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Stimulant effects of 3,4-methylenedioxymethamphetamine in the nucleus accumbens of rat

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This study examined the behavioral effects in rats of intracerebral administration of S(+)-3,4-methylenedioxymethamphetamine (S-MDMA) using an automated holeboard and open-field apparatus. Administration of S-MDMA into the nucleus accumbens septi produced locomotor hyperactivity. Although the stimulant effects of S-MDMA administered systemically are antagonized by fluoxetine pretreatment, the activating effects of S-MDMA administered into the nucleus accumbens were not antagonized by fluoxetine. A similar increase in locomotor activity was observed after S-amphetamine administration into the nucleus accumbens. In contrast, the selective 5-HT-releasing drug and S-MDMA congener N-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine (MBDB) produces MDMA-like locomotor hyperactivity when administered systemically but did not alter locomotor activity when injected into the nucleus accumbens. These data indicate that S-MDMA actions in the nucleus accumbens are pharmacologically distinct from the primary effects of systemically administered S-MDMA. Behavioral effects of S-MDMA in the nucleus accumbens may result from the catecholamine-releasing properties that S-MDMA shares with S-amphetamine and not via the 5-HT-releasing properties that it shares with MBDB.

MDMA (3,4-methylenedioxymethamphetamine); Amphetamine; Nucleus accumbens septi; Behaviour; Locomotion

1. Introduction

Derivatives of amphetamine differ in their ability to release catecholamines and indoleamines. Amphetamine congeners with substitutions at the 3 and 4 positions of the phenethylamine ring, for example, are more potent serotonin (5-HT)-releasing drugs than their structural parent amphetamine (Anderson et al., 1978). For example, 3,4-methylenedioxymethamphetamine (MDMA) is a potent 5-HT-releasing agent (Nichols et al., 1982) that has been widely used recreationally because of its novel mood-altering effects (Peroutka et al., 1988). Although psychotherapeutic applications for MDMA have been proposed (Grinspoon and Bakalar, 1986), the potential neurotoxic effects of MDMA on central 5-HT neurons have raised concerns about the clinical safety of this drug (Battaglia et al., 1987; Schmidt, 1987).

MDMA produces a characteristic behavioral syndrome in rats consisting primarily of locomotor hyperactivity (Gold et al., 1988; Spanos and Yamamoto, 1989). The spatial pattern of MDMA-induced locomotion differs from both the pattern of activity produced by classical psychostimulants such as amphetamine and the pattern of activity induced by hallucinogens such as 2,5-substituted phenethylamines (Paulus and Geyer, 1991; Callaway et al., 1991b). Similar distinctions between MDMA-like drugs and classical psychostimulants or hallucinogens have been obtained using drug-discrimination paradigms in animals (Glennon and Misenheimer, 1989; Oberlender and Nichols, 1988) as well as anecdotal reporting in humans (Anderson et al., 1978; Peroutka et al., 1988). These data suggest that the detailed analysis of drug effects on the unconditioned behavior of rats can detect behavioral properties of drugs that are correlated with the subjective effects of these drugs.

Detailed characterization of drug effects on animal behavior thus allows the testing of hypotheses about the mechanisms mediating the behavioral effects of these drugs. For example, previous studies have indicated that fluoxetine pretreatment prevents the uptake carrier-dependent release of 5-HT by S-MDMA (Hekmatpanah and Peroutka, 1990) and prevents the locomotor stimulant effects of S-MDMA (Callaway et al., 1990). Depletion of 5-HT with para-chlorophenylalanine also antagonizes S-MDMA-induced hyperactiv-

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ity (Callaway et al., 1990). Furthermore, a congener of MDMA that releases 5-HT but has little direct effect on catecholamine release, N-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine (MBDB) (Johnson et al., 1986), produces patterns of hyperactivity that resemble MDMA-induced activity (Callaway et al., 1991b). Finally, pretreatment with methiothepin, propranolol or pindolol, drugs that share affinity for 5-HT_1-like receptors, antagonizes S-MDMA-induced hyperactivity, but pretreatment with 5-HT_2 antagonists does not reduce the response to S-MDMA (Callaway et al., in press). These studies suggest that the locomotor activating effects of S-MDMA result from increased 5-HT release and subsequent activation of 5-HT_1-like receptors.

Much previous work indicates that the locomotor hyperactivity induced by amphetamine and related catecholamine-releasing drugs is mediated via dopamine release in the region of the nucleus accumbens septi. For example, specific lesions of dopaminergic terminals in the nucleus accumbens but not in the overlying dorsal striatum prevent the locomotor activating effects of amphetamine (Kelley et al., 1975). Similar antagonism of amphetamine-induced behavior is observed after injection of dopamine antagonists into the nucleus accumbens (Pijnenburg et al., 1975). Furthermore, microinjection of dopamine agonists directly into the nucleus accumbens produces behavioral effects that resemble the effects of systemically administered amphetamine in a variety of paradigms (Kelley et al., 1989; Pijnenburg et al., 1976; Solomon and Staton, 1982; Swerdlow et al., 1990). Because these results point to a central role of the nucleus accumbens in stimulant drug actions, the present investigation was designed to identify the contribution of MDMA actions in the nucleus accumbens to the behavioral effects of systemically administered MDMA. These studies employed the active S(+) enantiomer of MDMA (Nichols et al., 1982).

2. Materials and methods

2.1. Subjects

Male, Sprague–Dawley rats (Harlan, Indianapolis, IN) weighing 300–400 g were housed two per cage under a reverse light-dark cycle (lights off: 07:00–19:00 h). Food and water were provided ad libitum. All experiments were performed during the dark phase in darkness.

2.2. Intracerebral injections

Animals were surgically prepared for intracerebral drug administration using techniques adapted from Swerdlow et al. (1990). Briefly, each rat was anesthetized with 2.0% halothane in air. With the head fixed in a Kopf stereotaxic device, the skull surface was exposed, and bilateral burr holes were drilled in the skull overlying the nucleus accumbens or dorsolateral striatum. Bilateral guide tubes (23-gauge, stainless-steel) were lowered through the burr holes until their ventral tips were positioned 3.0 mm dorsal to the designated injection site. Coordinates used for injections into the nucleus accumbens were 3.2 mm anterior (A) to bregma, 1.7 mm lateral (L) to the midline and 7.8 mm ventral (V) to the skull surface with the incisor bar raised 5 mm relative to the interaural line. For injections into the dorsolateral striatum, the coordinates were A +3.0 mm, L ±3.3 mm, V −4.0 mm. The guide tubes were fixed to the skull using methacrylate dental cement and stainless-steel skull screws. Animals were allowed at least one week of recovery prior to any behavioral testing. During this time, patency of the guide tubes was maintained with 31-gauge, stainless-steel obdurators.

For intracerebral injections, animals were brought from their home cages to the laboratory at least 60 min prior to testing. During injections, animals were restrained gently by hand. The obdurators were removed from the guide tubes. Injectors made from 31-gauge stainless-steel tubing were inserted through each guide tube. Each injector extended 3.0 mm beyond the tip of the guide tube, thereby reaching the target injection site. A 1.0-μl volume of vehicle or drug was delivered through each injector from Hamilton syringes via 30 cm lengths of fluid-filled polyethylene tubing (PE-10) at a rate of 1 μl/90 s. Flow was confirmed by the movement of a small air bubble in the tubing. The injectors were left in place for 60 s after completing the injection to allow for diffusion of drug, and then replaced with the obdurators. Animals were immediately placed into the behavioral testing apparatus. Testing typically commenced within 3 min after the start of injections. Each animal was injected on a maximum of three occasions with at least 1 week between injections. Previous studies have indicated that the primary behavioral effects of systemically administered MDMA persist after the second and third administration (Callaway et al., 1991b). All treatment groups were balanced with regards to the order of injections and the treatment history of the animals. Injection sites were confirmed histologically at the end of behavioral experiments (fig. 1).

2.3. Behavioral testing

Behavioral testing was performed in a behavioral pattern monitor (BPM) as previously described (Callaway et al., 1990, 1991a) The BPM is a 30.5 × 61.0 cm Plexiglas box with a metal floor. Three 2.5-cm holes are

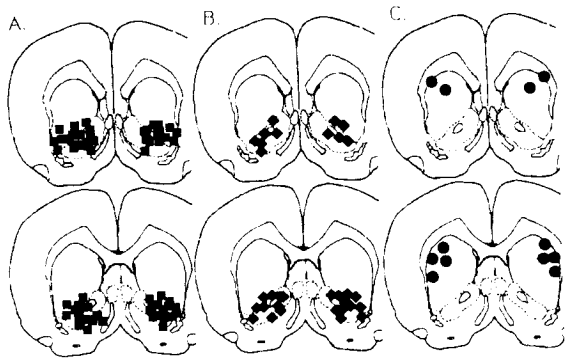

Fig. 1. Location of injection sites as confirmed by histology. Sectioned brains revealed cannula tracks extending into the target sites. The tips of the cannula tracks are indicated for the S-MDMA dose–response and fluoxetine interaction study (A), the MBDB and S-amphetamine study (B) and the intracaudate S-MDMA study (C).

situated symetrically in each long wall and the floor, and a single hole is situated in one short wall. A 4×8 grid of infrared photobeams is projected through the BPM, allowing localization of animals with a resolution of 3.8 cm. Additional photobeams are placed in each of the holes, allowing detection of investigatory nosepokes (holepokes). A metal touchplate located 15 cm above the metal floor allows detection of rearings against the wall. All photobeams and the touchplate are monitored continuously by a computer that records both the duration and the nature of changes in beam status. The detailed series of X–Y positions, holepokes and rearings in the BPM can thus be reconstructed off-line, and summary statistics calculated. For this study, locomotor activity was quantified as the number of transitions (crossings) between any of eight 15.75×15.75 cm sectors during any 10-min interval (Geyer et al., 1986). The total number of rearings and holepokes per 10-min or 30-min interval was also calculated. All data were analyzed by one- or two-way mixed design analysis of variance with repeated measures (Dixon, 1990). Drug treatment and pretreatment if any were used as factors, and the value of each behavioral measure at different time points was considered as the repeated measure. Tests were excluded from analysis if the flow of drug during intracerebral injections was unconfirmed or unilateral. Unconfirmed or unilateral flow was encountered in 25 of 133 attempted injections (19%).

2.4. Procedure

In the first study, 32 rats were prepared with guide tubes aimed at the nucleus accumbens. Rats received i.p. injections of saline or fluoxetine (10 mg/kg) in a volume of 2 ml/kg at 60 min prior to intracerebral injections. This dose of fluoxetine prevents the activating effects of systemically adminstered S-MDMA (Callaway et al., 1990) or MBDB (Callaway et al., 1991a) without altering the activation induced by S-amphetamine. Saline or S-MDMA (10 or 30 μg) was administered intracerebrally in a volume of 1.0 μl. Some rats received no pretreatment injection, but these animals did not differ from saline-pretreated animals on any behavioral measure. Therefore, data from uninjected and saline-pretreated animals were combined. In order to confirm the anatomical specificity of S-MDMA actions, an additional six rats were prepared with bilateral guide tubes in the dorsolateral striatum, through which saline or S-MDMA (10 μg) was administered intracerebrally in a volume of 1.0 μl. For comparison, an additional 16 rats were prepared with bilateral guide tubes in the nucleus accumbens. Saline, MBDB (10 μg) or S-amphetamine (5 or 10 μg) was administered intracerebrally in a 1.0-μl volume.

2.5. Drugs

The National Institute on Drug Abuse provided S(+)-MDMA HCl. RS(±)-MBDB HCl was a gift from Dr. David E. Nichols of Purdue University (West Lafayette, IN). Fluoxetine HCl was a gift from Eli Lilly Laboratories (Indianapolis, IN). S(+)-Amphetamine sulfate was purchased from Sigma Chemical Company (St Louis, MO). All drugs were dissolved in saline, with doses based on salt weights.

3. Results

3.1. Effects of S-MDMA

Bilateral administration of 10 or 30 μg S-MDMA into the nucleus accumbens produced locomotor hyperactivity lasting 30–40 min (fig. 2). This hyperactivity was reflected by a significant effect of S-MDMA dose on crossings ($F(2,62) = 12.67$; $P < 0.0001$). Comparisons within each 10 min epoch revealed that the activity of animals that received 10 μg S-MDMA was elevated relative to saline controls during each interval between 20 and 40 min while the activity of animals that received 30 μg S-MDMA was elevated during each interval between 20 and 50 min. During the initial 10 min of the session, locomotor activity was decreased by 30 μg S-MDMA but unaffected by 10 μg S-MDMA, resulting in a significant interaction between S-MDMA dose and time for crossings ($F(10,310) = 7.67$; $P < 0.0001$). Detailed analysis of the spatial structure of locomotor paths, based on methods described previously (Paulus and Geyer, 1991), revealed no differences between saline-treated and S-MDMA-treated animals at any dose or injection site (data not shown). In contrast, systemically administered MDMA pro-

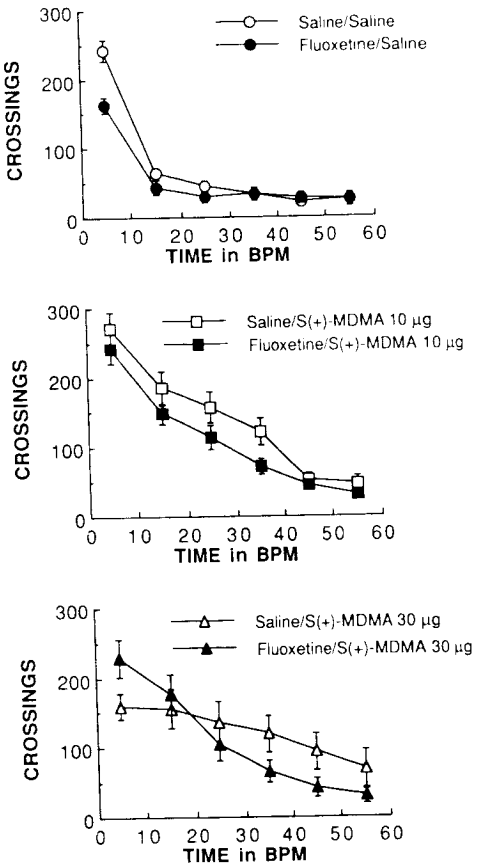

Fig. 2. Locomotor hyperactivity induced by injection of S-MDMA into the nucleus accumbens. Each point represents the mean (±S.E.M.) crossings per 10 min. In the top panel, animals were pretreated with i.p. saline (n = 16) or 10 mg/kg fluoxetine (n = 11) 60 min prior to injection of saline into the nucleus accumbens. In the middle panel, animals were pretreated with i.p. saline (n = 11) or fluoxetine (n = 12) 60 min prior to injection of 10 µg S-MDMA into the nucleus accumbens. In the bottom panel, animals were pretreated with i.p. saline (n = 13) or fluoxetine (n = 7) 60 min prior to injection of 30 µg S-MDMA into the nucleus accumbens. * Significant difference between saline/S-MDMA and fluoxetine/S-MDMA groups, $P < 0.05$.

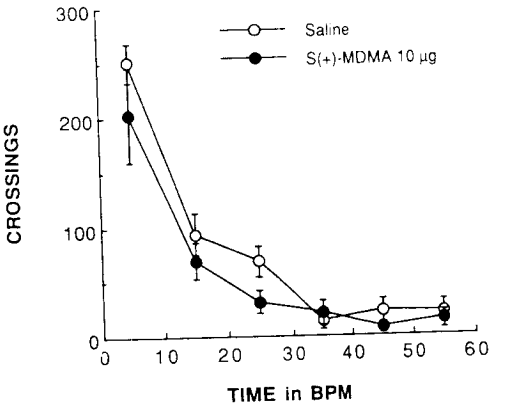

Fig. 3. Effect of injection of 10 µg S-MDMA into the dorsolateral striatum on locomotor activity. Each point represents the mean (±S.E.M.) crossings per 10 min. Either saline (n = 6) or 10 µg S-MDMA (n = 6) was injected intracerebrally immediately prior to testing.

duces robust changes in the spatial pattern of activity (Callaway et al., 1991b).

Administration of S-MDMA into the nucleus accumbens also increased rearings (table 1). A significant interaction between S-MDMA dose and time ($F(10,310) = 2.90$; $P < 0.01$) reflected that the number of rearings was increased in animals receiving 30 µg S-MDMA relative to saline-treated animals during the 30–60 min interval. No effect of intra-accumbens S-MDMA on holepokes was observed. For comparison, doses of systemically administered S-MDMA sufficient to increase locomotor activity robustly decrease holepokes and rearings (Callaway et al., 1990).

Administration of 10 µg S-MDMA into the dorsolateral striatum did not alter locomotor activity (fig. 3) or rearings (table 1) relative to saline controls (fig. 3). However, administration of S-MDMA into the dorsolateral striatum suppressed holepokes ($F(1,10) = 14.39$; $P < 0.01$) (table 1).

TABLE 1

The effects of intracerebral S-MDMA on investigatory responding were examined. S-MDMA or saline vehicle was injected bilaterally into the nucleus accumbens septi or dorsolateral striatum of rats in a 1.0-µl volume. After drug administration, animals were immediately placed into the BPM where locomotor activity, holepokes and rearings were continuously monitored for 60 min.

	Injection site				
	Nucleus accumbens septi			Dorsolateral striatum	
	Saline	MDMA		Saline	MDMA
		10 µg	30 µg		10 µg
Holepokes					
0–30 min	45.7 ± 6.2	79.0 ± 31.7	52.5 ± 9.0	44.8 ± 6.7	25.8 ± 3.9 [a]
30–60 min	17.7 ± 3.9	20.0 ± 5.8	38.0 ± 11.8	9.7 ± 5.2	3.7 ± 1.9
Rearings					
0–30 min	42.6 ± 6.9	70.6 ± 14.8	52.8 ± 15.6	38.0 ± 9.0	30.8 ± 10.0
30–60 min	10.2 ± 2.6	19.3 ± 7.7	30.4 ± 6.9 [a]	6.2 ± 4.1	4.7 ± 2.4

[a] Significantly different from saline control, $P < 0.05$.

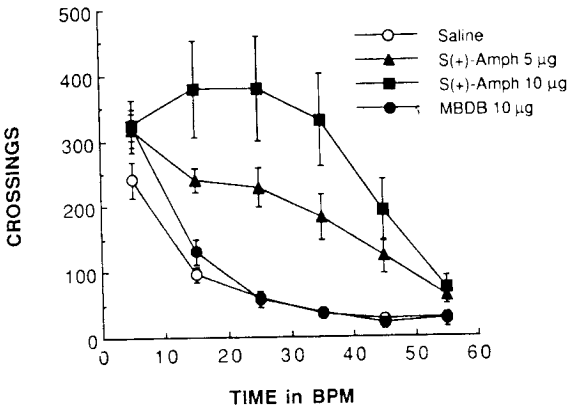

Fig. 4. Effect of injection of MBDB or S-amphetamine into the nucleus accumbens on locomotor activity. Each point represents the mean (±S.E.M.) crossings per 10 min. Either saline (n = 7), 10 μg MBDB (n = 6), 5 μg S-amphetamine (n = 7) or 10 μg S-amphetamine (n = 6) was injected into the nucleus accumbens immediately prior to testing.

3.2. Interaction with fluoxetine

Fluoxetine pretreatment failed to antagonize the stimulant effect of intra-accumbens S-MDMA (fig. 2). However, a significant interaction between pretreatment, S-MDMA dose and time for crossings ($F(10,310) = 4.35$; $P < 0.0001$) was observed. Post hoc comparisons revealed that the suppression of activity by 30 μg S-MDMA in saline-pretreated animals during the 0–10 min interval was not evident in fluoxetine-pretreated animals (fig. 2). The activity of saline-pretreated and fluoxetine-pretreated groups was not significantly different at any other time point or drug dose. The effect of fluoxetine on the S-MDMA-induced increase in rearings was impossible to evaluate because of the profound suppression of rearings by fluoxetine alone ($F(1,62) = 14.59$; $P < 0.001$), as previously described (Callaway et al., 1990) (data not shown).

3.3. Effects of S-amphetamine and MBDB

For comparison, administration of 5 or 10 μg of S-amphetamine into the same region of the nucleus accumbens produced a dose-dependent increase in locomotor activity lasting 50–60 min (crossings: $F(2,17) = 10.89$; $P < 0.001$) (fig. 4). No effect of S-amphetamine on holepokes, rearings or the spatial structure of the locomotor path was observed (data not shown). In contrast, administration of 10 μg of MBDB into the nucleus accumbens produced no significant effect on locomotor activity (fig. 4), holepokes or rearings. Because S-MDMA and MBDB produce similar forms of hyperactivity after systemic administration (Callaway et al., 1991a), the failure of MBDB administered into the nucleus accumbens to affect locomotor activity was replicated in a separate group of animals that had been habituated to the BPM for 60 min prior to injection. Confirming the present results, no changes in locomotor activity, holepokes or rearings were observed after administration of 3 μg, 10 μg or 30 μg of MBDB into the nucleus accumbens (data not shown).

4. Discussion

The primary finding of this study is that administration of the amphetamine derivative S-MDMA into the nucleus accumbens produces locomotor hyperactivity in rats (fig. 2). The more potent catecholamine-releasing drug S-amphetamine produces a similar increase in activity when administered by the same route (fig. 4). However, intra-nucleus accumbens septi administration of MBDB, a congener of MDMA that selectively releases 5-HT with little or no effect on dopamine release, did not alter locomotor activity (fig. 4). These data suggest that S-MDMA acts in the nucleus accumbens to increase activity via the catecholamine-releasing properties that it shares with S-amphetamine and not via the 5-HT-releasing properties that it shares with MBDB. In contrast, after systemic administration both S-MDMA and MBDB increase locomotor activity via release of presynaptic 5-HT (Callaway et al., 1990, 1991a). S-MDMA administration into the nucleus accumbens and systemic MDMA administration thus affect behavior via pharmacologically distinct mechanisms.

Similar increases in activity were observed after S-MDMA administration to untreated or fluoxetine-pretreated animals, supporting the conclusion that S-MDMA acts in the nucleus accumbens by non-serotonergic mechanisms. By interfering with the 5-HT uptake carrier, fluoxetine prevents 5-HT release induced by S-MDMA (Hekmatpanah and Peroutka, 1990), and thereby antagonizes the behavioral effects of systemically administered S-MDMA (Callaway et al., 1990). In the present study, fluoxetine pretreatment did antagonize the slight suppression of activity induced by the highest dose of S-MDMA during the 0–10 min interval, suggesting that 5-HT release mediates this suppression (fig. 2). It is possible that this decrease in activity represents the inhibition of motor behavior that is frequently described as the functional consequence of 5-HT action in the striatum (Costall et al., 1976; Jones et al., 1981). Interestingly, MBDB did not produce any measurable suppression of activity (fig. 4). This observation is consistent with previous reports that 5-HT administration into the nucleus accumbens only inhibits activation induced by catecholamine stimulation without significantly altering baseline activity (Jones et al., 1981). According to this model, only the S-MDMA-treated animals exhibit 5-HT-sensitive catecholamine-induced activation, while

5-HT release after MBDB administration does not affect baseline activity.

Administration of S-MDMA into the dorsolateral striatum did not alter locomotor activity (fig. 3), confirming the anatomical specificity of the activation induced by S-MDMA in the nucleus accumbens. Similarly, previous studies have demonstrated that administration of other catecholamine-releasing drugs into the dorsal and/or lateral striatum does not increase locomotor activity (Carr and White, 1987; Kelley et al., 1989; Towell et al., 1987). Administration of S-MDMA at this site decreased the frequency of holepokes (table 1), perhaps indicating that drug-induced monoamine release in the striatum interferes with normal exploratory activity. This conclusion is consistent with hypotheses that increased dopamine release in the dorsal striatum mediates the behaviorally disruptive stereotypy exhibited by many animals after high doses of amphetamine. S-MDMA actions in the dorsolateral striatum may contribute to the decreases in holepokes observed after systemic administration of S-MDMA (Callaway et al., 1990).

Several measures distinguish the behavioral response to S-MDMA administered into the nucleus accumbens from the response to systemically administered S-MDMA. For example, administration of S-MDMA into the nucleus accumbens increased the number of rearings at several time points and did not alter the number of holepokes (table 1). In contrast, systemically administered RS-MDMA or S-MDMA decreases both rearings and holepokes relative to saline controls (Gold et al., 1988; Callaway et al., 1990). Furthermore, the spatial pattern of locomotion after each of the drug treatments in the present study did not differ from the pattern of locomotion exhibited by saline-treated controls. However, when administered systemically, both S-MDMA and MBDB produce characteristic reductions in entries into the center of the chamber and relative increases in straight locomotor paths (Paulus and Geyer, 1991; Callaway et al., 1991). Thus, the behavioral effects of S-MDMA in the nucleus accumbens are phenomenologically distinguishable from the effects of systemically administered S-MDMA. In virtually all of these measures, the effects of S-MDMA administered into the nucleus accumbens resemble the effects of systemic amphetamine rather than systemic S-MDMA (Geyer et al., 1987).

In summary, these studies have identified a behavioral effect of S-MDMA administration into the nucleus accumbens that is probably mediated via local catecholamine release. However, S-MDMA was much less potent than S-amphetamine in the present studies, suggesting that S-MDMA actions in the nucleus accumbens may only become relevant after systemic administration of relatively high doses of S-MDMA. Significantly, the primary behavioral effects of low doses of systemically administered S-MDMA in this paradigm, including locomotor activation, also are produced by MBDB (Callaway et al., 1991) and are fluoxetine-sensitive (Callaway et al., 1990). These data are consistent with reports that, in addition to its novel behavioral effects, MDMA produces amphetamine-like side-effects in humans (Peroutka et al., 1988) and produces amphetamine-like cues in rats (Glennon et al., 1988). Thus, these studies indicate that S-MDMA can produce behavioral effects via actions in the nucleus accumbens, but that these actions do not explain the primary behavioral effects of systemically administered S-MDMA and MBDB.

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