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European Journal of Pharmacology 349 (1998) 205–210

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3,4-Methylenedioxymethamphetamine-induced acute changes in dopamine transporter function

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Received 13 January 1998; revised 25 February 1998; accepted 3 March 1998

Abstract

The acute effects of the amphetamine designer drug, 3,4-methylenedioxymethamphetamine (MDMA or 'ecstasy'), on dopamine transporter function in rat striatum were investigated and compared to other psychostimulants known to influence monoaminergic systems. A single MDMA injection (10–20 mg/kg; s.c.) caused a dose-related decrease in [^{3}H]dopamine uptake into striatal synaptosomes prepared 1 h after MDMA administration. This rapid effect on [^{3}H]dopamine uptake returned to control levels 24 h after treatment. A single administration of other amphetamine analogs, such as methamphetamine (15 mg/kg; s.c.), *p*-chloroamphetamine (10 mg/kg; i.p.) or methcathinone (30 mg/kg; s.c.), also rapidly decreased striatal [^{3}H]dopamine uptake. In contrast, a single or multiple administrations of cocaine (30 mg/kg; i.p.) had no effect on [^{3}H]dopamine transport into striatal synaptosomes. These changes in dopamine transporter activity by the amphetamine analogs may occur via reactive oxygen species-mediated mechanisms.

Keywords: MDMA (Methylenedioxymethamphetamine); Dopamine transporter; Oxygen species, reactive; *p*-Chloroamphetamine; Methcathinone; Methamphetamine; Cocaine; Striatum

1. Introduction

3,4-Methylenedioxymethamphetamine (MDMA; 'ecstasy') has attracted considerable public and scientific attention due to its recreational use and neurotoxic potential. Many of the behavioral and biochemical effects of MDMA (for a review, see Green et al., 1995) indicate that this substituted amphetamine acts similarly, but not identically, to other amphetamine analogs such as methamphetamine.

Recent studies from this laboratory have indicated that a single and multiple methamphetamine administrations to rats induce a rapid and temporary reduction of striatal dopamine transporter function (Fleckenstein et al., 1997b) that is distinct from the long-term transporter deficits associated with nerve terminal degeneration (Wagner et al., 1980). Although the mechanism by which methamphetamine causes this short-term reduction has not been identified, reactive oxygen species may play a role in this decrease in dopamine transporter activity. MDMA administration (Colado and Green, 1995; Cadet et al., 1995), like methamphetamine (Hirata et al., 1995; Kondo et al., 1994; Giovanni et al., 1995; Fleckenstein et al., 1997c), likely promotes the formation of reactive oxygen species. Reactive oxygen species reduce neurotransporter function suggesting that these drugs may alter the uptake of neurotransmitters by their ability to initiate oxidative inactivation of transporter proteins (Volterra et al., 1994; Pögün et al., 1994; Berman et al., 1996; Fleckenstein et al., 1997a).

In the present study, we examined the possibility that MDMA and other stimulants of abuse alter the activity of dopamine transporters. Uptake of [^{3}H]dopamine into rat striatal synaptosomes following in vivo administration of MDMA was measured. For comparison, effects of methamphetamine, *p*-chloroamphetamine, methcathinone, or cocaine were also examined. The results reveal that MDMA caused a rapid, reversible decrease in the transport of dopamine into striatal synaptosomes. *p*-Chloroamphetamine, methcathinone and methamphetamine also rapidly decreased synaptosomal [^{3}H]dopamine uptake;

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0014-2999/98/$19.00

however, cocaine treatment had no effect on synaptosomal [^{3}H]dopamine transport, suggesting that the effect of cocaine on the dopamine transporter was distinct from the amphetamine analogs.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats (200–300 g; Simonsen Laboratories, Gilroy, CA) were maintained under conditions of controlled temperature and lighting, with food and water provided ad libitum. Rats were killed by decapitation. All procedures were conducted in accordance with approved National Institutes of Health guidelines.

2.2. Drugs and chemicals

(±)-3,4-MDMA hydrochloride, (±)-methamphetamine hydrochloride, (±)-*N*-methcathinone hydrochloride, and (−)-cocaine hydrochloride were supplied generously by the National Institute on Drug Abuse (Rockville, MD). Pargyline hydrochloride was supplied kindly by Abbott Laboratories (North Chicago, IL). (±)-*p*-Chloroamphetamine hydrochloride was purchased from Sigma Chemical (St. Louis, MO). [7,8-^{3}H]Dopamine (43 Ci/mmol) was purchased from Amersham Life Sciences (Arlington Heights, IL). Drugs were administered as indicated in the legends of appropriate figures, and doses were calculated as the respective free bases.

2.3. Synaptosomal [^{3}H]dopamine uptake

Uptake of [^{3}H]dopamine was determined according to a modification of a method described by Boja et al. (1992). Fresh striatal tissue was homogenized in ice-cold 0.32 M sucrose and centrifuged ($800 \times g$ for 12 min; 4°C). For kinetic experiments, striatal tissue was pooled from two saline-treated rats for control values, and two MDMA-treated rats for treatment values. The supernatant (S1) was then centrifuged ($22\,000 \times g$ for 15 min; 4°C), and the resulting pellet (P2) was resuspended in ice-cold 0.32 M sucrose. Assays were conducted in modified Kreb's buffer (in mM: 126 NaCl, 4.8 KCl, 1.3 $CaCl_2$, 16 sodium phosphate, 1.4 $MgSO_4$, 11 dextrose, 1 ascorbic acid; pH 7.4). Each assay tube contained synaptosomal tissue (i.e., resuspended P2 obtained from 1.5 mg original wet weight striatal tissue) and 1 μM pargyline. Nonspecific values were determined in the presence of 1 mM cocaine. After preincubation of assay tubes for 10 min at 37°C, assays were initiated by addition of [^{3}H]dopamine (0.5 nM final concentration, or up to 10 μM for kinetic experiments). Samples were incubated at 37°C for 3 min (or 5 min for kinetic experiments) and then filtered through Whatman GF/B filters soaked previously in 0.05% polyethylenimine. Filters were washed rapidly 3 times with 3 ml ice-cold 0.32 M sucrose using a Brandel filtering manifold. Radioactivity trapped in filters was counted using a liquid scintillation counter.

2.4. Data analysis

Statistical analyses between 2 groups were conducted using 2-tailed Student's *t*-test. Analyses among three or more groups were conducted using analysis of variance followed by a Fisher Least Significant Difference (LSD) test. Differences among groups were considered significant if the probability of error was less than 5%.

3. Results

Results presented in Fig. 1 demonstrate that MDMA administration caused a dose-related decrease in [^{3}H]dopamine uptake into striatal synaptosomes prepared from rats decapitated 1 h after administration. The decline in [^{3}H]dopamine uptake was significant with a dose of 10 mg/kg (79% of control), and was at maximum with a dose of 15 or 20 mg/kg (70.5 or 70.4% of control, respectively).

Consistent with previous reports of a rapid and reversible decrease in striatal [^{3}H]dopamine uptake after methamphetamine administration (see Section 4), results presented in Fig. 2 demonstrate that striatal [^{3}H]dopamine uptake returned to control levels 24 h after MDMA administration (15 mg/kg).

Results presented in Fig. 3A depict the effects of methamphetamine, *p*-chloroamphetamine, or methcathinone on striatal synaptosomal [^{3}H]dopamine uptake 1 h after administration. A single administration of methamphetamine (15 mg/kg; s.c.), *p*-chloroamphetamine (10

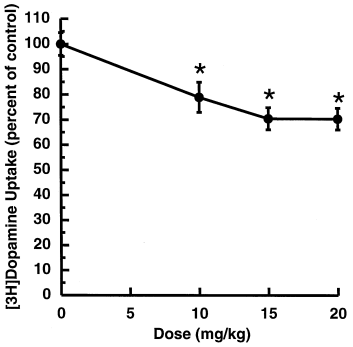

Fig. 1. Dose–response effects of MDMA administration on [^{3}H]dopamine uptake in rat striatal synaptosomes. Rats received MDMA (10–20 mg/kg, s.c.) or saline vehicle (1 ml/kg, s.c.) 1 h prior to decapitation. Values represent means of [^{3}H]dopamine uptake as a percentage of saline-treated controls, and vertical lines represent 1 S.E.M. of determinations ($n = 6$). Control [^{3}H]dopamine uptake was 704.4 fmol [^{3}H]dopamine/mg protein. *Values for MDMA-treated rats that are significantly different from saline-treated rats ($P \leq 0.05$).

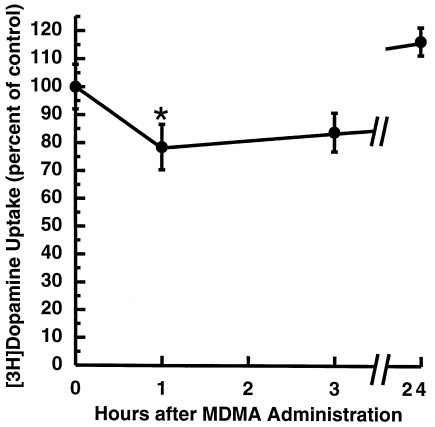

Fig. 2. Time–response effects of MDMA administration on [^{3}H]dopamine uptake in rat striatal synaptosomes. Rats received MDMA (15 mg/kg, s.c.) 1 to 24 h, or saline vehicle (1 ml/kg, s.c.; zero time value) 1 h, prior to decapitation. Values represent means as a percentage of saline-treated controls (zero time value), and vertical lines represent 1 S.E.M. of determinations ($n = 7–8$). Control [^{3}H]dopamine uptake was 413.3 fmol [^{3}H]dopamine/mg protein. ∗Values for MDMA-treated rats that are significantly different from saline-treated rats ($P \leq 0.05$).

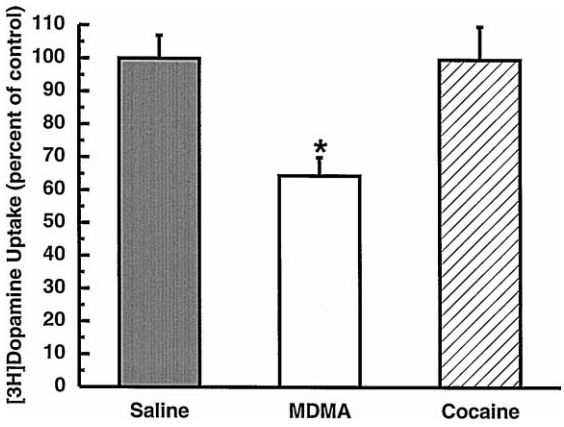

Fig. 4. Effects of multiple MDMA administrations or multiple cocaine administrations on [^{3}H]dopamine uptake in rat striatal synaptosomes. Rats received MDMA (4×15 mg/kg, 2-h intervals, s.c.), cocaine (4×30 mg/kg, 2-h intervals, i.p.), or saline vehicle (4×1 ml/kg, 2-h intervals, i.p.) 1 h prior to decapitation. Columns represent means as a percentage of saline-treated controls, and vertical lines represent 1 S.E.M. of determinations ($n = 6–7$). Control [^{3}H]dopamine uptake was 18.71 fmol [^{3}H]dopamine/mg original wet weight tissue. ∗Values for drug-treated rats that are significantly different from saline-treated rats ($P \leq 0.05$).

mg/kg; i.p.), or methcathinone (30 mg/kg; s.c.) decreased [^{3}H]dopamine uptake by 37, 27, or 28%, respectively. In contrast, results obtained from a separate experiment (Fig. 3B) demonstrate that a single administration of cocaine (30 mg/kg; i.p.) did not decrease [^{3}H]dopamine uptake into striatal synaptosomes 1 h after administration. In addition, multiple administrations of cocaine (30 mg/kg/administration; four administrations at 2-h intervals) had no effect, while multiple MDMA administrations (15 mg/kg/administration; four administrations at 2-h intervals) decreased [^{3}H]dopamine uptake by 35.6% (Fig. 4). This decrease in synaptosomal [^{3}H]dopamine uptake after multiple MDMA administrations was associated with a decrease in transporter V_{max} (2388.0 and 1409.7 fmol/mg original wet weight tissue/5 min for saline- and MDMA-treated rats, respectively), while transporter K_m was virtually unaffected (99.6 and 98.9 nM for saline- and MDMA-treated rats, respectively). The doses selected for methamphetamine, *p*-chloroamphetamine, methcathinone, and cocaine in these experiments have been shown previously to induce profound changes in monoaminergic systems (Fleckenstein et al., 1997b; Johnson et al., 1990; Gygi et al., 1996; Church et al., 1987).

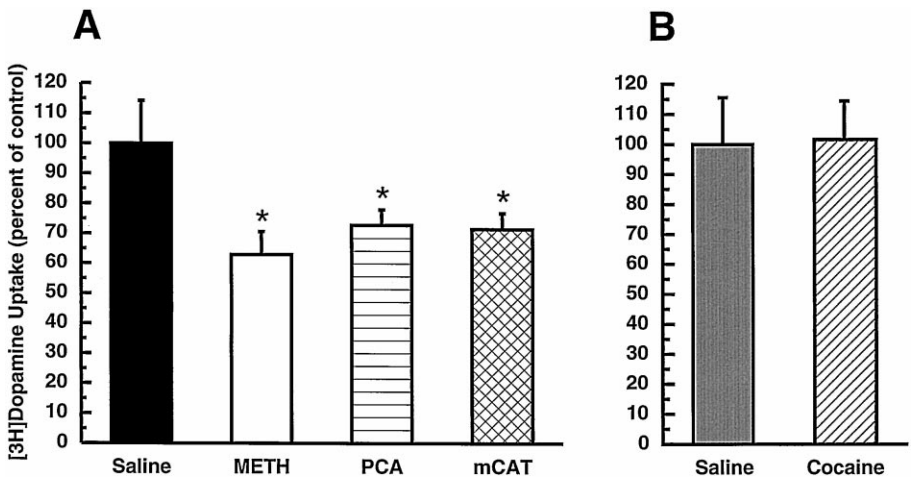

Fig. 3. Left panel: Effects of methamphetamine (METH), *p*-chloroamphetamine (PCA), or methcathinone (mCAT) administration on [^{3}H]dopamine uptake in rat striatal synaptosomes. Rats received METH (15 mg/kg, s.c.), PCA (10 mg/kg, i.p.), mCAT (30 mg/kg, s.c.), or saline vehicle (1 ml/kg, s.c.) 1 h prior to decapitation. Right panel: Rats received cocaine (30 mg/kg, i.p.) or saline (1 ml/kg, i.p.) 1 h prior to decapitation. Columns represent means of [^{3}H]dopamine uptake as a percentage of saline-treated controls, and vertical lines represent 1 S.E.M. of determinations ($n = 5–6$). Control [^{3}H]dopamine uptake was 11.62 and 13.9 fmol [^{3}H]dopamine/mg original wet weight tissue for left and right panels, respectively. ∗Values for drug-treated rats that are significantly different from saline-treated rats ($P \leq 0.05$).

4. Discussion

MDMA treatment causes long-term deficits in 5-hydroxytryptamine (5-HT) systems as demonstrated by reductions in brain 5-HT content (Ricaurte et al., 1993) and density of [^{3}H]paroxetine-labeled 5-HT uptake sites (Battaglia et al., 1987), decreased activity of tryptophan hydroxylase (Stone et al., 1987), and reductions in 5-HT-immunoreactive staining (O'Hearn et al., 1988). Apart from these well-characterized MDMA-induced deficits selective for 5-HT neurons, the results from the present study show a rapid, reversible effect on dopaminergic neurons. As early as 1 h after a single administration, MDMA diminished dopamine transporter function, as demonstrated by a decrease in striatal synaptosomal [^{3}H]dopamine uptake from MDMA-treated rats. Since [^{3}H]dopamine uptake returned to control levels by 24 h, it appears that the MDMA-induced effect on the dopamine transporter was temporary. This laboratory has recently reported a rapid and reversible effect on striatal [^{3}H]dopamine uptake by methamphetamine administration (Fleckenstein et al., 1997b), and a similar finding was described after *p*-chloroamphetamine treatment (Sanders-Bush et al., 1975).

Similar to methamphetamine (Fleckenstein et al., 1997b), the MDMA-induced reduction in [^{3}H]dopamine uptake resulted from a decrease in transporter V_{max} without a change in K_m. These data are consistent with previous findings from this laboratory that exposure of the dopamine transporter to the reactive oxygen species-generating enzyme, xanthine oxidase, decreases the V_{max} of the transporter (Fleckenstein et al., 1997a), and support the hypothesis that reactive oxygen species formation may contribute to the effect induced by MDMA.

It is not likely that the decrease in [^{3}H]dopamine uptake caused by MDMA treatment was due to a loss of dopamine transporters, since [^{3}H]dopamine uptake was restored much more quickly than the time likely required to synthesize replacement dopamine transporter (i.e., the $t_{1/2}$ of dopamine transporter turnover is approximately 6.3 days; Fleckenstein et al., 1996). Also, it does not appear that the rapid change in dopamine transporter activity caused by MDMA administration was due to neuronal cell death, since dopamine transporter function returned rapidly (i.e., 24 h after treatment). In addition, other indicators of damage to dopamine neurons, such as long-term reductions in tyrosine hydroxylase activity, are not observed after single or multiple administrations of MDMA (Stone et al., 1986).

As suggested by this laboratory for methamphetamine-induced decreases in striatal [^{3}H]dopamine uptake (Fleckenstein et al., 1997b), the diminution of dopamine transporter function by MDMA may be due to reversible modification of the transporter structure. This may occur via an interaction between drug-initiated reactive oxygen species and the dopamine transporter protein. Dopamine transporters are among many neuronal proteins that are susceptible to oxidative modification (Volterra et al., 1994; Pögün et al., 1994; Berman et al., 1996; Metzger et al., 1996). Administration of MDMA, methamphetamine or amphetamine can induce the formation of reactive oxygen species (Stone et al., 1989; Cadet et al., 1995; Fleckenstein et al., 1997c; Giovanni et al., 1995; Huang et al., 1996). Dopamine may contribute to this effect, as it can promote the formation of reactive oxygen species (Graham, 1978). Thus, drug-induced increases in extracellular dopamine may result in auto-oxidation of this monoamine leading to the production of reactive oxygen species: subsequently, these may oxidize the dopamine transporter and reduce [^{3}H]dopamine uptake into striatal synaptosomal preparations. The observed restoration of dopamine transporter function may be due to reducing events reversing the oxidative effects initiated by MDMA administration.

It appears that the administration of these drugs in vivo does not result in residual drug, in the ex vivo synaptosomal assay, at concentrations sufficient to affect directly dopamine uptake. For example, it has been demonstrated that methamphetamine administered in vivo is present in the synaptosomal preparation only at levels far below those necessary to affect [^{3}H]dopamine uptake when added directly to striatal synaptosomes (Fleckenstein et al., 1997b). Although unlikely, we cannot absolutely exclude the possibility that metabolites, or residual MDMA at the transporter, are involved since drug concentrations were not measured in these studies.

The results showing a rapid decrease in striatal [^{3}H]dopamine uptake by acute administration of *p*-chloroamphetamine, methcathinone and methamphetamine as well as MDMA suggest that the amphetamine analogs cause a similar rapid effect on the dopamine transporter. Because all of these compounds cause dopamine release (Nash and Nichols, 1991; Nash and Yamamoto, 1992; Sharpe et al., 1986; Glennon et al., 1987), dopamine may play a causal role in the diminution of dopamine transporter activity. In contrast, no change was observed for [^{3}H]dopamine uptake into striatal synaptosomes after a single or multiple administrations of cocaine suggesting that cocaine does not induce a similar effect regardless of the dosing regimen employed. Cocaine is distinguished from the amphetamine analogs studied in that it increases extracellular dopamine by blocking monoamine transporters, while the amphetamine analogs release dopamine by reversing the transporter activity (Liang and Rutledge, 1982; Fisher and Cho, 1979). It is possible that binding of cocaine to the transporter affords protection to the protein against the oxidative action of extracellular dopamine. This difference may contribute to the different pharmacological features of these drugs.

The results from this study implicate novel mechanisms by which the dopamine transporter can be regulated pharmacologically as well as physiologically, and further demonstrate a newly observed effect of amphetamine analogs on dopaminergic neurons. As normal function of

this transporter is to regulate the action of released dopamine, disruption of dopamine transporter function can lead to deleterious effects such as changes in dopaminergic transmission and behavior (Giros et al., 1996). In addition, decreased reuptake of released dopamine may promote the formation of extraneuronal dopamine-related reactive oxygen species. On the other hand, diminution of dopamine transporter activity may attenuate amphetamine analog-mediated release of dopamine. In addition, previous studies suggest that inhibition of 5-HT transporter function attenuates MDMA-induced neurotoxicity to 5-HT neurons (Schmidt and Taylor, 1990) suggesting that temporary abatement of dopamine transporter function may even have a protective role in dopaminergic neurotoxicity. Future investigations to characterize further amphetamine analog-induced modification of the dopamine transporter protein, and it's functional significance, are warranted.

Acknowledgements

The authors acknowledge gratefully the excellent technical assistance of Meisha Beyeler and Tracy Mercer. This research was supported by grants DA 00869, DA 04222 and DA 11389 from the National Institute on Drug Abuse.

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