K43 Brain Serotonin Transporter Reduction in Human Polydrug MDMA (Ecstasy) Users

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After attending the presentation, attendees will be alerted to the question whether use of MDMA (ecstasy) might cause damage to the brain.

This presentation will impact the forensic and general community by advising on the possible risks of MDMA use and by illustrating the need to conduct drug hair analyses to confirm use or lack of use of MDMA and other recreational drugs when investigating possible effects of MDMA on the human brain.

Background: MDMA (3,4-methylenedioxymethamphetamine, ecstasy) is an analog of methamphetamine that is widely used recreationally and is also being tested in clinical trials for the treatment of post-traumatic stress disorder. Recreational interest in MDMA is related in part to the ability of the drug to cause increased energy and sociability. Animal data indicate that chronic ecstasy exposure can cause a long term reduction in brain serotonin neurone markers, raising the public health issue of actual damage to brain serotonin neurones and associated behavioral problems in the human. However, brain neuroimaging studies in MDMA users measuring levels of a serotonin neurone marker, the serotonin transporter (SERT), have been contradictory, with most investigations not confirming by drug testing use of MDMA or other drugs.

Objective and Hypothesis: The objective was to test the hypothesis, based on animal data, that brain levels of SERT are decreased in living human MDMA users.

Methods and Subjects: SERT levels were estimated by measuring binding of 11C-DASB in a Positron Emission Tomography (PET) procedure in 50 normal subjects and 49 MDMA users. MDMA users were withdrawn from the drug for approximately 7 weeks and reported using approximately two tablets/session, two sessions/month, and 200 lifetime tablets over four years duration.

Results: All MDMA users tested positive for MDMA in hair. As expected, of the 49 MDMA users, most (40) tested positive in hair for methylenedioxyamphetamine (MDA), a metabolite of MDMA. The levels of MDA in 39 of these subjects were lower than that of MDMA, suggesting that MDA had derived from metabolism of MDMA. However, one subject demonstrated higher levels of MDA than MDMA in hair, suggesting that this subject might have ingested both MDA and MDMA.

Many MDMA users also used other stimulant drugs and there was a discrepancy between self-reported use of other stimulants vs. drug hair findings (e.g., 32/49 subjects testing positive for methamphetamine in hair vs. only 9 reporting use by self-report; 23 vs. 14 for cocaine). This discrepancy is likely explained in part by inclusion of other stimulants in tablets marketed as “ecstasy” and possibly by the expectation of the ecstasy user that he/she would more likely be included for study if other drugs were not reported as used.

Most MDMA users reported increased sociability and body temperature while on the drug (typically in a club setting) and partial tolerance developing to the behavioral effects of MDMA. Consistent with the literature, most MDMA users reported a dysphoric drug discontinuation/withdrawal syndrome (sometimes severe) occurring one or more days following last use of the drug. There was no consistent response when MDMA users were asked to report whether they were more empathetic (caring) to others while on the drug.

Brain SERT binding was significantly decreased in the MDMA users as compared with control values, but the regional pattern was highly selective with the cerebral cortical brain regions (frontal, -27%; temporal, -27%, insular, -26%, anterior cingulate, -20%; occipital, -46%) bearing the brunt of the loss. High SERT density subcortical regions (caudate, putamen) were strikingly normal. There was marked overlap between the ranges of the control and MDMA user values. SERT binding was similar in those who tested and did not test positive for methamphetamine in hair.

Conclusions: The PET findings showing a cerebral cortical loss of SERT in MDMA users are similar to those recently obtained by a Johns Hopkins group and may help bring some consistency to this confusing literature.

Taken together, our data suggest that cerebral cortical SERT levels will be decreased, for at least two months after last use of the drug, in chronic MDMA users who use, on average, two tablets/session and two sessions/month. However, use of other drugs (methamphetamine, cocaine, cannabis) is a potentially important confound that could modify this conclusion. The observed discrepancy between recent use of drugs (other than MDMA) by self-report vs. drug hair testing also raises the possibility that other studies that do not conduct drug hair testing for stimulant drugs such as methamphetamine and cocaine may well have underestimated use of these drugs.

The special sensitivity of cerebral cortex vs. subcortical brain areas to SERT loss might be explained by

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differences in serotonin nerve ending characteristics or proximity to cell bodies. Finally, we emphasize that our findings cannot distinguish between actual loss of serotonin neurones and loss of SERT within intact neurones.

MDMA, Ecstasy, Serotonin Transporter

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