

## **MDMA ['ecstasy'] and new designer drugs**

**Professor Richard Green**

3,4-Methylenedioxymethamphetamine (MDMA or ecstasy) was first synthesised and patented in 1912 as a precursor of other pharmacologically active compounds by the E. Merck company in Germany. It was examined by the US military in the 1950s, presumably as a chemical warfare agent since it is chemically related not only to other amphetamines but also mescaline. However the first report that it was psychoactive in humans was a paper in 1978 by Shulgin and Nichols. It rapidly became a well known 'designer drug'; that is a compound with a chemical structural and pharmacological similarity to existing and illegal recreational drugs but, by being novel and not specifically listed, had escaped legal control. In 1985 the US Drug Enforcement Agency (DEA) classified MDMA as a Schedule 1 drug due to its high abuse potential and lack of known clinical use. The drug rapidly became illegal in most other countries but despite this its popularity surged often being taken at 'rave' or 'techno' dance clubs and parties. The peak of use came in the late 1980s and 1990s and a recent survey has suggested a marked decline in its popularity.

In humans MDMA usually produces a relaxed euphoric state with empathy and emotional openness and decreased emotions. However it can produce a variety of acute adverse effects. These include raised blood pressure and heart rate, nausea and sweating. However the most commonly reported adverse effect is raised body temperature (hyperthermia). At its most severe this results in a variety of other problems which can lead to death, the problems being essentially identical to those seen with heat stroke. While such problems were relatively rare in relation to the huge numbers of young persons taking the drug each week (estimated at around half a million during the 1990s) such fatalities led to a variety of "shock, horror" headlines in the popular press about the dangers of the drug. The problems were mitigated by the awareness of dance clubs that room temperature should be kept down and that water should be generally available for dancers. Interestingly the conditions experienced by young people in dance clubs of loud noise, crowded rooms and lack of fluids for drinking had been shown around 50 years earlier to enhance the toxic effects of amphetamine-like drugs (of which MDMA is one) in rodents.

In parallel with the increase in the recreational use of MDMA there was an increase in studies on the way that MDMA acted in the brain of experimental animals. It was shown that MDMA administration produced a rapid and substantial release of the chemicals dopamine and 5-hydroxytryptamine (5-HT

or serotonin) from the nerve endings in the brain (neurotransmitters). Dopamine is involved in reward and pleasure seeking and 5-HT in mood so these findings went some way to explaining the effects of the drug in humans. Good evidence was also obtained to suggest that the hyperthermia was related to the release of dopamine.

It had been known for some time that high doses of amphetamine can cause damage to nerve endings in the rodent brain (often called neurotoxicity) and so a substantial number of investigations were undertaken to determine whether MDMA also caused neurotoxic damage. There was good agreement that MDMA was indeed neurotoxic. It was found that following MDMA there was an initial rapid loss of 5-HT in the brain due to the release of this neurotransmitter from the nerve endings. The concentration of 5-HT then started to recover, but after a day or so the concentration then decreased again and remained low for several months. This long-term loss was found to be due to damage to 5-HT nerve endings and was shown to occur not only in the brain of rats but also in monkeys where damage could be detected up to 3 years after the MDMA was first given. Interestingly the damage was very specific with no damage to the nerve endings that contained other neurotransmitters such as dopamine or noradrenaline.

Naturally this finding resulted in a series of investigations in human recreational users to discover whether they would exhibit abnormal behaviour or mood or had memory problems which might indicate that damage to the brain had occurred. A variety of papers were published that indicated this possibility, but no unequivocal data have been obtained to date. This is perhaps not surprising as it would be unethical to design and conduct a study that would compare 'before and after' effects in humans. Consequently one can only study the brain function of people who have taken an illegal drug over a period of time with no knowledge of the functioning before they started using the drug. Furthermore one has little knowledge of how much drug has been consumed. The drug has been obtained illegally and therefore no reliable information is available as to either the purity or the dose consumed. Even dose frequency is dependent on information supplied by the user and this too may be inaccurate. To further complicate matters most recreational drug users take more than one type of legal (alcohol, nicotine) or illicit (cannabis, cocaine, opioids) drug and often at the same time. So is any apparent brain abnormality due to MDMA, another drug, or the combination of MDMA and other drugs?

To produce neurotoxic damage in the brain of rats one does have to give either a quite high single dose or, more reliably, high repeated doses of the drug over a couple of days. This does not reflect the way that most recreational users

take the drug, although 'binge dosing', that is several doses taken over just a few hours, was in vogue for a while. Studies on the concentration of MDMA in the blood of recreational users suggest that the concentration is always likely to be far below that required to initiate neurotoxicity in rats. However we cannot know what repeated low dosing over several years might cause. Furthermore the fact that most young persons only use MDMA for a relatively short period of their life might help to limit potential damage. It is interesting to note that in rats MDMA itself does not cause neurotoxicity, there being good evidence that it is a metabolite that is responsible. This metabolite, which has still not been identified unequivocally, produces free radicals (highly reactive particles with an unpaired electron) and it is free radicals that are responsible for the damage to 5-HT nerve endings.

While MDMA use has declined, other related drugs have recently appeared and again are causing much comment in newspapers, and usually with the same degree of misinformation as that seen with MDMA. In particular the cathinones, the most notable being mephedrone ('meow meow'), produced much ill-informed press comment. The cathinones are related to the active substance contained in khat, a recreationally smoked plant. Crucially the cathinone compounds have a similar chemical structure to amphetamine and MDMA and it has been proposed that they are likely therefore to have a very similar pharmacological profile to MDMA. Earlier studies on MDMA in both laboratory animals and humans may prove valuable in pointing the way to understanding the actions of mephedrone. The cathinones have now been made illegal; but given the evidence of MDMA this is unlikely to influence use, a more likely factor is whether they go out of fashion.

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**Professor Richard Green is Special Professor of Neuropharmacology in the School of Biomedical Sciences at the University of Nottingham. In 2010 he was awarded the British Association for Psychopharmacology Lifetime Achievement Award in recognition of his outstanding and long-term contribution to psychopharmacology.**