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Drug discrimination studies with MDMA and amphetamine

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Abstract. The term entactogen has recently been introduced to describe a new pharmacological class of compounds best represented by 3,4-methylenedioxymethamphetamine, MDMA, and its alpha-ethyl homologue MBDB. The present study was designed to test the similarities of the discriminative stimulus properties produced by MDMA and MBDB, as well as to elaborate further the distinction between entactogens, hallucinogens and stimulants. Two groups of rats were trained to discriminate saline from either racemic MDMA hydrochloride (1.75 mg/kg) or *S*-(+)-amphetamine sulfate (1.0 mg/kg) in a two-lever drug discrimination task. The (±)-MDMA cue completely generalized to *S*-(+)-MDMA, *S*-(+)-amphetamine, (±)-MDA, *S*-(+)-MBDB, (±)-MBDB, *R*-(−)-MDMA, and *R*-(−)-MBDB, but not to LSD or DOM. The *S*-(+)-amphetamine cue generalized to (±)-methamphetamine, but not to racemic MDMA or MBDB, nor to their optical isomers. The *S*-(+)-isomers of both MDMA and MBDB were more potent than the *R*-(−)-isomers. The results indicate that MDMA and MBDB may share a component of their discriminative stimulus properties which is different from both stimulants and hallucinogens. Although MDA and MDMA have been shown to be amphetamine-like, the lack of stimulant effects for MBDB suggests that amphetamine-like stimulant activity is not necessary for a compound to share discriminative stimulus properties with MDMA.

Key words: Drug discrimination – Entactogens – Hallucinogens – Stimulants – Stereoselectivity – MDMA – MBDB – MDA – Amphetamine – LSD – DOM

Beta-phenylethylamine (PEA) derivatives represent an important group of biologically active compounds. Hallucinogens and central nervous system (CNS) stimulants, two distinctly different classes of psychopharmacological agents, are both represented by various PEA derivatives. We have been interested for many years in understanding the structure-activity relationships (SARs) of PEA hallucinogens (Nichols 1981). Recently, our attention has been directed to a series of PEA derivatives with a 3,4-methylenedioxy-aromatic substitution which are not readily categorized into existing drug classes. Methylenedioxyamphetamine (MDA) (Fig. 1) and methylenedioxymethamphetamine (MDMA, "ecstasy") (Fig. 1) both induced subjective states in humans that are distinguishable from those produced by hallucinogens and stimulants (Alles 1957; Naranjo et al. 1967; Shulgin and Nichols 1978).

The drug discrimination (DD) paradigm has emerged as a useful tool for defining categories of drugs in an animal model (Overton 1984). The major advantages of this procedure are the abilities to classify the effects of novel drugs as similar or dissimilar to the effects of known drugs, as well as to measure the potency of drugs that elicit the same discriminative response (Barry 1974). In addition, the reliability, sensitivity, and specificity of DD studies make them valuable for analyzing the neuronal mechanisms underlying the effects of diverse classes of compounds (Appel and Cunningham 1986).

Alpha-methyl-PEA, also known as amphetamine, is the prototype CNS stimulant. Data from DD studies indicate that, with few exceptions, aromatic substitution of amphetamine generally results in the loss of amphetamine-like discriminative stimulus (DS) properties (Young and Glennon 1986). The most active hallucinogenic PEA derivatives possess a 4,5-aromatic disubstitution with a methoxy group at either the 2- or 3-position (Nichols 1981), the prototypical hallucinogenic "amphetamine" being 2,5-dimethoxy-4-methylamphetamine (DOM, STP). Many di- and trimethoxylated amphetamine derivatives share DS properties with DOM, while monomethoxylated analogues substitute for amphetamine, and MDA substitutes for both (Young and Glennon 1986). Martin et al. (1978) noted that in the chronic spinal dog, MDA had actions similar to both LSD and to amphetamine. Shannon (1980) later proposed that MDA might represent a unique class of drugs.

Drug discrimination studies indicate that the DS properties of MDA are stereospecific (Young and Glennon 1986). The activity of *R*-(−)-MDA seems to be responsible for the complete substitution of (±)-MDA for hallucinogenic training drugs such as 5-methoxy-N,N-dimethyltryptamine (Glennon et al. 1981), DOM (Glennon et al. 1982) and LSD (Nichols et al. 1986). At higher doses, in rats trained to discriminate *S*-(+)-amphetamine from saline, (±)-MDA produces complete substitution, presumably due to the activity of the *S*-(+)-isomer (Glennon and Young 1984a, b). N-methylation of MDA, producing MDMA, abolishes the hallucinogen-like DS effects (Glennon et al. 1982; Nichols et al. 1986) but not the stimulant-like activity (Glennon and Young 1984b; Evans and Johanson 1986; Kamien et al. 1986).

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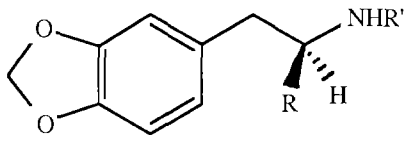

	R	R'
S-(+)-MDA	CH_3	H
S-(+)-MDMA	CH_3	CH_3
S-(+)-MBDB	CH_2CH_3	CH_3

Fig. 1. Chemical structures of the more active enantiomers of methylenedioxy-substituted test compounds

Both MDA and MDMA have raised concerns with regard to their availability on the illicit drug market, especially in light of recent evidence of their neurotoxic potential (Ricuarte et al. 1985; Stone et al. 1986). MDA (Naranjo et al. 1967; Turek et al. 1974) and MDMA (Greer and Tolbert 1986; Wolfson 1986) have also stimulated the interest of certain psychiatrists, who investigated the use of the subjective states induced by these compounds to facilitate the psychotherapeutic process. Therefore, a better understanding of the behavioral effects of the 3,4-methylenedioxy-substituted series of PEA derivatives relative to hallucinogenic and stimulant PEAs was thought to be valuable.

We have previously reported on the synthesis and evaluation of N-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine (MBDB) (Fig. 1) the alpha-ethyl homologue of MDMA (Nichols et al. 1986). Like MDMA, the racemate and optical isomers of MBDB do not substitute for LSD in rats (Nichols et al. 1986). The clinical activities of MBDB and MDMA were found to be similar and clearly distinguishable from those of hallucinogens and stimulants. Based on structure-activity relationship considerations, it was concluded that MBDB should not be classified as an hallucinogen or psychedelic, but should instead be viewed as representative of a novel class of psychoactive agent, which was called entactogens. The description of this proposed drug category was elaborated further in a subsequent report (Nichols 1986).

We now report data from DD experiments using rats trained to discriminate either MDMA (1.75 mg/kg) or *S*-(+)-amphetamine (1.0 mg/kg) from saline in a two-lever, food reinforced, fixed ratio paradigm. Substitution testing was performed with the racemates and optical isomers of MDMA and MBDB in order to investigate the similarity of their DS properties and stereoselectivity. For comparative purposes, the MDMA group was also tested with (±)-MDA, *S*-(+)-amphetamine, LSD, and DOM, while (±)-methamphetamine was included among the compounds tested in the *S*-(+)-amphetamine group.

Materials and methods

Subjects. Thirty three male Sprague-Dawley rats (Harlan Laboratories, Indianapolis, IN) weighing 200–240 g at the start of the experiment were used. None of the rats had previously received drugs or behavioral training. They were housed individually with free access to water and given a rationed amount of supplemental feeding (Lab Blox) after experimental sessions so as to maintain them at 85% of their free-feeding weight. The animal facility was maintained at a constant temperature of 22–24 °C, with lights on at 6 a.m. and off at 8 p.m.

Apparatus. Six standard operant chambers (Coulbourn Instruments) consisted of modular test cages enclosed within sound-attenuated cubicles with fans providing ventilation and background noise. Electronic pellet dispensers and data recording were controlled by solid state logic, interfaced through a Coulbourn Instruments Dynaport to an IBM PC, all located in an adjacent room.

Procedure. A two-lever procedure with a fixed ratio (FR) 50 schedule of food reinforcement (Bioserv, 45 mg dustless pellets) was used. Eighteen rats were assigned to the MDMA group and 15 to the *S*-(+)-amphetamine group. To avoid positional preference, nine rats of the former group and eight rats from the latter group were trained on drug-L, saline-R while the remainder were trained on drug-R, saline-L. Training sessions lasted 15 min and were conducted at the same time each day, Monday through Saturday. Levers were cleaned with 10% ethanol solution between subjects in order to avoid olfactory cues (Extance and Goudie 1981).

After initial shaping, drug or saline was administered, by intraperitoneal (IP) injection 30 min prior to sessions, randomly ordered, with neither treatment given for more than three consecutive sessions. Only the stimulus-appropriate lever was present. When stabilized response rates were attained, both levers were presented simultaneously and the rats were required to respond on the stimulus-appropriate lever to receive reinforcement. The schedule of reinforcement was gradually increased from FR 1 to FR 50. This phase of the training continued until each rat had achieved an accuracy of at least 85% (number of correct presses $\times 100$/number of total presses before the first reinforcement) for eight of ten consecutive sessions. Then, every third session was used as a test period as long as the rat maintained an accuracy of at least 85% on the two preceding maintenance sessions (drug and saline). Test solutions were also administered IP, 30 min prior to the session. Test sessions were run under conditions of extinction, with the rats removed from the operant box immediately after 50 presses were completed on one lever. If 50 presses on one lever were not completed in 5 min, the session was ended and scored as a disruption. The data for a test session were discarded if the 85% criterion was not met on the following two maintenance sessions (Colpaert et al. 1982). Treatments were randomized at the beginning of the study.

Data analysis. The scoring of the data was done in a quantal fashion. The lever on which the rat first emitted 50 responses was scored as the "selected" lever. The percentage of rats selecting the drug lever for each dose of test compounds was then used to determine ED_{50} values with 95% confidence intervals, using the method of Litchfield and Wilcoxon (1949).

Drugs. Except for *S*-(+)-amphetamine sulfate (Smith Kline & French), methamphetamine·HCl (Aldrich), DOM·HCl (NIDA), and LSD tartrate (NIDA), all drugs were synthesized as the hydrochloride salts in our laboratory, by pre-

viously described methods (Nichols et al. 1986). Analysis of the optical isomers of MDMA and MBDB indicated greater than 98–99% enantiomeric excess (Nichols et al. 1986). Solutions were prepared by dissolving the compounds in saline at a concentration that allowed the appropriate dose to be given in a volume of 1 ml/kg. The doses refer to the salt forms.

Results

The discrimination of MDMA from saline was successfully learned by the rats. Initial attempts to train on a dose of 1.25 mg/kg MDMA·HCl resulted in a low average accuracy and a prolonged mean number of sessions to criterion from the beginning of training (65 ± 20) ($\pm$SE). The training dose was changed to 1.75 mg/kg by a gradual increase of 0.1 mg/kg/week over a 5-week period. The average accuracy improved from 71% to 88% by the end of the 5th week. Two additional weeks of training were given before substitution tests began. Two of the rats in the MDMA group failed to reach the criterion performance and were dropped from the study. Two additional rats from this group died during the experiments.

By contrast, all the rats in the *S*-(+)-amphetamine group rapidly learned the discrimination task. The mean number of sessions to criterion for this group was 31 ± 2 ($\pm$SE). Average response rates in the MDMA group were found to be 121 ± 10 and 101 ± 11 response/min (mean $\pm$ SE) for saline and MDMA, respectively. The difference between these rates is not significant ($P > 0.05$, Student's *t*-test). For the *S*-(+)-amphetamine group the response rates averaged 113 ± 39 and 77 ± 36 responses/min for saline and *S*-(+)-amphetamine, respectively. The rate of responding after *S*-(+)-amphetamine was not significantly different than after saline ($P > 0.05$, Student's *t*-test).

The results of the substitution tests with the isomers of MDMA and MBDB in the MDMA group are illustrated in Fig. 2. The ED_{50} from MDMA was 3.40 μM/kg (0.78 mg/kg, $N = 8$–9 at each of five doses), slightly less than half of the training dose. None of the rats ($N = 8$) tested with saline selected the drug lever. Both enantiomers of MDMA and MBDB, as well as racemic MBDB and MDA, completely substituted for the racemic MDMA (1.75 mg/kg) stimulus. There was no significant difference between the ED_{50} of racemic MDA (4.06 μM/kg, 0.87 mg/kg, $N = 8$ at each of four doses), MDMA, or MBDB (4.19 μM/kg, 1.02 mg/kg, $N = 8$ at each of five doses). The enantiomers of MDMA and MBDB, however, possessed significantly different potencies. The ED_{50} values were 5.03 μM/kg (1.15 mg/kg), 1.92 μM/kg (0.44 mg/kg), 6.71 μM/kg (1.63 mg/kg), and 3.67 μM/kg (0.89 mg/kg) for *R*-(−)-MDMA, *S*-(+)-MDMA, *R*-(−)-MBDB, and *S*-(+)-MBDB, respectively. The *S*/*R* potency ratios, based on the ED_{50} values, were 2.6 for MDMA and 1.8 for MBDB. None of the compounds produced a large number of disruptions at the doses tested, but the *S*-(+)-isomer of MDMA was the most potent in this respect.

The results of substitution testing with *S*-(+)-amphetamine, LSD, and DOM in the MDMA group are given in Table 1. *S*-(+)-amphetamine completely substituted for MDMA ($ED_{50} = 4.22$ μM/kg, 0.78 mg/kg), but at a dose (1.2 mg/kg) which disrupted more than half of the rats tested. After higher doses of *S*-(+)-amphetamine (1.4 and 2.0 mg/kg) the percentage of rats selecting the MDMA lever decreased. LSD produced a maximum of 78% of the rats selecting the MDMA lever, at a dose (0.16 mg/kg) which disrupted more than one third of the rats tested. DOM produced a maximum of 56% of the rats selecting the MDMA lever at a dose of 0.5 mg/kg.

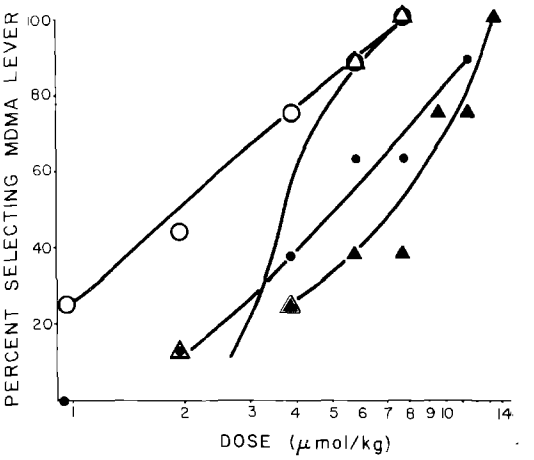

Fig. 2. Dose-response curves for *S*-(+)-MDMA (○), *R*-(−)-MDMA (●), *S*-(+)-MBDB (△), and *R*-(−)-MBDB (▲), in rats trained to discriminate MDMA·HCl (1.75 mg/kg) from saline. For each point, $N = 8$–9 rats

Table 1. Results of substitution testing in rats trained to discriminate MDMA·HCl (1.75 mg/kg) from saline

Drug	Dose		N[a]	%D[b]	%SDL[c]
	μM/kg	mg/kg			
S−(+)-AMP	2.17	0.4	12	25	22
	3.26	0.6	13	38	50
	4.35	0.8	14	43	63
	5.43	1.0	12	33	38
	6.52	1.2	13	54	83
	7.60	1.4	13	54	67
	10.87	2.0	13	62	60
DOM	0.51	0.125	12	33	50
	1.02	0.25	11	18	44
	2.04	0.5	10	10	56
	3.06	0.75	12	33	50
	4.04	1.0	12	50	50
	5.06	1.25	13	38	38
	6.08	1.5	5	100	–
LSD	0.047	0.02	10	20	13
	0.093	0.04	8	0	38
	0.186	0.08	13	31	56
	0.372	0.16	14	36	78
	0.558	0.24	13	54	67

[a] N = total number of rats tested
[b] %D = Percentage of rats disrupted out of the total N
[c] %SDL-Percentage of responding rats selecting the drug lever

In the *S*-(+)-amphetamine-trained group, the ED_{50} for *S*-(+)-amphetamine was found to be 1.68 μM/kg (0.31 mg/kg, $N = 8$ at each of six doses), about one third the training dose. (±)-Methamphetamine completely substituted, with an ED_{50} of 3.08 μM/kg (0.57 mg/kg, $N = 8$ at each of four doses) and all rats tested with saline ($N = 8$) selected the saline lever. Table 2 shows the data from the substitution testing of the racemates and enantiomers of MDMA and

Table 2. Results of substitution testing with rats trained to discriminate *S*-(+)-amphetamine·sulfate (1.0 mg/kg) from saline. The terms *N*, %D, and %SDL are defined as in Table 1

Drug	Dose		*N*	%D	%SDL
	μM/kg	mg/kg			
MDMA	3.82	0.88	8	0	13
	7.63	1.75	8	0	25
	9.81	2.25	14	43	25
	11.45	2.63	7	86	–
R-(−)-MDMA	3.82	0.88	8	0	0
	7.63	1.75	8	0	0
	11.45	2.63	14	43	0
	15.26	3.51	6	83	–
S-(+)-MDMA	1.91	0.44	8	0	0
	3.82	0.88	13	46	0
	4.78	1.10	11	27	13
	5.73	1.31	6	83	–
MBDB	3.59	0.88	8	0	0
	7.19	1.75	8	0	25
	8.99	2.19	15	47	37
	10.78	2.63	15	67	0
	14.37	3.50	8	63	0
	21.56	5.25	5	100	–
R-(−)-MBDB	3.59	0.88	10	20	13
	7.19	1.75	11	27	0
	14.37	3.50	10	20	13
	21.56	5.25	5	100	–
S-(+)-MBDB	1.80	0.44	9	11	0
	3.59	0.88	9	11	13
	7.19	1.75	8	0	25
	8.99	2.19	15	53	14
	10.78	2.67	6	100	–

MBDB, none of which completely substituted for *S*-(+)-amphetamine.

Discussion

The results suggest that MDMA and MBDB share discriminative stimulus effects. This is based on the complete substitution and similar stereoselectivity of these two agents. MDMA has been previously observed to substitute for MDA, 1.5 mg/kg (Glennon and Young 1984b), and possess a similar stereoselectivity ($S > R$) in DD studies (Glennon and Young 1984b). The present study demonstrates that MDA completely substitutes for MDMA, indicating an overlap of DS properties. The observed stereoselectivity for the behavioral activity of MBDB parallels that observed in a clinical evaluation (Nichols et al. 1986). The greater potency of the *S*-(+)-isomer of MDMA, compared to (±)- and *R*-(−)-MDMA, is in agreement with a behavioral study involving schedule-controlled responding in mice (Glennon et al. 1987) and with a clinical report (Anderson et al. 1978). Schechter (1987), however, has recently reported that (±)-MDMA was more potent than either isomer in a study with rats trained to discriminate 1.5 mg/kg (±)-MDMA from water.

The data from DD studies with MDMA seem to indicate that this drug produces complex DS properties made of up various components (for example, see Schechter 1986). The development of new compounds with MDMA-like activity may be useful in analyzing these components. We have previously argued that the biological activity of MBDB is unlike that of hallucinogens (Nichols 1986). Based on structure-activity relationships, the combination of N-methylation and alpha-ethylation in a phenethylamine abolishes hallucinogenic activity (Nichols 1981) and this is supported by the inability of MBDB to completely substitute for LSD (Nichols et al. 1986). The results of the present study suggest that MBDB mimics the behavioral effects of MDMA, but not those of *S*-(+)-amphetamine. It seems likely, therefore, that the extension of the side chain methyl to an ethyl in MBDB attenuates the stimulant-like effects of MDMA. Support for this can be found in the 7-fold potency decrease in substituting for S-(+)-amphetamine (1.0 mg/kg) when the alpha-methyl of methamphetamine is replaced by an alpha-ethyl (unpublished results). These results are consistent with the hypothesis that the common activity of MDMA and MBDB is distinct from both hallucinogen (psychedelic) and stimulant activity.

There are several lines of evidence that distinguish the DS effects of MDMA from those of hallucinogens. When DOM (1.0 mg/kg) was used as a training drug, no generalization to MDMA was observed (Glennon et al. 1982). The present study confirms the lack of similarity of the MDMA and DOM stimuli, since DOM failed to completely substitute for MDMA. We have previously reported that the racemic mixtures and optical isomers of MDMA and MBDB do not completely substitute for a 0.08 mg/kg training dose of LSD tartrate (Nichols et al. 1986). In the present study, however, LSD (0.16 mg/kg) produced MDMA lever selection in 78% of the responding rats. The DS properties of both LSD (Appel and Cunningham 1986) and DOM (Glennon et al. 1986) seem to be mediated by a direct agonist activity at 5-HT_2 receptors. This mechanism does not seem to be directly involved in the behavioral properties of MDMA. Evidence for this is seen in the reversal of stereoselectivity between MDMA ($S > R$) and the hallucinogenic PEAs ($R > S$), the lack of significant affinity of both MDMA isomers for 5-HT_2 receptors (Lyon et al. 1986), and the inability of the selective 5-HT_2 antagonist, pirenpirone, to reverse the disruption of operant responding in mice caused by either isomer of MDMA (Rosecrans and Glennon 1987). The increased percentage of rats selecting the MDMA lever after LSD, compared with DOM, may be attributable to an LSD-like component of the MDMA stimulus, possibly mediated by pharmacological properties other than 5-HT_2 agonist activity.

We have previously suggested that transmitter release may play a role in the biological activity of MDMA (Nichols et al. 1982). Reports of in vitro studies indicate that MDMA stimulates the release of [^{3}H]-5-HT from rat brain synaptosomes (Nichols et al. 1982), hippocampal slices (Johnson et al. 1986), and caudate slices (Schmidt et al. 1987), and inhibits the uptake of serotonin into hippocampal synaptosomes (Steele et al. 1987). The greater potency of the *S*-(+)-isomer as a 5-HT releaser (Nichols et al. 1982; Schmidt et al. 1987) and uptake inhibitor (Steele et al. 1987) supports the hypothesis that indirect serotonin agonist effects may be related to the DS properties of MDMA.

The results of the present study provide some evidence which supports the idea that the complex DS properties of MDMA include a component which is amphetamine-like. Previous studies have demonstrated that MDMA completely substitutes for *S*-(+)-amphetamine in rats (Glennon

and Young 1984b), pigeons (Evans and Johanson 1986) and monkeys (Kamien et al. 1986). Consistent with these findings, *S*-(+)-amphetamine was recognized in this experiment as MDMA-like. Complete substitution, however, was accompanied by disruption in 7 of the 13 rats tested. This seems to indicate that only a relatively large dose of *S*-(+)-amphetamine provides effects that are shared with MDMA. Stolerman and D'Mello (1981) have discussed "the commonly expressed view that drug-produced stimulus control is mediated by multiple effects of the agents concerned; drugs with only partially overlapping profiles of action might have to be given in relatively large doses to provide the shared effects with sufficient intensity." It may be that MDMA and amphetamine have profiles of action which overlap to the extent that cross-transfer occurs, yet also differ significantly with respect to their primary pharmacological activities.

Evidence of a non-amphetamine-like component of the DS properties of MDMA is apparent in the present set of experiments. It should be noted, for example, that cross-transfer did not occur. In contrast to the previously mentioned reports, MDMA failed to produce *S*-(+)-amphetamine lever selection in more than 25% of the responding rats. Procedural differences such as reinforcement schedule, the reward used, and numbers of animals tested may account for the discrepancy. Further experiments with *S*-(+)-amphetamine tested in rats trained to discriminate MDMA from saline, using procedures identical to those in which MDMA has been shown to substitute for *S*-(+)-amphetamine, should therefore be useful. Differences between the effects of MDMA and *S*-(+)-amphetamine have also been observed when compared in an unpunished, schedule-controlled behavioral paradigm in pigeons (Boszormenyi et al. 1987).

In view of the effects of MDA and MDMA on dopamine uptake and release (Johnson et al. 1986; Stone et al. 1986; Steele et al. 1987), it seems reasonable that they share some DS properties with *S*-(+)-amphetamine. Schechter and Rosecrans (1973) suggested that the DS properties of *S*-(+)-amphetamine may be mediated by central dopaminergic mechanisms, and there is much evidence to support this. In vitro studies in rat striatum (Schmidt et al. 1987) indicate that MDA and MDMA are both an order of magnitude more potent in releasing [^{3}H]-serotonin than [^{3}H]-dopamine. As the dose increases, however, a level is probably reached where dopaminergically-mediated behavioral effects become evident.

It seems likely that amphetamine-like activity is *not* necessary for a compound to share DS properties with MDMA. This is evident in the complete substitution of the racemate and optical isomers of MBDB for MDMA, and their inability to substitute for *S*-(+)-amphetamine. While the former effect may relate to common serotonergic mechanisms (Johnson et al. 1986; Steele et al. 1987), the latter may be related to the inability of MBDB to induce the release of [3H]-dopamine from rat caudate slices (Johnson et al. 1986), or to inhibit [^{3}H]-dopamine uptake into rat striatal synaptosomes (Steele et al. 1987). The lack of amphetamine-like stimulant activity of MBDB in humans has been previously observed (Nichols et al. 1986). It should also be noted that Schechter (1986) reported complete substitution of MDMA for fenfluramine (2.0 mg/kg), a serotonergic agent devoid of amphetamine-like DS properties (White and Appel 1981).

Clearly, more work is needed in order to understand how entactogens differ from other known compounds, for example fenfluramine. The similarity of DS properties seen in the present study, between MDA, MDMA and MBDB, the obvious SAR differences compared to hallucinogens (Nichols 1986), as well as the differences that are emerging when they are compared to stimulants, seem to support the idea (Nichols et al. 1986) that these compounds may represent a unique class of drugs.

Amphetamine has been referred to as "a seemingly inexaustible starting base for the synthetic medicinal chemist in the design and development of novel medicinals, and the wellspring of a continuous flow of novel therapeutic agents for the practicing physician" (Biel and Bopp 1978). It is our view that entactogens, presently represented by MBDB, MDMA and *S*-(+)-MDA, should be regarded as a novel pharmacological class, whose potential as therapeutic agents remains to be explored.

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