

Concern over research reawakens ecstasy neurotoxicity debate

When George Ricaurte and colleagues at Johns Hopkins School of Medicine (Baltimore, MD, USA) announced that even single doses of methylendioxyamphetamine (MDMA) given to monkeys caused extensive damage to dopaminergic neurons, the often-repeated concern was that young adults using ecstasy were increasing their risk of parkinsonism as they aged (*Science* 2002; **297**: 2260–63). But questions arising from the retraction of these data on Sept 5 have grown into a full-blown controversy over MDMA risks.

After failing to replicate original studies, the team discovered that the drug used was in fact methamphetamine, from a vial wrongly labelled MDMA. 3 weeks later, another report that involved the mislabelled drug was retracted (*Eur J Pharmacol* 2002; **453**: 239–44), but the scientific community had highlighted concerns over the original study since publication.

On Sept 17, Colin Blakemore, now newly appointed head of the UK Medical Research Council, with Les Iversen, a pharmacologist at Oxford University, UK, wrote to the editor-in-chief of *Science* to request a review of processes, especially at a time when “anti-rave” legislation was being debated in US Congress. “I am seriously worried about the damage that this fiasco has done to one of the most eminent scientific journals in the world”, says Iversen. “Colin Blakemore and I have asked the editor Donald Kennedy to take further action to clear the journal’s name, and we have suggested publication of the original referees’ reports of the Ricaurte paper as one possible action”. Blakemore has called for an independent inquiry, with disclosure of correspondence and other evidence connected with the paper.

A *Nature* editorial on Sept 18 reiterated the scientists’ concerns, starting with the statement “it was a pretty peculiar result in the first place”. Una McCann, coauthor and wife of Ricaurte, is quick to dispel suggestions that the team acted slowly in spotting the drug error. “It is true that, initially, we were surprised to see dopaminergic neurotoxicity in squirrel monkeys. Indeed, we specifically state this in the

paper, and indicate that this is why we thought it was important to confirm the results in another non-human primate species (baboons) . . . Finally, we assumed, after replicating our data in multiple squirrel monkeys, and then extending it to another species (in addition to confirming the finding with immunocytochemistry, autoradiography, and silver staining methods) that the data were solid. We do not believe that anyone else in our shoes with knowledge of the literature would have believed that there was some sort of error. Indeed, none of the experts in the field who were chosen for peer review suggested such a thing.”

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K Seaton and T Evans/SPL

The right stuff: MDMA molecule

The motive for high-profile publication in *Science* has also been questioned. *Nature* (2003; **425**: 223) recalls the unusual public endorsement of the findings by Alan Leshner, director of the American Academy for the Advancement of Science (AAAS) and former head of the National Institute on Drug Abuse (NIDA). The AAAS, which publishes *Science*, has been quick to dismiss allegations of political influence as “baseless and without merit”, despite concerns published in *The Scientist* that the AAAS exaggerated the original studies in a press release. According to a spokesperson, Kennedy is “still contemplating” the comments by Blakemore and Iversen. But, says Iversen, “we have been assured that an internal review is going on in the journal and we hope to learn the outcome of this shortly”.

Ricaurte and his team are keen to stress that “this labelling error does not call into question the results of multiple previous studies demonstrating the serotonin neurotoxic potential of MDMA in various animal species,

including several non-human primate species”. But *Nature* notes: “The impression that low doses of ecstasy, or MDMA, are extremely dangerous—misleadingly borne out by Ricaurte’s study, but not by two decades of observing the drug being used—will hamper legitimate research to determine whether MDMA could have useful psychotherapeutic properties.” That research, sponsored by the Multidisciplinary Association for Psychedelic Studies (MAPS; Sarasota, FL, USA), has been slow to gain regulatory approvals, while a pilot study in Spain was temporarily halted recently by national authorities. MAPS president, Rick Doblin, largely blames Ricaurte, who, he alleges, was promoting the concept that typical doses of MDMA had lasting neurotoxic effects, long after the team must have failed to replicate key findings.

McCann counters that “it was not until mid to late July, 2003, that we were certain that we were dealing with mislabelled drug bottles”. And, she stresses, the team stands by “our data indicating that single dosages of MDMA lead to toxic changes in some brain areas of the squirrel monkey that are still evident 2 weeks after drug administration”. But Doblin suggests the team has a history of misrepresenting findings, including a deliberate failure to publish studies that found no effect of single low doses of oral MDMA on serotonin neurons. These data were not published, McCann responds, because full dose-ranging studies had not been done.

Doblin has filed a freedom of information act to the NIDA, which has funded much of the Johns Hopkins team’s research, and requested a full inquiry and publication of all studies with the mislabelled vials, and those done to replicate original findings. NIDA had not announced any such inquiry by the time this journal went to press, despite the strong emphasis placed by its new director on science-based drug education. The fear is that renewed scientific uncertainties could undermine the credibility of education campaigns on MDMA.

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