

Toxicodynamics and long-term toxicity of the recreational drug, 3,4-methylenedioxymethamphetamine (MDMA, ‘Ecstasy’)

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Abstract

The recreational drug, ($\pm$)3,4-methylenedioxymethamphetamine (MDMA, ‘Ecstasy’), is a potent serotonin (5-HT) neurotoxin in animals. Whether humans who use MDMA incur 5-HT neural injury is unknown. The present studies utilized positron emission tomography (PET) in conjunction with the 5-HT transporter ligand, [^{11}C]McN-5652 to assess the status of brain 5-HT neurons in human MDMA users. Like nonhuman primates treated with neurotoxic doses of MDMA, humans with a history of MDMA use showed lasting decrements in global brain [^{11}C]McN-5652 binding, with decreases in [^{11}C]McN-5652 binding positively correlated to the extent of previous MDMA use. These results suggest that human MDMA use results in brain 5-HT neurotoxicity. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Over the last decade, findings in experimental animals have raised concern that the popular recreational drug 3,4-methylenedioxymethamphetamine (MDMA, ‘Ecstasy’) might damage brain serotonin (5-HT) neurons in humans. Animals treated with MDMA develop lasting decrements in a number of 5-HT axon terminal

markers including 5-HT, its major metabolite, 5-hydroxyindoleacetic acid (5-HIAA), its rate-limiting synthetic enzyme, tryptophan hydroxylase (TPH), and its uptake site, the 5-HTT (see Steele et al., 1994). Immunocytochemical studies suggest that decrements in 5-HT axonal markers after MDMA exposure are related to loss of 5-HT axons, with 5-HT nerve cell bodies in the brain stem remaining unaffected (O’Hearn et al., 1988). In MDMA-treated monkeys, the loss of 5-HT axonal markers is extremely long-lasting (Insel et al., 1989; Fischer et al., 1995; Scheffel et al., 1998), and in various brain regions may be permanent (Hatzidimitriou et al., 1999).

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The issue of whether MDMA also produces neurotoxic effects in humans is of considerable scientific interest and public health concern, particularly since doses of MDMA that produce neurotoxicity in nonhuman primates overlap with those used recreationally by humans (McCann et al., 1997). Until recently, it was impossible to directly evaluate the status of 5-HT neurons in the living brain. However, with the advent of positron emission tomography (PET) and the development of (+)[¹¹C]McN-5652, a radioligand that selectively binds to the 5-HT transporter (5-HTT), this is now feasible (Szabo et al., 1995).

The present studies utilized PET imaging with [¹¹C]McN-5652 to assess the status of brain 5-HT neurons in living human and nonhuman primates previously exposed to MDMA. Studies in nonhuman primates (baboons) were designed to validate PET imaging with [¹¹C]McN-5652 as a reliable method for detecting MDMA-induced 5-HT neurotoxicity in the living brain. Once validated, the same method was used to measure 5-HTT density in a cohort of abstinent MDMA users. The results of these studies were recently published (Scheffel

et al., 1998; McCann et al., 1998), and are the subject of this presentation.

2. Studies in baboons

As recently described (Scheffel et al., 1998) following baseline PET scans with (+)[¹¹C]McN-5652 and (–)[¹¹C]McN-5652 (25–32 mCi of each radioligand), baboons weighing 25.6–32.7 kg were treated with a neurotoxic regimen of MDMA (5 mg/kg, s.c., twice daily for four consecutive days). Two to three weeks after MDMA treatment, the animals were re-imaged using the same radioligands, at the same dose of radioactivity. Dynamic PET acquisitions were obtained over 115 min following infusion of each radioligand. Time activity curves were calculated for 13 brain regions. Significant decreases in mean radioactivity levels were observed post-MDMA treatment using (+)[¹¹C]McN-5652, but not when using (–)[¹¹C]McN-5652 (Fig. 1).

Mean reductions in specific activity (calculated as the difference between (+) and (–)[¹¹C]McN-

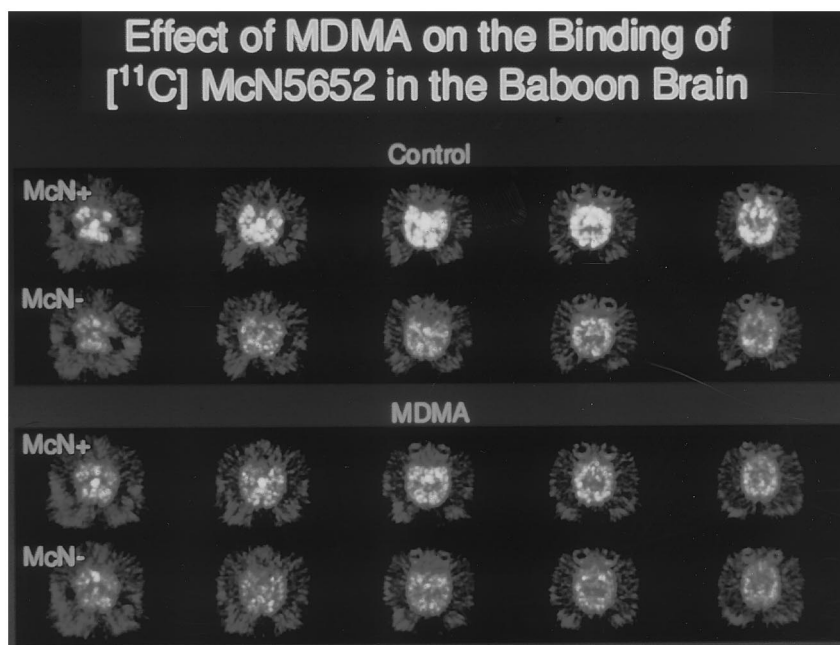


Fig. 1. Axial PET images before (top) and after (bottom) MDMA showing distribution of (+) and (–)[¹¹C]McN-5652 binding in the brain of a baboon. PET images were acquired 55–95 min after tracer injection.

5652) differed among brain regions, and ranged from 44% in the pons to 89% in the occipital cortex, a finding consistent with the known susceptibility of various brain regions to MDMA-induced 5-HT neurotoxicity (Scanzello et al., 1993; Fischer et al., 1995). Further, there was an excellent correlation between PET findings and post-mortem neurochemical findings in the same animals (Scheffel et al., 1998), although PET measures tended to underestimate the extent of 5-HT terminal loss (Kerenyi et al., 1999). These observations suggest that PET imaging with [^{11}C]McN-5652 is a reliable method for detecting MDMA-induced brain 5-HT neurotoxicity in the living primate brain.

3. Studies in humans

Having validated PET imaging with [^{11}C]McN-5652 as a reliable method for detecting MDMA-induced 5-HT neurotoxicity in living primates, studies were undertaken with humans having a history of recreational MDMA use. As described in detail elsewhere (McCann et al., 1998), subjects agreed to abstain from psychoactive drug use for at least 3 weeks, and understood they would undergo drug screens prior to the study. Subjects underwent structured diagnostic psychiatric interviews using the SCID-IV, and had no current Axis I diagnosis in which 5-HT has been implicated. Control subjects had no previous experience with MDMA and were free of Axis I psychiatric diagnoses. Toxicological drug screens were performed before PET scans; subjects were excluded if they tested positive for drugs or if they suffered from neuropsychiatric diseases in which 5-HT has been implicated.

PET imaging studies with [^{11}C]McN-5652 were carried out as previously described (McCann et al., 1998). Briefly, two PET studies were performed in each subject, one with (+) [^{11}C]McN-5652 and another with (–) [^{11}C]McN-5652, with a time difference of 150 min between injections. Arterial blood samples were obtained every 3–7 s during the first 2–3 min post injection, and at increasing time intervals thereafter, until 95 min post injection. The arterial plasma samples were

analyzed by high performance liquid chromatography (HPLC), and the input function was corrected for metabolized radioligand activity. Region of interest (ROI) placement was based on co-registered MRI/PET images. To analyze radioligand binding, a one-tissue compartment, three-parameter model proved to be statistically most reliable, and was used. In this model, the DV is obtained from the ratio of uptake (K_1) and release (k_2) parameters; thus $DV = K_1/k_2$. The assumption was made that the tissue DV of (+) [^{11}C]McN-5652 consisted of three components: specific binding, nonspecific binding and free ligand, whereas the DV of (–) [^{11}C]McN-5652 consisted of only two components: nonspecific binding and free ligand. Logarithmic transforms of DVs corrected for non-specific binding were used in order to achieve a normal distribution both in the control and MDMA groups, and to permit the application of analysis of variance techniques.

Control and MDMA subjects were well-matched with regard to age, gender distribution and level of education. On average, MDMA subjects reported having used MDMA on more than 200 occasions over a 4- to 5-year period. As a group, MDMA subjects had not used the drug for 19 weeks, although most of the subjects reported only a 3- to 5-week abstinence period (the longer average time since last use for the group was due to a few subjects who had not used MDMA for several years). Although control and MDMA subjects had similar transport of [^{11}C]McN-5652 from blood to brain (K_1) for all brain regions examined, MDMA users had significant global decreases in DVs of specific binding of [^{11}C]McN-5652 (MANOVA $F = 7.47$, $P = 0.011$), suggesting that they had a reduced density of brain 5-HTT sites compared to controls. Decreases in 5-HTT binding were correlated with extent of previous MDMA use ($r = -0.50$, $P = 0.005$). The covariance effects of age and gender were not significant ($F = 0.04$, $P = 0.95$; $F = 2.04$, $P = 0.16$, respectively). There was no correlation between the duration of the MDMA abstinence period and the extent of specific [^{11}C]McN-5652 binding ($r = -0.09$, $P = 0.75$). All MDMA subjects tested negative for recent drug use, as detected by the EMIT[®] method.

Findings in humans indicate that recreational MDMA use is associated with a global, dose-related reduction in brain 5-HTT, a structural element of the brain 5-HT neuron. They do not, however, rule out the possibility that decreased 5-HTT binding is secondary to pre-existing differences in 5-HT function, although this is deemed unlikely because the distribution of 5-HTT loss parallels that found in MDMA-treated animals, and none of the MDMA users had neuropsychiatric conditions in which 5-HT has been implicated. Since all subjects had abstained from use of any psychoactive drugs for at least 3 weeks prior to study, it is unlikely that pharmacological factors significantly influenced PET findings. Finally, although most of the MDMA users participating in the study had also experimented with other recreational drugs, none of these drugs are known 5-HT neurotoxins in animals, and are not likely to account for the observed differences.

4. Conclusion

The present preclinical and clinical observations provide direct evidence for loss of an element of the 5-HT terminal in abstinent human MDMA users. Taken in conjunction with previous data indicating selective decrements in concentrations of CSF 5-HIAA in MDMA users (McCann et al., 1994) and similar findings in MDMA-treated animals with documented neurotoxic lesions (Scheffel et al., 1998), these data strongly suggest that human MDMA users are susceptible to MDMA-induced brain 5-HT neurotoxicity. Additional studies are needed to confirm and extend these findings. In particular, possible functional consequences of MDMA-induced brain 5-HT neurotoxicity await delineation.

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