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Potentiation of 3,4-methylenedioxymethamphetamine-induced dopamine release and serotonin neurotoxicity by 5-HT_2 receptor agonists

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Abstract

The effects of the 5-HT_2 receptor agonists 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) and 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeODMT) on 3,4-methylenedioxymethamphetamine (MDMA)-induced dopamine release and 5-HT depletion in the striatum were studied. The MDMA-induced increase in the extracellular concentration of dopamine in the striatum was enhanced significantly in rats treated with either DOI (2 mg/kg, ip.) or 5-MeODMT (15 mg/kg, ip.), as assessed using in vivo microdialysis. Neither DOI nor 5-MeODMT alone altered the extracellular concentration of dopamine in the striatum. The striatal concentration of 5-HT was decreased, but not significantly, 7 days following a single administration of MDMA (10 mg/kg, sc.). However, 7 days following the concomitant treatment with DOI and MDMA the striatal concentration of 5-HT was significantly less than that in rats treated with MDMA alone or the vehicle-treated controls. It is concluded that activation of 5-HT_2 receptors is an important determinant of the acute increase in extracellular dopamine and, consequently, the long-term depletion of brain 5-HT produced by MDMA.

Keywords: DOI (1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane); MDMA (3,4-methylenedioxymethamphetamine); 5-MeODMT (5-methoxy-*N*,*N*-dimethyltryptamine); Microdialysis; Neurotoxicity; 5-HT_2 receptor

1. Introduction

The single or repeated administration of 3,4-methylendioxymethamphetamine (MDMA) produces a long-lasting neurotoxicity of 5-hydroxytryptamine (5-HT, serotonin) neurons, as evidenced by a reduction in the density of 5-HT axon terminals, the number of 5-HT reuptake sites labelled by [^{3}H]paroxetine, tryptophan hydroxylase activity and 5-HT concentrations (Commins et al., 1987; Schmidt, 1987; Stone et al., 1987; Battaglia et al., 1988; O'Hearn et al., 1988). The neurotoxicity resulting from high dose MDMA administration is selective for 5-HT; it is localized to the axon terminals and reversible (Battaglia et al., 1988; 1991; Scanzello et al., 1993).

Considerable evidence exists that is supportive of the hypothesis that the depletion of 5-HT in the brain is due, in part, to the prolonged and excessive release of dopamine elicited by MDMA administration (Stone et al, 1988; Nash, 1990). Thus, treatments (e.g., α-methyl-*p*-tyrosine, 6-hydroxydopamine lesions of the substantia nigra) which diminish the acute, sustained increase in extracellular dopamine concentrations produced by MDMA administration also attenuate the long term depletion of brain 5-HT (Stone et al., 1988; Schmidt et al., 1990; Brodkin et al., 1993). The protection against MDMA-induced 5-HT neurotoxicity provided by decreasing the acute, sustained increase in dopamine function can be restored by the administration of the dopamine precursor L-dihydroxyphenylalanine (Schmidt et al., 1991). Finally, a positive correlation exists between the magnitude of the acute release of dopamine and the extent of long-term 5-HT depletion produced by the administration of MDMA or structurally related phenalkylamines (Johnson et al.,

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1990; Nash and Nichols, 1991). Thus, efforts to determine the acute effect of MDMA on dopaminergic function are crucial in understanding the 5-HT neurotoxicity produced by MDMA and related compounds.

Data from in vitro studies utilizing brain slices or synaptosomes are suggestive that MDMA-induced dopamine release, like that evoked by amphetamine (Fischer and Cho, 1979; Liang and Rutledge, 1982), likely occurs via a carrier-mediated mechanism (Johnson et al., 1986, 1991; Schmidt et al., 1987). Additional support for this mechanism of action has come from in vivo microdialysis studies. For example, the local application of MDMA directly to the striatum elicits a marked increase in the extracellular concentration of dopamine that is attenuated in rats treated with inhibitors of the dopamine transporter, such as mazindol (Nash and Brodkin, 1991). Therefore, based on these data and the structural similarities between MDMA and amphetamine, it seems reasonable to conclude that MDMA releases dopamine via a carrier-mediated mechanism.

However, there is evidence that the extent of MDMA-induced dopamine release may involve mechanisms in addition to the dopamine transporter. For example, unilateral infusion of MDMA onto dopamine cell bodies in the substantia nigra results in an ipsilateral, but not contralateral, increase in striatal dopamine content (Schmidt and Taylor, 1988), which cannot be accounted for easily by a carrier-mediated event. Equally difficult to align with a carrier-mediated mechanism of dopamine release by MDMA are the findings that the administration of 5-HT_2 receptor antagonists (i.e., including 5-HT_{2A} and 5-HT_{2C} receptor antagonists according to the nomenclature of Humphrey et al., 1993), such as ketanserin and $R(+)$-α-(2,3-dimethoxyphenyl)-1-[2(4-fluorophenylethyl)]-4-piperidine methanol (MDL 100,907), attenuates the acute increase in dopamine release after systemic (Nash, 1990; Schmidt et al., 1992) but not local (Nash and Brodkin, 1991) MDMA administration. Based, in part, on these observations, it has been hypothesized that 5-HT_2 receptors exert a facilitatory role in MDMA-induced dopamine release. The purpose of the present study was to test the hypothesis that activation of 5-HT_2 receptors enhances MDMA-induced dopamine release and potentiates MDMA-induced depletion of brain 5-HT.

2. Materials and methods

2.1. Drugs

The racemic mixture of MDMA hydrochloride was provided by the National Institute of Drug Abuse. 1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane (DOI) hydrochloride and 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeODMT) hydrochloride were purchased from Research Biochemical (Natick, MA) and Sigma Chemical Co. (St. Louis, MO), respectively. Drug injections were accomplished in a volume of 1 ml/kg.

2.2. Animals

Adult (225–300 g) male rats of the Sprague-Dawley strain (Zivic Miller Laboratories, Allison Park, PA) were used in these studies. The animals were housed three per cage in a temperature and light-controlled room until the day of drug administration. The rats were housed individually for 24–48 h after drug treatment and then returned to their home cages. Food and water were available ad libitum.

2.3. In vivo microdialysis and biochemical procedures

Rats were implanted with a stainless steel guide cannula under ketamine/xylazine (70/7 mg/kg, i.m.) induced anesthesia 48–72 h prior to the insertion of the dialysis probe. On the morning of the dialysis experiment, a concentric style dialysis probe (4.5 mm of exposed membrane) was inserted through the guide cannula into the striatum: A, 1.2 mm; L, 3.1 mm; V, −6.5 mm from bregma, according to the stereotaxic atlas of Paxinos and Watson (1986). A modified Krebs-Ringer buffer (mM: NaCl, 145; Na_2HPO_4, 6; $CaCl_2$, 1.2; KH_2PO_4, 1.0; KCl, 2.0; pH 7.4) was delivered through the probe at a rate of 1.8 μl/min. After a 2-h equilibration period, dialysis samples were collected every 30 min. At least four baseline samples were obtained prior to drug treatment.

2.4. Biochemical measurements

The extracellular concentration of dopamine in the striatum was quantified with high performance liquid chromatography with electrochemical detection using methods similar to those described elsewhere (Nash and Brodkin, 1991; Brodkin et al., 1993). Briefly, dialysis samples were injected onto a 2 mm C18-column (Phenomenex, Torrance, CA) connected to a LC-4B amperometric detector (Bioanalytical Systems, West Lafayette, IN). The mobile phase consisted of 35 mM citric acid, 54 mM sodium acetate, 50 mg/l of disodium ethylenediamine tetraacetate, 70 mg/l of octanesulfonic acid sodium salt, pH 4.2 pumped at a flow rate of 0.3 ml/min.

For post mortem analysis of brain 5-HT the rats were killed by decapitation 7 days after MDMA administration. Striatal samples were dissected from 1 mm slices, and the tissue was kept frozen (−40°C) until analyzed for 5-HT. At the time of assay, the samples were sonicated for 5 s in 0.2 N perchloric acid contain-

ing 0.1% cysteine. The samples were subjected to centrifugation, and an aliquot of the resulting supernatant fluid was analyzed for 5-HT by high performance liquid chromatography with electrochemical detection using the conditions described for the analysis of extracellular dopamine content.

2.5. Statistical analyses

Analysis of the tissue concentrations of 5-HT was performed using a two-way analysis of variance. Differences between treatment groups were determined with the use of the Student-Newman-Keuls test. Data from dialysis experiments was analyzed using a two-way repeated measures analysis of variance (Sigmastat, Jandel Scientific). Multiple pairwise comparisons were performed using the Student-Newman-Keuls test. Treatment differences were considered statistically significant at $P < 0.05$.

3. Results

The maximal extracellular concentration of dopamine in the striatum following the administration of MDMA (10 mg/kg, s.c.) was approximately 10 times greater than that determined during the baseline period (Fig. 1). The dopamine content in the dialysis samples was maximal between 30–60 min following MDMA administration. In rats treated with DOI (2 mg/kg, i.p.) 15 min prior to the administration of MDMA (10 mg/kg, s.c.), the increase in the extracellular concentration of dopamine was significantly ($P < 0.05$) greater than that in rats treated with MDMA alone at the 60, 90 and 120 min post-administration times. The administration of DOI alone did not significantly alter the extracellular concentration of dopamine in the striatum (Fig. 1).

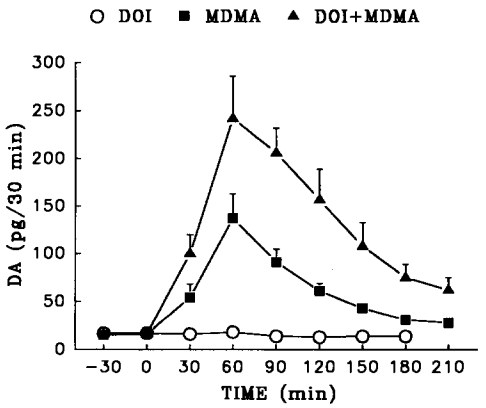

Fig. 1. Effect of DOI on the MDMA-induced release of striatal dopamine. DOI (2 mg/kg, i.p.) or its vehicle was injected 15 min prior to MDMA (10 mg/kg, s.c.), which was injected at time 0. Dialysis samples were obtained every 30 min for 3.5 h following MDMA administration. Each symbol and vertical line represent the mean ± S.E.M. of six to seven rats. An absence of a vertical line indicates that the S.E.M. was less than the diameter of the symbol. Values for rats injected with the combination of DOI and MDMA were significantly ($P < 0.05$) greater than those for rats given MDMA alone at the 60, 90 and 120 min time points.

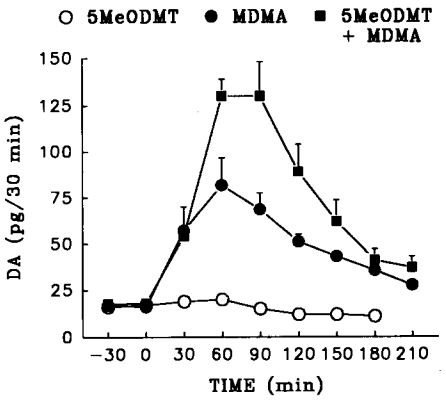

Fig. 2. Effect of 5-MeODMT on the MDMA-induced release of striatal dopamine. 5-MeODMT (15 mg/kg, i.p.) or its vehicle was injected simultaneously with MDMA (10 mg/kg, s.c.) at time 0. Each symbol and vertical line represent the mean ± S.E.M. of six to seven animals. An absence of a vertical line indicates that the S.E.M. was less than the diameter of the symbol. Values for the rats injected with the combination of 5-MeODMT and MDMA were significantly ($P < 0.05$) greater than those for rats given MDMA alone at the 60 and 90 min time points.

The administration of 5-MeODMT (15 mg/kg, i.p.) also enhanced the MDMA-induced release of striatal dopamine. Extracellular concentrations of dopamine in the striatum of rats treated with 5-MeODMT and MDMA were significantly ($P < 0.05$) greater than those in rats treated only with MDMA at the 60 and 90 min post-administration times (Fig. 2). The administration of 5-MeODMT alone did not significantly alter the

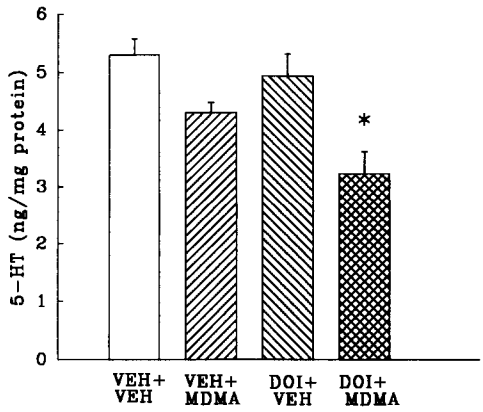

Fig. 3. Effect of DOI on the MDMA-induced depletion of 5-HT in the striatum. Rats were injected with DOI (2 mg/kg, i.p.) or its vehicle 15 min prior to an injection of MDMA (10 mg/kg, s.c.) or its vehicle. The rats were killed by decapitation 7 days following drug treatment. Column heights and vertical lines represent the mean ± S.E.M. of 5–17 rats. * $P < 0.05$ compared to each of the other values.

extracellular concentrations of dopamine in the striatum (Fig. 2).

The effect of DOI (2 mg/kg, i.p.) on MDMA-induced depletion of 5-HT in the striatum is depicted in Fig. 3. The tissue concentration of 5-HT was determined 7 days following a single injection of MDMA (10 mg/kg, s.c.) alone or in combination with DOI (2 mg/kg, i.p.). The administration of MDMA alone produced a slight, but non-significant, decrease in the striatal concentration of 5-HT as compared to the vehicle-treated group. However, the co-administration of DOI and MDMA resulted in a significant ($P < 0.05$) depletion of 40% of the striatal concentration of 5-HT as compared to the other treatment groups (Fig. 3).

4. Discussion

The systemic administration of ketanserin, a 5-HT_2 receptor antagonist, has been reported to attenuate the acute increase in the extracellular concentration of striatal dopamine produced by MDMA administration, as well as attenuate the MDMA-induced increase in striatal dopamine synthesis (Nash, 1990; Nash et al., 1990; Nash and Brodkin, 1991). Consistent with these results is the report of Schmidt et al. (1992) in which another 5-HT_2 receptor antagonist, MDL 100,907, was shown to attenuate the MDMA-induced increase in striatal dopamine synthesis and increase in extracellular concentration of dopamine. In these studies, the administration of the 5-HT_2 receptor antagonists alone did not alter striatal dopamine synthesis or release. On the basis of these findings, it has been suggested that the extent of MDMA-induced dopamine release is dependent, in part, upon the activation of 5-HT_2 receptors. If this hypothesis is correct, then stimulation of 5-HT_2 receptors should facilitate MDMA-induced dopamine release. The results of the present study are supportive of this hypothesis, viz., treatment with the selective 5-HT_2 receptor agonist, DOI, or the non-selective serotonin agonist 5-MeODMT enhanced the stimulatory effect of MDMA on striatal dopamine release. Interestingly, the systemic administration of either agonist alone at the doses used in the present studies did not alter striatal dopamine release.

The present findings are consistent with the recent report of Huang and Nichols (1993) in which it was demonstrated that DOI alone had no effect on dopamine synthesis, but it potentiated the increase in dopamine synthesis produced by amphetamine. Thus, receptors of the 5-HT_2 subtype appear to function in a modulatory fashion under conditions in which dopamine synthesis and/or release are markedly enhanced. One explanation for the ability of DOI to potentiate MDMA-induced dopamine release is that there is a state-dependent facilitation by DOI of the MDMA-induced increase in striatal dopamine synthesis; this effectively would allow for a greater amount of releasable dopamine.

The site of action whereby 5-HT_2 receptors modulate dopaminergic function is unresolved. One explanation is that 5-HT_2 receptors located in the substantia nigra modulate the striatonigral feedback regulation of dopaminergic neurons. Recently, Nash et al. (1993) reported that MDMA administration results in a concomitant increase in 5-HT release and decrease in the release of γ-amino butyric acid (GABA) in the substantia nigra. Moreover, infusion of the 5-HT_2 receptor antagonist ritanserin through the dialysis probe in the substantia nigra attenuated the suppression of nigral GABA release produced after the systemic administration of MDMA. Furthermore, MDMA-induced dopamine release in the striatum of rats given ritanserin into the substantia nigra was significantly less than that elicited in control animals. Thus, it can be hypothesized that 5-HT_2 receptors in the substantia nigra, which become activated following MDMA-induced 5-HT release, function to suppress nigral GABA release. In view of the postulated role of nigral GABA in the feedback regulation of nigrostriatal dopaminergic neurons (Groves et al., 1975), removal of GABA-mediated feedback inhibition would result in an excessive and/or sustained increase in striatal dopamine release.

However, the hypothesized role of nigral 5-HT_2 receptors to modulate MDMA-induced dopamine release in the striatum does not preclude additional sites for 5-HT_2 receptor modulation. There is evidence that 5-HT may act via multiple 5-HT receptor subtypes within the striatum to facilitate dopamine release from nerve terminals (Benloucif and Galloway, 1991; Benloucif et al., 1993). Moreover, Schmidt et al. (1994) have reported that the direct intrastriatal administration of the 5-HT_2 receptor antagonist MDL 100,907 attenuates MDMA-induced dopamine release in the striatum. Finally, 5-HT_2 receptors in the terminal fields of other dopaminergic systems also have been reported to mediate a stimulatory effect of 5-HT on dopamine release. Recently, Parsons and Justice (1993) have demonstrated that 5-HT can act directly within the nucleus accumbens to facilitate basal dopamine release in this brain region through a 5-HT_2 receptor-mediated mechanism. Collectively, the results of these studies are suggestive that 5-HT may act via 5-HT_2 and/or other receptor subtypes to facilitate dopamine release from axon terminals.

The present results could be viewed in favor of a role of 5-HT_2 receptors in the depletion of striatal 5-HT elicited by MDMA. It could be argued that subthreshold activation of these sites was achieved by 10 mg/kg of MDMA and additional activation by DOI or 5-MeODMT was required to elicit neurotoxicity. However, the recent report by Huang and Nichols

(1993) is suggestive that 5-HT_2 receptor activation per se is not a determinant of 5-HT neurotoxicity. These investigators reported that there was no reduction in [^{3}H]paroxetine binding following the co-administration of DOI and amphetamine. The combination of amphetamine and DOI was utilized to mimic the conditions following MDMA administration in which extracellular dopamine is increased and 5-HT_2 receptor stimulation is achieved indirectly via serotonin release. Thus, elevations in extracellular dopamine, such as that produced by amphetamine, and activation of 5-HT_2 receptors alone are not sufficient to elicit 5-HT neurotoxicity. On the basis of these findings it is suggested that MDMA-induced 5-HT depletion is dependent upon an increase in the extracellular concentration of dopamine and an activation of carrier-mediated 5-HT release. One hypothesis is that MDMA administration results in an activation of the 5-HT transporter, the facilitated uptake of dopamine into the serotonin nerve terminal and the subsequent autoxidation of dopamine and degeneration of the 5-HT terminal. With consideration of this hypothesis, the potentiation by DOI of the MDMA-induced depletion of striatal 5-HT concentrations would be viewed as a result of the enhancement of MDMA-induced release of dopamine in the striatum.

It is not possible to exclude pharmacokinetic interactions as an explanation for potentiation of MDMA-induced dopamine release and 5-HT neurotoxicity by DOI and 5-MeODMT. The primary route of inactivation of phenethylamines is hydroxylation of the aromatic ring. Inasmuch as DOI and MDMA have ring substitutions, DOI would have to increase the brain concentration of MDMA by preventing its metabolism through other metabolic pathways. The possibility that pharmacokinetic interactions underlie the account for the results of the present study seems unlikely in view of the fact that potentiation of the effects of MDMA also was produced by 5-MeODMT, an indole-type 5-HT_2 receptor agonist that is structurally unrelated to DOI and MDMA.

The acute, stimulatory effect of MDMA on striatal dopamine release has been well documented (Yamamoto and Spanos, 1988; Hiramatsu and Cho, 1990; Nash, 1990). Evidence is suggestive that MDMA, like other amphetamines, enhances dopamine release via a carrier-mediated mechanism that involves newly synthesized, non-vesicular dopamine (Nash and Brodkin, 1991; Schmidt et al.,1992). Thus, MDMA-induced dopamine release in the striatum is attenuated in rats treated with the dopamine synthesis inhibitor α-methyltyrosine (Schmidt et al., 1992; Nash et al., 1993) or with inhibitors of the dopamine transporter, e.g., mazindol (Nash and Brodkin, 1991). However, the findings that MDMA-stimulated dopamine release is modulated by 5-HT_2 receptor agonists and antagonists, as shown in the present study and earlier work (Nash, 1990; Schmidt et al., 1992), provides evidence for the contention that MDMA-induced dopamine release is dependent not only on the dopamine transporter but also upon impulse-dependent processes. In further support of this view is the finding that MDMA-induced dopamine release in the striatum is significantly attenuated in rats in which tetrodotoxin has been administered into the striatum through the dialysis probe (Gudelsky, unpublished observations). In contrast, dopamine release elicited by amphetamine is relatively unaffected by tetrodotoxin (Yamamoto, unpublished observations). Thus, whereas amphetamine-induced dopamine release is believed to be largely, if not entirely, carrier-mediated, MDMA-induced dopamine release appears to be dependent upon carrier-mediated and impulse-dependent processes.

The results of the present studies are consistent with the hypothesis that 5-HT_2 receptors enhance state-dependent dopaminergic activity and that the sustained increase in extracellular dopamine produced by MDMA plays a role in the long term neurotoxic effect on 5-HT axon terminals. In addition to the mechanistic interpretation of these results, there seemingly are implications for risk to human health associated with the concomitant abuse of MDMA and hallucinogenic agents, e.g., lysergic acid diethylamide, which are 5-HT_2 receptor agonists. If the results of the present study can be extrapolated to humans, there may be increased risk for 5-HT neurotoxicity in those individuals who ingest MDMA and hallucinogenic agents concomitantly.

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