digestive juices in the stomach help to break down food and, in this case, the tablets containing the medication.

The tablets break down, releasing the medication which can then pass through the wall of the gut into the bloodstream (absorption), and be distributed around the body. The quicker the medicine gets into the bloodstream the quicker it can get to work. Once the medication is absorbed, it can act and do the job it is supposed to. Once in the bloodstream, AEDs are carried to the site of action: in this case, the brain.

How well and quickly the drugs get to their site of action depends on how well the part of the body is supplied with blood, and how easily the drug gets from the blood stream into the part of the body.

Although the brain has a good supply of blood, there is a barrier between the blood and the brain that helps protect the brain from infections and toxic chemicals. This means that drugs do not pass easily into the brain.

Once drugs have played their active role, they start to break down (metabolise) so that they can be excreted from the body (passed out through the digestive tract, like food and drink, or in the urine). How long before AEDs start to be metabolised varies from one to another and is referred to as their half-life.

To be excreted in the urine, AEDs have to be broken down so that they can dissolve in water, and then the kidneys can get rid of them. Some AEDs become inactive when they are metabolised. Most AEDs are metabolised in the liver (hepatic metabolism) where they are changed into water-soluble metabolites with the help of different enzymes. Some AEDs – gabapentin, vigabatrin, levetiracetam, and pregabalin are not metabolised, not affected by hepatic enzymes, and they are excreted in the same form in the urine.

**how AEDs stop seizures**

AEDs make the brain less likely to have seizures by altering and reducing the excessive electrical activity (or excitability) of the neurones that normally cause a seizure. Different AEDs work in different ways and have different effects on the brain. How exactly some AEDs work is still not fully understood.

**targets in the brain**

There are several different ways in which AEDs stop seizures happening, by working on particular targets in the brain. AEDs may affect the neurotransmitters responsible for sending messages, or attach themselves to the surface of neurones and alter the activity of the cell by changing how ions (chemicals found in the body that have an electrical charge) flow into and out of the neurones.

See our factsheet a closer look – neurones

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We will look at four targets (although there are others):
- sodium ion channels;
- calcium ion channels;
- the GABA system and receptor agonists; and
- glutamate receptor antagonists.

**Sodium ion channels**

Sodium channels are the parts of the neurone that affect how electrical signals or messages are passed along the length of a neurone. ‘Action potentials’ are events that cause the cell membrane of the neurone to depolarize and repolarize (when the balance of ions inside and outside the neurone changes, which causes the electrical charge of the neurone to change). This is because they change the amount of ions inside and outside the cell, which then changes the electrical charge of the cell. This is how messages travel along a neurone. Sodium channels affect how ‘excitable’ neurones are and how easily messages are sent from one brain cell to another.

Some AEDs (such as phenytoin, lamotrigine, and carbamazepine) work by affecting the sodium channels of neurones. AEDs that bind or attach themselves to the sodium channels affect how ions flow through the channels, and stop the channel becoming activated or creating an action potential. This slows down how fast and how well the sodium channels work, which effectively stops the neurone from sending repeated messages.

**Calcium ion channels**

Calcium ions, like sodium ions, are involved in sending electrical messages through the brain. Calcium channels are particularly involved with sending a message from one neurone to another, by affecting the release of neurotransmitters (chemicals that help to send messages from one neurone to another) across the synapse where two neurones meet, and by affecting the movement of calcium ions in the receiving neurone. AEDs that target calcium channels (such as zonisamide and topiramate) work by blocking the calcium channels. This prevents messages being sent across the synapse from one neurone to another either by stopping the release of neurotransmitters, or by preventing calcium entering the second neurone.

One particular type of calcium channel, called the T-type channel, is involved in keeping the normal rhythm of brain activity. This channel is also involved in the specific brain activity that happens in absence seizures.

AEDs that specifically target, and block, the T-type calcium channel (such as ethosuximide), work specifically on reducing absence seizures.

**GABA system and receptor agonists**

GABA (gamma amino butyric acid) is a type of inhibitory neurotransmitter in the brain, which effectively stops brain messages from continuing to be sent (switches messages off). GABA helps chloride ions pass into neurones, which affects the resting membrane potential of the cell and makes it difficult for the neurone to send messages. AEDs that work on the GABA system and its receptors are agonists (a substance that helps another substance to work better), and effectively increase the movement of chloride into cells, and increase the ‘switching off’ of messages.

AEDs such as gabapentin work by increasing the production of GABA, and sodium valproate and vigabatrin work by decreasing the breakdown of GABA, both of which result in an increased amount of GABA. AEDs such as benzodiazepines (including clonazepam and clobazam) increase how often GABA receptors open. Barbiturates (such as phenobarbitone) increase how long the receptors are open for, again affecting the release and movement of GABA. Increasing the making of GABA, reducing its breakdown, and increasing its movement, all result in increasing its inhibitory effect (more GABA means more prevention of messages being sent).

**Glutamate receptor antagonists**

Glutamate is a type of amino acid, and is a major excitatory neurotransmitter in the brain. Messages are sent from one neurone to another in excitation, due to the movement of sodium and calcium ions into cells, and potassium out of cells. This movement of ions through the cell membranes is helped by glutamate, which binds to different receptors on the cell membrane.

Drugs that bring about and prevent glutamate uptake (antagonists) stop glutamate from helping the movement of ions through the cell membrane and so prevent the spread of the messages from one neurone to another. The AED perampanel works specifically on glutamate receptors, while some other AEDs (such as topiramate) work on glutamate receptors as well as other targets. Different AEDs use different targets, or a combination of targets. For some it is known which targets they use, but for others it is not yet known.