Psychoactive drugs: From absorption to elimination

Professor David Clark describes factors that can influence indirectly the way that psychoactive drugs impact on the brain and influence behaviour. He describes examples of individual differences in drug response that can arise from these factors.

Last issue, we considered how psychoactive drugs exert their effects in the brain to influence behaviour. However, there are other events and factors not directly concerning the brain that can influence drug effects. A psychoactive drug must travel from the site of administration to reach its target organ or site of action in the brain. This process can be influenced by absorption, distribution, metabolism and elimination of the drug.

The absorption of a drug is in part dependent upon its route of administration. Drugs can be applied topically for a localised response, *eg* cream for an abrasion. Drugs administered in this manner are not normally absorbed into the body as well as other forms of administration.

Since psychoactive drugs must enter the bloodstream to reach their site of action, the most common route of administration for this purpose is orally, in either liquid or tablet form. When a drug is required to act more rapidly, or is known to be broken down in the gastrointestinal tract, the preferred route of administration is by injection. Drugs of misuse, such as heroin, are often administered intravenously, *ie* directly into a vein.

Certain drugs are smoked, *eg* cannabis, crack cocaine, heroin, with absorption occurring through the lining of the lungs. This is a route of administration that is more socially acceptable, requires less paraphernalia, and is a less of a risk than intravenous injections, where sharing of needles may occur (possibly resulting in HIV/AIDS). Some psychoactive drugs, for example cocaine and amphetamine, are also taken by the intranasal route.

When a drug is administered a significant proportion of it reaches the bloodstream. Most drugs are dissolved in the water phase of blood plasma. Within this phase, some of the drug molecules will be bound to proteins and may therefore not freely diffuse out of the plasma. The drug is then transported around the body and can cross capillary walls to reach its target tissue(s). Psychoactive drugs must also pass the blood-brain barrier, a specialised barrier to protect cells in the brain.

If we look at the different routes of administration of cocaine, the pharmacological effects of the drug are the same regardless of route.

However, the rate of onset, intensity and duration of effects are dependent on the route of administration. Oral ingestion, not usually used for illicit purposes, achieves maximal plasma levels the most slowly, followed by the intranasal route. Intravenous and smoked cocaine achieve maximal blood (and therefore brain) concentrations most rapidly. Maximal plasma levels occur in seconds.

These differences in absorption of cocaine (and other drugs) impact at a behavioural level in several ways, one of which concerns long-term behavioural change. The learning of a habit – which is the psychological process underlying dependence – is influenced by the time interval between the act of drug-taking and the drug's rewarding impact on the brain. The shorter the interval, the greater the likelihood of the drug-taking habit developing.

Metabolism is a process whereby enzyme systems in the body transform drugs into safer molecules which can then be excreted by various routes of elimination. These enzyme systems are primarily located in cells in the liver, but can be found in other cells. There are a number of consequences of metabolism, the main one being that an active drug is converted into an inactive form. This is largely responsible for termination of drug action. Other forms of metabolism involve an active drug being metabolised into another active drug, which may or may not have the same pharmacological action of the parent drug, or even being converted into a toxic compound.

The most common route for drug excretion is through the kidneys into the urine. Drugs and their metabolites are filtered out from the plasma through the capillaries within the glomeruli of the kidneys. Drugs and metabolites can also be eliminated by the body in other ways, *eg* salivary glands, sweat glands.

'The learning of a habit is influenced by the time interval between the act of drug-taking and the drug's rewarding impact on the brain. The shorter the interval, the greater the likelihood of the drug-taking habit developing.'

There are genetically determined individual differences in pharmacokinetics through individual variations in the amount and characteristics of enzymes involved in metabolism and the amount of binding protein. These individual differences result in individual differences in drug response. One important factor influencing drug pharmacokinetics is age. Growing older is associated with a reduction in total drug clearance for many drugs, in particular central nervous system depressants.

Pronounced individuals differences are noted in the metabolism of alcohol. Over 90 per cent of alcohol is metabolised in the liver. The major metabolic pathway is oxidation by alcohol dehydrogenase (ADH) to acetaldehyde, which in turn is oxidised by aldehyde dehydrogenase (ALDH) to acetate, which is metabolised into carbon dioxide and water. Acetaldehyde is highly toxic. Women have less ADH then men are therefore likely to have higher blood alcohol concentrations when they drink because less alcohol is metabolised before it is distributed around the body in the blood. This difference in metabolism helps explain why, in general, women become intoxicated at lower levels of alcohol than men.

There are at least four isoenzymes of ALDH in humans. ALDH2, the isoenzyme largely responsible for the oxidation of acetaldehyde exists in two forms, one of which is virtually inactive. As many as 50 per cent Orientals (Japanese, Chinese and Korean men and women) have a low activity of ALDH2 and this results in a flush reaction when these people drink. This reaction is unpleasant, and individuals with low activity ALDH2 are less inclined to drink and are less vulnerable to developing alcohol dependence.