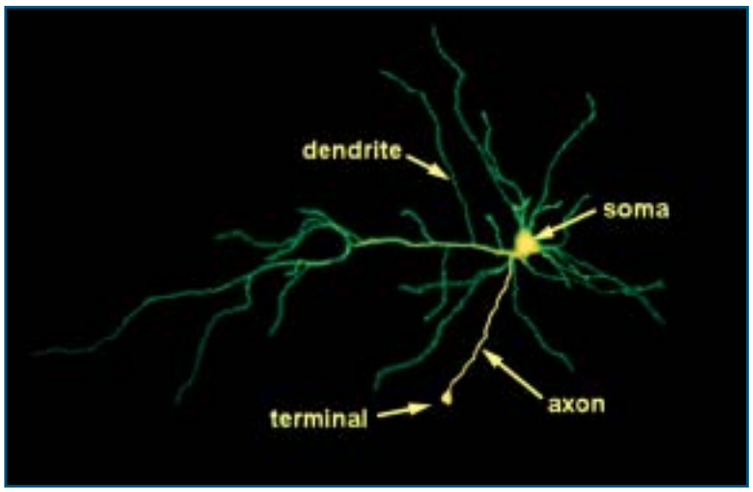
Drugs, chemicals, the brain and behaviour

Professor David Clark looks at how drugs of misuse influence chemical and electrical events in the brain, and how these changes may relate to their effects on behaviour.



Neuronal structure

Psychoactive drugs produce alterations in mood, thinking, perception and behaviour by altering chemical messenger systems in the brain. The most widely discussed of these chemicals – or neurotransmitters as they are called – is dopamine, but others involved include serotonin, GABA (gamma-aminobutyric acid) and glutamate.

The brain comprises billions of nerve cells (or neurons) which communicate with each other using electrical and chemical signals.

A neuron comprises a cell body (soma), dendrites and an axon. The dendrites and soma receive chemical information from neighbouring neurons. This chemical information is converted to electrical currents that travel along and converge on the soma. A major electrical impulse (the action potential) is then produced and this travels down the axon to the end of the neuron, the presynaptic terminal.

The presynaptic terminal is separated from another neuron by a small gap, known as the synapse. In general, the action potential cannot jump across the synapse – communication between the two neurons is by chemical neurotransmitters such as dopamine. The dopamine is stored in vesicles in the presynaptic terminal – these vesicles protect the dopamine being broken down by 'scavenger' molecules that exist within the free space of the presynaptic terminal.

When an action potential reaches the terminal, the vesicles move towards the presynaptic membrane, fuse with it, and release their contents (dopamine molecules) into the synapse. Once in the synaptic cleft, dopamine molecules can bind to specific recognition sites or proteins (known as dopamine receptors) on the postsynaptic membrane of neighbouring neurons.

This interaction can be thought of in terms of a keyhole and lock. The dopamine molecules enter the keyhole (receptor) and turn the lock. In biological terms, this means a dopamine molecule binding to a receptor activates or inhibits enzymes, or increases or decreases the flow of ions. Whatever the mechanism, the net result is an increase or decrease in the generation of electrical impulses (action potentials) in the neuron being impinged upon.

Once the dopamine molecule has activated the receptor, it is broken down (or deactivated) in one of several ways. The most common mechanism involves dopamine molecules being taken back up into the presynaptic terminal by an uptake pump (also a protein). Once in the presynaptic terminal, dopamine molecules are destroyed unless they have been taken back into a storage vesicle.

Drugs can be synthesised that bind to dopamine receptors and mimic the actions of the neurotransmitter – these drugs are known as agonists. On the other hand, there are drugs that bind to dopamine receptors but have no intrinsic activity of their own. However, by virtue of the fact that they bind to the receptor, they can prevent the neurotransmitter exerting its functional effects. These drugs are known as antagonists.

Our understanding of the relationship between the brain neurochemical events and behaviour has been enhanced by research undertaken in laboratory animals, in particular the rat.

This research has shown that drugs of misuse such as amphetamine, cocaine and heroin alter chemical and electrical events in neurons containing dopamine as a neurotransmitter, and this is the major mechanism by which they alter behaviour.

Amphetamine increases the release of dopamine in sets of neurons (or a neuronal pathway) that involve(s) dopamine as a neurotransmitter. There is an increase in dopamine receptor activation – and an increase in certain behaviours.

Cocaine binds to dopamine uptake pumps and prevents them from removing dopamine from the synapse. This leads to an increase in synaptic levels of dopamine, and an increase in dopamine receptor activation. Heroin and morphine activate opiate receptors in certain areas of the brain, where they increase electrical signals in dopamine-containing neurons and enhance the activation of dopamine receptors by dopamine.

The fact that laboratory animals such as the rat will self administer drugs such as amphetamine, cocaine and heroin has allowed us to greatly enhance our understanding of the mechanisms underlying their rewarding effects and their abuse by humans.

There is one particular neuronal pathway that has been shown to be associated with the rewarding effects of drugs of misuse – a pathway projecting from an area of the midbrain containing dopamine cell bodies called the ventral tegmental area, to a structure in the forebrain known as the nucleus accumbens.

Interestingly, this mesoaccumbens dopamine pathway has also been shown to be associated with natural consummatory behaviours, such as eating, drinking and sexual behaviour. Research has also led to suggestions that drugs of misuse not only act upon brain pathways involved in natural consummatory behaviours, but they actually hijack these pathways. They operate in a way that ultimately involves a person choosing drugs as a means of satisfaction, rather than behaviours that satisfy more natural human needs.

The mesoaccumbens dopamine pathway is thought to be involved in the rewarding effects of all drugs of misuse. However, since the brain is organised in circuits, a drug exerting direct effects primarily on one neurotransmitter system in a specific brain region will indirectly influence the activity of other neurotransmitter systems in other parts of the brain. Drugs of misuse cause a cascade of events in the brain that underlie their psychological effects. Of course, trying to understand the way that pharmacological effects at a cellular level are translated into psychological experiences is extremely complex and fraught with difficulties.

And we must also remember, as described in a previous Background Briefing, the drug's ultimate effects are not just dependent on their pharmacological actions in the brain. There is also the influence of set and setting.

You can read more about the neurobiology of addiction at www.nida.nih.gov/pubs/Teaching.