

# “Ecstasy” and Serotonin Neurotoxicity

## *New Findings Raise More Questions*

**T**HE ARTICLE by Reneman et al<sup>1</sup> in this issue of the ARCHIVES is timely and provocative and highlights several areas of controversy in the fields of substance abuse, drug-induced neurotoxic effects, and neuroimaging. The authors present evidence that the illicit recreational drug 3,4-methylenedioxymethamphetamine (MDMA, or “ecstasy”) may cause persistent cognitive deficits<sup>2-9</sup> and that these deficits are related to the extent of previous MDMA use. Based on single-photon emission computed tomography (SPECT) imaging with <sup>123</sup>I-labeled 2β-carbomethoxy-3β-(4-iodophenyl)tropane (β-CIT), they conclude that MDMA causes neurotoxic injury to cortical serotonin (5-HT) axon terminals that may be reversible. This is the first study to evaluate a separate cohort of previous MDMA users who have abstained from use for longer than 1 year, and thus has the potential to provide information regarding long-term effects of exposure to MDMA.

### *See also page 901*

With respect to cognitive effects of MDMA, there is some question regarding the role of concomitant marijuana use in the cognitive deficits observed in MDMA users. Reports by Rodgers<sup>10</sup> and Croft et al<sup>11</sup> indicate that marijuana is an important confounding factor in studies of cognitive function in MDMA users, with marijuana use predicting much of the observed cognitive decline. This is a nettlesome problem, since most MDMA users also use marijuana. In the present study, although the “ex-MDMA” group of subjects abstained from MDMA for at least 1 year, they continued substantial marijuana use, potentially accounting for diminished cognitive performance. Nevertheless, the present findings of im-

paired verbal memory are cause for concern and underscore the need for longitudinal studies in MDMA users to evaluate the persistence of functional deficits and to determine whether tardive adverse effects emerge. Clearly, future studies aimed at elucidating cognitive effects of MDMA use will need to control for concomitant marijuana use. Moreover, the relationship between MDMA-induced serotonin neurotoxicity and cognitive deficits in MDMA users needs further investigation and will require assessment of several brain regions (eg, hippocampus) in addition to cerebral cortex.

Data obtained using SPECT with the radioligand [<sup>123</sup>I]β-CIT insert themselves into the ongoing debate regarding the suitability of this method for measuring serotonin transporter (SERT) sites in cerebral cortex. Several laboratories<sup>12-14</sup> have demonstrated the capability of [<sup>123</sup>I]β-CIT for measurement of brainstem and mid brain SERT. However, as noted by Heinz and Jones,<sup>15</sup> there is little evidence that SPECT with [<sup>123</sup>I]β-CIT can accurately measure specific binding to cortical SERT sites, with studies in a nonhuman primate demonstrating no change in the level of cortical [<sup>123</sup>I]β-CIT binding following administration of the serotonin reuptake inhibitor, citalopram.<sup>12</sup> Nevertheless, one other research group<sup>16</sup> has also reported reductions in the binding of [<sup>123</sup>I]β-CIT in occipital cortex of MDMA users. To address the question of whether MDMA-induced brain serotonin injury in cerebral cortex can be detected by SPECT with [<sup>123</sup>I]β-CIT, studies using large nonhuman primates, such as baboons, with similar cortical SERT distributions and densities as humans are required, ideally before and after MDMA treatment.

An important issue regarding SPECT sensitivity deserves clarification. The authors note in the “Comment” section that reductions in cor-

tical [<sup>123</sup>I]β-CIT in MDMA users were on the order of 9%, while previous binding studies in nonhuman primates<sup>17</sup> given doses of MDMA similar to those used by humans exhibit far greater deficits in cortical 5-HT axonal markers, ranging from 83% to 95%. This disparity leads the authors to conclude that MDMA is less toxic toward humans than primates. However, it has not been established that reduced binding of [<sup>123</sup>I]β-CIT corresponds directly with decreased 5-HT axonal markers measured using in vitro tissue samples. Notably, SPECT studies in MDMA-treated monkeys using [<sup>123</sup>I]INQUIP,<sup>18</sup> a SERT (5-HT transporter) radioligand with similar cortical/cerebellar binding ratios to [<sup>123</sup>I]β-CIT, found that MDMA-treated monkeys exhibited cortical reductions of less than 5% by SPECT, while in vitro measures indicated reductions greater than 75%. These values reveal a large disparity between SERT levels determined by SPECT and by direct in vitro tissue samples. This difference between 2 dissimilar methods raises questions regarding the sensitivity of SPECT for detecting SERT in cerebral cortex, as recognized by the authors. Thus, until the sensitivity and accuracy of SPECT with [<sup>123</sup>I]β-CIT for measuring SERT density in neocortex is established, conclusions regarding the degree of MDMA-induced cortical damage may be premature.

While the results of Reneman and coauthors and others suggest that MDMA can produce cognitive impairment (memory loss), several important questions concerning causality and mechanisms remain unresolved. Does decreased binding of β-CIT measured with SPECT reliably indicate a loss of SERT in neocortex? Does the decrease in SERT result from frank axonal degeneration or from reduced SERT expression in surviving axons? Histologic studies in animals demonstrate that MDMA causes extensive loss of 5-HT axons in numerous brain regions,<sup>17,19,20</sup>

and a similar pattern of neurotoxic effects likely occurs in humans. An unresolved issue is whether the 5-HT axonal damage in neocortex is directly responsible for cognitive changes. Moreover, the regional localization of 5-HT axon loss that produces cognitive decline should be determined since denervation of hippocampus may cause memory loss, while the neocortical changes might be unrelated.

The observation that [<sup>123</sup>I]β-CIT binding in cortex returns to normal in subjects who were abstinent for 1 year leads the authors to conclude that MDMA-induced damage to cortical 5-HT axon terminals may be reversible. This interpretation must be viewed with caution since, as mentioned earlier, the sensitivity of [<sup>123</sup>I]β-CIT for measuring cortical SERT reliably is not established. Moreover, axonal regeneration in the adult brain may lead to abnormal, dysfunctional circuitry. The notion of spontaneous recovery has important public health implications since drug users may be led to believe that MDMA-induced damage can be reversed merely by abstaining from MDMA. However, experimental studies report that MDMA's neurotoxic effects on serotonin neurons in primates are extremely long-lasting and may be permanent.<sup>17,21</sup>

The findings by Reneman and colleagues suggest several future directions for research in MDMA neurotoxicity. As noted previously, preclinical studies in nonhuman primates are essential for the interpretation of findings in humans. For example, it is important to establish that SPECT with [<sup>123</sup>I]β-CIT is capable of reliably detecting MDMA-induced serotonin neurotoxicity in primate neocortex, and if so, the sensitivity of the method should be determined in multiple regions of cerebral cortex. Similarly, abnormal magnetic resonance spectroscopy, positron emission tomography, or functional magnetic resonance imaging data from human MDMA users can best be interpreted with reference to data from nonhuman primates that exhibit documented neurotoxic injury. A similar approach could be applied to functional consequences of MDMA use, including cognitive and neuroendocrine changes seen in MDMA users. Such studies will help clarify the relationship between neurotoxic injury

and functional deficits. Another direction for clinical research in MDMA is to determine the long-term effects of MDMA use. These studies should address questions of potential recovery, as well as the possibility that tardive effects of MDMA on serotonin neurons may become manifest with age. Additionally, as knowledge grows regarding the mechanisms of MDMA-induced neurotoxicity, it may be possible to define genetic risk factors for the development of toxicity or methods for preventing injury and promoting recovery in those who have sustained damage.

In conclusion, the article by Reneman and colleagues raises several important questions. Fortunately, the tools for addressing many of these questions are available, and will undoubtedly be used to shed light on many issues regarding the neurotoxic effects of MDMA and its functional consequences in humans. Meanwhile, it is urgent to focus public attention on the current results indicating that MDMA may cause long-term damage and dysfunction in the human brain.

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## REFERENCES

1. Reneman L, Lavalaye J, Schmand B, de Wolff FA, van den Brink W, den Heeten GJ, Booij J. Cortical serotonin transporter density and verbal memory in individuals who stopped using 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy"): preliminary findings. *Arch Gen Psychiatry*. 2001;58:901-906.
2. Bolla KI, McCann UD, Ricaurte GA. Memory impairment in abstinent MDMA ("ecstasy") users. *Neurology*. 1998;51:1532-1537.
3. Gouzoulis-Mayfrank E, Daumann J, Tuchtenhagen F, Pelz S, Becker S, Kunert HJ, Fimm B, Sass H. Impaired cognitive performance in drug free users of recreational ecstasy (MDMA). *J Neurol Neurosurg Psychiatry*. 2000;68:719-725.
4. McCann UD, Merti M, Eligulashvili V, Ricaurte GA. Cognitive performance in (±) 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") users: a controlled study. *Psychopharmacology (Berl)*. 1999;143:417-425.
5. Morgan MJ. Memory deficits associated with recreational use of "ecstasy" (MDMA). *Psychopharmacology (Berl)*. 1999;141:30-36.
6. Parrott AC, Lasky J. Ecstasy (MDMA) effects upon mood and cognition: before, during and after a Saturday night dance. *Psychopharmacology (Berl)*. 1998;139:261-268.
7. Parrott AC, Lees A, Garnham NJ, Jones M, Wesnes K. Cognitive performance in recreational users of MDMA or "ecstasy": evidence for memory deficits. *J Psychopharmacol*. 1998;12:79-83.
8. Verkes RJ, Gijssman HJ, Pieters MS, Schoemaker RC, de Visser S, Kuijpers M, Pennings EJ, de Bruin D, Van de Wijngaart G, Van Gerven JM, Cohen AF. Cognitive performance and serotonergic function in users of ecstasy. *Psychopharmacology*. 2001;153:196-202.
9. Zakzanis KK, Young DA. Memory impairment in abstinent MDMA ("ecstasy") users: a longitudinal investigation. *Neurology*. 2001;56:966-969.
10. Rodgers J. Cognitive performance amongst recreational users of "ecstasy." *Psychopharmacology (Berl)*. 2000;151:19-24.
11. Croft RJ, Mackay AJ, Mills AT, Gruzeliier JG. The relative contributions of ecstasy and cannabis to cognitive impairment. *Psychopharmacology (Berl)*. 2001;153:373-379.
12. Laruelle M, Baldwin RM, Mallison RT, Zea Ponce Y, Zoghbi SS, Al-Tikriti MS, Sybirska EH, Zimmermann RC, Wisniewski G, Neumeyer JL, Millius RA, Wan S, Smith EO, Roth RH, Charney DS, Hoffer PB, Innis RB. SPECT imaging of dopamine and serotonin transporters with [<sup>123</sup>I] beta-CIT: pharmacological characterization of brain uptake in nonhuman primates. *Synapse*. 1993;13:295-309.
13. Pirker W, Asenbaum S, Kasper S, Walter H, Angelberger P, Koch G, Pozzera A, Deecke L, Podreka I, Brucke T. β-CIT SPECT demonstrates blockade of 5HT-uptake sites by citalopram in the human brain in vivo. *J Neural Transm*. 1995;100:247-256.
14. Tauscher J, Pirker W, de Zwaan M, Asenbaum S, Brucke T, Kasper S. In vivo visualization of serotonin transporters in the human brain during fluoxetine treatment. *Eur Neuropsychopharmacol*. 1999;9:177-179.
15. Heinz A, Jones DW. Serotonin transporters in ecstasy users. *Br J Psychiatry*. 2000;176:193-195.
16. Semple DM, Ebmeier KP, Glabus MF, O'Carroll RE, Johnstone EC. Reduced in vivo binding of the serotonin transporter in the cerebral cortex of MDMA ("ecstasy") users. *Br J Psychiatry*. 1999;175:63-69.
17. Hatzidimitriou G, McCann UD, Ricaurte GA. Altered serotonin innervation patterns in the forebrain of monkeys treated with (±)3,4-methylenedioxymethamphetamine seven years previously: factors influencing abnormal recovery. *J Neurosci*. 1999;19:5096-5107.
18. Jagust WJ, Eberling JL, Biegion A, Taylor SE, VanBrocklin HF, Jordan S, Hanrahan SM, Roberts JA, Brennan KM, Mathis CA. Iodine-123-5-iodo-6-nitroquipazine: SPECT radiotracer to image the serotonin transporter. *J Nucl Med*. 1996;37:1207-1214.
19. Molliver ME, Berger UV, Mamounas LA, Molliver DC, O'Hearn E, Wilson MA. Neurotoxicity of MDMA and related compounds: anatomic studies. *Ann N Y Acad Sci*. 1990;600:640-664.
20. O'Hearn E, Battaglia G, De Souza EB, Kuhar MJ, Molliver ME. Methylenedioxymethamphetamine (MDA) and methylenedioxymethamphetamine (MDMA) cause selective ablation of serotonergic axon terminals in forebrain: immunocytochemical evidence for neurotoxicity. *J Neurosci*. 1988;8:2788-2803.
21. Fischer C, Hatzidimitriou G, Wlos J, Katz JL, Ricaurte GA. Reorganization of ascending 5-HT axon projections in animals previously exposed to the recreational drug (+/-)3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). *J Neurosci*. 1995;15:5476-5485.