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# MDMA Stimulus Generalization to the 5-$HT_{1A}$ Serotonin Agonist 8-Hydroxy-2-(di-*n*-propylamino)tetralin

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GLENNON, R. A. AND R. YOUNG. *MDMA stimulus generalization to the 5-$HT_{1A}$ serotonin agonist 8-hydroxy-2-(di-n-propylamino)tetralin.* PHARMACOL BIOCHEM BEHAV **66**(3) 483–488, 2000.—The abused substance *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane, or MDMA, serves as a training drug in animals. Because the 5-$HT_{1A}$ receptor antagonist NAN-190 has been shown to partially antagonize the MDMA stimulus, and because NAN-190 binds at several different types of receptors, in the present study we examined other agents (e.g., adrenergic, dopaminergic, σ) in tests of stimulus generalization and stimulus antagonism to determine their influence on the MDMA stimulus. Each of these agents (i.e., clenbuterol, S(−)propranolol, R(+)SCH-23390, amantadine, NANM) was without effect on MDMA-appropriate responding. The finding that NAN-190 behaves as a 5-$HT_{1A}$ partial agonist in some studies prompted examination of the 5-$HT_{1A}$ receptor agonist 8-OH DPAT and its optical isomers. MDMA-stimulus generalization occurred to racemic 8-OH DPAT ($ED_{50}$ = 0.3 mg/kg), R(+)8-OH DPAT ($ED_{50}$ = 0.2 mg/kg), and to the 5-$HT_{1A}$ receptor partial agonist S(−)8-OH DPAT ($ED_{50}$ = 0.4 mg/kg). The results suggest that the MDMA stimulus might possess a 5-$HT_{1A}$ component of action. Furthermore, because 8-OH DPAT is known to enhance the stimulus effects of hallucinogens as discriminative stimuli, and because MDMA reportedly enhances the effects of hallucinogenic agents in humans ("flipping," "candy flipping"), this latter MDMA-induced phenomenon might involve a 5-$HT_{1A}$ mechanism. © 2000 Elsevier Science Inc.

Hallucinogens Designer drugs Candy flipping Stimulus mechanisms

THE phenylisopropylamine amphetamine is a prototypical central stimulant, whereas the phenylisopropylamine 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (i.e., DOM) is a prototypical classical hallucinogen. The phenylisopropylamine stimulants seem to produce their actions via a dopaminergic mechanism [reviewed: (26)], whereas evidence has implicated a 5-$HT_2$ serotonergic mechanism in the actions of the classical hallucinogens [reviewed: (12)]. Structural modification of phenylisopropylamines results in agents with varying potencies as stimulants or hallucinogens, and can even result in agents with a combination of these actions (12). Other structural modifications alter the pharmacology of the resulting phenylisopropylamines in a unique fashion. For example, *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDMA, "Ecstasy," "XTC") is a well-known drug of abuse that is considered to possess both central stimulant and empathogenic properties (18,25). That is, in addition to being able to produce amphetamine-like actions, this agent induces feelings of well-being and empathy towards others. MDMA also serves as a discriminative stimulus in animals [e.g., (14)]. Although the mechanism of action of MDMA in producing its stimulus effects has yet to be fully elucidated, there is considerable evidence that both serotonin and dopamine neurotransmitter systems might be involved. For example, we (15) and others (20) have shown that 5-$HT_2$ serotonin receptor antagonists (e.g., pirenpirone, ketanserin) and $D_2$ receptor dopamine antagonists (e.g., haloperidol) can partially antagonize the stimulus effects of MDMA in animals trained to discriminate MDMA from vehicle. Schechter (20) has further demonstrated that an MDMA-stimulus generalizes to the 5-HT–releasing agent norfenfluramine, and it has been shown that fenfluramine pretreatment enhances MDMA-appropriate responding in MDMA-trained animals (4). Moreover, it has been demonstrated that the 5-$HT_{1A}$ receptor antagonist NAN-190 can antagonize the spontaneous tail flicks induced by MDMA in restrained rats (19). However, NAN-190 only

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partially antagonizes the stimulus effects of MDMA (15). When we initially developed NAN-190, we reported that it binds with modest affinity at β-adrenergic and $D_1$ dopaminergic receptors (16). Hence, the possibility exists that the partial antagonism of the MDMA stimulus by NAN-190 might involve, at least in part, an adrenergic or $D_1$ dopaminergic mechanism. In addition, NAN-190 (( receptor $K_i$ = 90 nM; unpublished data) and arylpiperazines structurally related to NAN-190 (1) bind with high affinity at sigma (σ) receptors (1); haloperidol is also a high-affinity sigma ligand (1). One of the goals of this investigation was to determine the influence of selected adrenergic and dopaminergic agents and a sigma ligand on the MDMA stimulus. Preliminary studies (data provided herein) suggested that the agents examined had little effect. NAN-190 also has been demonstrated to act as a weak 5-$HT_{1A}$ agonist or low-efficacy partial agonist in certain studies [e.g., (7,9,17,23,24)]. Consequently, it was of interest to determine whether or not a 5-$HT_{1A}$ receptor agonist could attenuate, or substitute for, the MDMA stimulus. That is, the results obtained with the only 5-$HT_{1A}$ agent examined thus far, NAN-190, may have been confounded or obscured by NAN-190's actions at other receptor populations or its actions as a 5-$HT_{1A}$ receptor partial agonist. To further investigate a role for 5-$HT_{1A}$ receptors in the stimulus effects of MDMA, we examined the effect of the 5-$HT_{1A}$ receptor agonist 8-hydroxy-2-(*N,N*-di-*n*-propylamino)tetralin (8-OH DPAT) both in tests of stimulus antagonism and in tests of stimulus generalization.

## METHOD

### *Subjects*

Six male Sprague–Dawley rats, weighing 350–400 g at the beginning of the study, were used as subjects. The animals were housed individually and, prior to the start of the study, their body weights were reduced to approximately 80% of their free-feeding weight. During the entire course of the study, the animals' body weights were maintained at this reduced level by partial food deprivation; in their home cages, the animals were allowed drinking water ad lib.

### *Apparatus*

The rats were trained (15-min training session) to discriminate intraperitoneal injections (15-min presession injection interval) of 1.5 mg/kg of MDMA from vehicle (sterile 0.9% saline) under a variable interval 15-s schedule of reward (i.e., sweetened milk) using standard (Coulbourn Instruments model E10-10) two-lever operant chambers.

### *Procedures*

The procedures employed are similar to that which we have used previously to train rats to discriminate MDMA (14). Briefly, daily training sessions were conducted with MDMA or saline; on every fifth day, learning was assessed during an initial 2.5-min nonreinforced (extinction) session followed by a 12.5-min training session. For half of the animals, the left lever was designated the drug-appropriate lever, whereas the situation was reversed for the remaining animals. Data collected during the extinction session included responses per minute (i.e., response rate) and number of responses on the drug-appropriate lever (expressed as a percent of total responses). Animals were not used in the stimulus generalization studies until they made >80% of their responses on the drug-appropriate lever after administration of MDMA, and <20% of their responses on the same drug-appropriate lever after administration of saline, for 3 consecutive weeks.

Tests of stimulus generalization were conducted to determine if the MDMA stimulus would generalize to various agents. During this phase of the study, maintenance of the MDMA-saline discrimination was ensured by continuation of the training sessions on a daily basis (except on a generalization test day; see below). On 1 of the 2 days before a generalization test, half of the animals would receive MDMA and half would receive saline; after a 2.5-min extinction session, training was continued for 12.5 min. Animals not meeting the original criteria (i.e., >80% of total responses on the drug-appropriate lever after administration of the training dose of training drug, and <20% of total responses on the same lever after administration of saline) during the extinction session were excluded from the immediately subsequent generalization test session. During the investigations of stimulus generalization, test sessions were interposed among the training sessions. The animals were allowed 2.5 min to respond under nonreinforcement conditions; the animals were then removed from the operant chambers and returned to their home cages. An odd number of training sessions (usually five) separated any two generalization test sessions. Doses of the test drugs were administered in a random order, using a 15-min presession injection interval, to groups of five to six rats. If a particular dose of a challenge drug resulted in disruption of behavior (i.e., no responding), only lower doses would be evaluated in subsequent weeks. Stimulus generalization was considered to have occurred when the animals, after a given dose of challenge drug made ≥80% of their responses on the MDMA-appropriate lever. Animals making fewer than five total responses during the 2.5-min extinction session were considered as being disrupted. Data are provided only for those animals that made >5 total responses during the extinction session. Where stimulus generalization occurred, $ED_{50}$ values were calculated by the method of Finney (8). The $ED_{50}$ doses are doses at which the animals would be expected to make 50% of their responses on the drug-appropriate lever.

Tests of stimulus antagonism were conducted in a similar manner. That is, during the investigations of stimulus antagonism, test sessions were interposed among the training sessions as described above. Antagonists were administered (45 min prior to testing) to those animals making criteria and, 15 min prior to testing, 1.5 mg/kg of MDMA or saline was administered. The animals were allowed 2.5 min to respond under nonreinforcement conditions; the animals were then removed from the operant chambers and returned to their home cages. Doses of the test drugs were administered in a random order, using a 45-min presession injection interval, to groups of five to six rats. If a particular combination resulted in disruption of behavior (i.e., no responding), only lower doses of antagonist would be evaluated in subsequent weeks. Stimulus antagonism was considered to have occurred when the animals, after a given dose of challenge drug and 1.5 mg/kg of MDMA made ≤20% of their responses on the MDMA-appropriate lever. Animals making fewer than five total responses during the 2.5-min extinction session were considered as being disrupted.

### *Drugs*

*N*-Methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane HCl (MDMA) was synthesized in-house and available from earlier investigations. R(+)SCH-23390 HCl [R(+)7-chloro-8-

hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine HCl], amantadine HCl, S(−)propranolol HCl, (±)-, R(+)- and S(−)8-OH DPAT HBr were purchased from Research Biochemicals/Sigma (Natick, MA), and clenbuterol HCl was purchased from Sigma Chemical Company (St. Louis, MO). NANM or *N*-allylnormetazocine HCl was a gift from NIDA. Solutions of all drugs were made fresh daily in 0.9% sterile saline and all agents were administered via intraperitoneal injection in a 1.0 ml/kg injection volume. All doses refer to the weight of the salt.

## RESULTS

Six animals were trained to discriminate 1.5 mg/kg of MDMA from saline vehicle. Several doses of MDMA were examined, and a dose–response curve was constructed (Table 1). The calculated $ED_{50}$ value for MDMA, $ED_{50}$ = 0.6 (95%CL = 0.3–1.0) mg/kg, is similar to that which we previously reported (i.e., 0.76 mg/kg) (14). In the first series of studies, several adrenergic agents were examined in tests of stimulus generalization and/or stimulus antagonism (Table 1). The $\beta_2$-adrenergic receptor agonist clenbuterol was examined in tests of stimulus generalization; doses of up to 0.1 mg/kg of clenbuterol resulted in a maximum of 4% MDMA-appropriate responding, whereas at a dose of 0.2 mg/kg of clenbuterol, none of the animals made more than five responses during the entire 2.5-min extinction session (i.e., behavioral disruption). Tests of stimulus antagonism were conducted with the β-adrenergic receptor antagonist S(−)propranolol. Administration of either 1 or 3 mg/kg of S(−)propranolol in combination with 1.5 mg/kg of MDMA had no effect on drug-appropriate responding, and a dose of 5 mg/kg resulted in disruption of the animals' behavior. As control, S(−)propranolol was examined in tests of stimulus generalization at doses of 3 and 5 mg/kg in combination with saline; these doses failed to produce >10% MDMA-appropriate responding. In each case, the highest administered dose of agent reduced the animals' response rates by 50% or more.

Next, the $D_1$ dopaminergic receptor antagonist R(+)SCH-23390 was examined in tests of stimulus antagonism (Table 1); doses of 0.01 and 0.1 mg/kg in combination with 1.5 mg/kg of MDMA had no effect on percent MDMA-appropriate responding, and 0.2 mg/kg resulted in disruption of behavior. As control, the highest nondisruption dose (i.e., 0.1 mg/kg) was examined in a test of stimulus generalization in combination with saline, and produced 8% drug-appropriate respond-

TABLE 1

RESULTS OF STIMULUS GENERALIZATION AND ANTAGONISM STUDIES USING MDMA-TRAINED ANIMALS

| | Presession Injection Interval (min)* | Dose (mg/kg) | *N*† | Percent Drug-Appropriate Responding (±SEM)‡ | Responses per Min (±SEM)‡ |
|---|---|---|---|---|---|
| MDMA | 15 | 0.25 | 6/6 | 5 (3) | 6.9 (2.2) |
| | | 0.75 | 6/6 | 59 (5) | 11.1 (4.7) |
| | | 1.50 | 6/6 | 100 | 9.5 (1.7) |
| Saline (1 ml/kg) | 15 | | 6/6 | 9 (2) | 12.8 (1.9) |
| Clenbuterol | 15 | 0.01 | 5/5 | 3 (3) | 6.6 (1.9) |
| | | 0.05 | 3/5 | 0 — | 3.2 (0.6) |
| | | 0.10 | 3/5 | 4 (4) | 4.4 (1.2) |
| | | 0.20 | 0/5 | —§ | |
| S(−)Propranolol + MDMA | 45 | 1.0 | 4/5 | 100 | 6.2 (2.6) |
| | | 3.0 | 4/5 | 98 (2) | 5.1 (1.4) |
| | | 5.0 | 2/5 | —§ | |
| S(−)Propranolol + saline | 45 | 3.0 | 5/5 | 0 | 8.2 (2.9) |
| | | 5.0 | 4/5 | 8 (5) | 4.6 (1.5) |
| R(+)SCH-23390 + MDMA | 45 | 0.01 | 5/5 | 100 | 5.4 (2.0) |
| | | 0.10 | 3/5 | 100 | 3.1 (0.6) |
| | | 0.20 | 0/5 | —§ | |
| R(+)SCH-23390 + saline | 45 | 0.1 | 4/5 | 8 (2) | 6.7 (1.2) |
| Amantadine | 15 | 5 | 6/6 | 2 (1) | 14.9 (3.5) |
| | | 10 | 5/6 | 7 (6) | 3.8 (1.6) |
| | | 13 | 4/6 | 0 | 5.6 (3.0) |
| | | 15 | 2/6 | —§ | |
| (+)NANM | 15 | 2 | 6/6 | 0 | 10.7 (6.9) |
| | | 4 | 5/6 | 3 (3) | 16.0 (10.6) |
| | | 6 | 4/5 | 6 (3) | 14.1 (6.2) |
| | | 8 | 2/6 | —§ | |
| (±)8-OH DPAT + MDMA | 45 | 0.1 | 5/5 | 97 (3) | 5.2 (1.6) |
| | | 0.3 | 3/5 | 100 | 6.4 (3.8) |
| | | 0.5 | 1/5 | —§ | |

*Time of administration of drug prior to testing. When an agent was examined as an antagonist (i.e., administered in combination with MDMA), the 1.5 mg/kg dose of MDMA was administered 15 min prior to testing. In the corresponding control studies where antagonist was administered in combination with saline, the saline was administered 15 min prior to testing.

†*n* = number of animals responding/number of animals administered drug.

‡Data collected during a 2.5-min extinction session.

§Behavioral disruption (i.e., fewer than half of the animals responded).

ing. Several doses of amantadine, a dopamine releasing agent, also were examined. Doses of up to 13 mg/kg produced <10% drug-appropriate responding, and 15 mg/kg resulted in disruption of behavior. After administration of the 13 mg/kg dose, the animals' response rates were decreased by approximately 50%.

The sigma receptor ligand NANM produced a maximum of 6% drug-appropriate responding at doses of up to 6 mg/kg, and disruption of behavior at 8 mg/kg (Table 1). Drug doses ≤6 mg/kg did not depress the animals' response rates.

The 5-$HT_{1A}$ receptor agonist (±)8-OH DPAT was examined in combination with MDMA to determine whether it could attenuate the MDMA stimulus (Table 1). Doses of 0.1 and 0.3 mg/kg in combination with 1.5 mg/kg of MDMA had little effect on MDMA-appropriate responding, and 0.5 mg/kg in combination with the training dose of the training drug resulted in disruption of behavior (i.e., no responding). As a control, doses of 8-OH DPAT were examined in tests of stimulus generalization. Administration of 0.5 mg/kg of 8-OH DPAT resulted in stimulus generalization. Consequently, additional doses were examined in tests of stimulus generalization using a 15-min presession injection interval, and the results are shown in Fig. 1. MDMA-stimulus generalization to racemic 8-OH DPAT, $ED_{50}$ = 0.3 (95%CL: 0.1–0.5) mg/kg, prompted an examination of 8-OH DPAT optical isomers. The MDMA stimulus generalized both to R(+)8-OH DPAT, $ED_{50}$ = 0.2 (95%CL: 0.1–0.4) mg/kg, and S(−)8-OH DPAT, $ED_{50}$ = 0.4 (95%CL: 0.2–0.8) mg/kg (Fig. 1). (Doses of 0.4 mg/kg of R(+)8-OHDPAT and 1 mg/kg of S(−)8-OH DPAT produced 100% MDMA-appropriate responding; for calculation of $ED_{50}$ values, these doses were assigned values of 99% drug-appropriate responding.) The animals' response rates decreased as the dose of 8-OH DPAT was increased. At the highest doses examined, response rates were depressed by >50%. At 0.5 mg/kg, 0.4 mg/kg, and 1.0 mg/kg of (±)8-OH DPAT, R(+)8-OH DPAT, and S(−)8-OH DPAT, the animals' response rates were 4.3 (±0.4), 4.4 (±1.5), and 3.5 (±1.3) responses per min, respectively. Administration of 0.5 mg/kg of R(+)8-OH DPAT to the MDMA-trained animals resulted in disruption of behavior (not shown in Fig. 1).

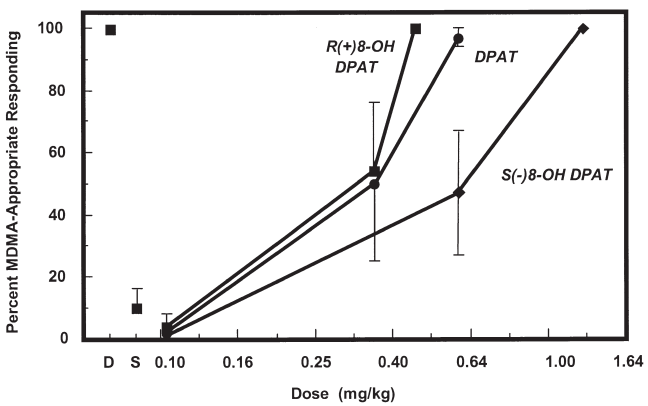


FIG. 1. MDMA stimulus generalization to racemic 8-OH DPAT (DPAT) and its R(+)- and S(−)-isomers ($n$ = 4 for each dose of racemate and $n$ = 5 for each dose of isomer); $ED_{50}$ values calculated for racemic 8-OH DPAT, R(+)8-OH DPAT, and S(−)8-OH DPAT are 0.3, 0.2, and 0.4 mg/kg, respectively. D = effect of 1.5 mg/kg of MDMA; S = effect of 1.0 ml/kg of saline. Data represent the mean±SEM.

## DISCUSSION

The MDMA stimulus failed to substitute to the adrenergic agent clenbuterol. The β-adrenergic antagonist S(−)propranolol was also without significant effect either as an agonist or antagonist. The $D_1$ dopamine antagonist R(+)SCH23390 failed to attenuate the MDMA stimulus, and the dopamine releasing agent amantadine failed to produce MDMA-like effects. The sigma receptor ligand NANM also failed to produce MDMA-like stimulus effects. The results indicate that these agents had relatively little effect on the MDMA stimulus under the conditions employed and, coupled with the results of previously published studies (15,20), suggest that adrenergic, dopaminergic, and sigma mechanisms are not sufficient to account for the stimulus actions of MDMA.

The 5-$HT_{1A}$ receptor agonist (±)8-OH DPAT, when administered in combination with the training dose of MDMA, had no effect on MDMA-appropriate responding but only reduced the animals' response rates. However, the MDMA-stimulus generalized to (±)8-OH DPAT ($ED_{50}$ = 0.3 mg/kg). Interestingly, 8-OH DPAT has been examined once before in MDMA-trained animals, and was shown to produce as much as 55% MDMA-appropriate responding (20). Evaluation of additional doses might have resulted in stimulus generalization; alternatively, differences in training or testing procedures relative to those used herein could have accounted for the observed results.

Although (±)8-OH DPAT is considered a 5-$HT_{1A}$ receptor agonist, and although both optical isomers bind at 5-$HT_{1A}$ receptors with comparable affinity, R(+)8-OH DPAT is a full agonist, whereas S(−)8-OH DPAT is only a partial agonist. Both isomers are capable of producing 5-$HT_{1A}$ agonist effects, but the R(+)isomer is two to four times more potent than its enantiomer (5,6). Consequently, we examined the individual optical isomers of 8-OH DPAT in the MDMA-trained animals and found that the MDMA stimulus generalized to both isomers and that the R(+)-isomer was twice as potent as its S(−)-isomer. Although the animals' response rates were depressed at doses of 8-OH DPAT (and its isomers) that produced >80% MDMA-appropriate responding, the fact remains that the MDMA-trained animals recognized the 5-$HT_{1A}$ agonist. It can be concluded, on this basis, that a portion of the stimulus effects of MDMA might involve a 5-$HT_{1A}$ component of action. This conclusion is consistent with our earlier finding that the mixed 5-$HT_{1A}$ receptor antagonist NAN-190 attenuates the stimulus effect of MDMA (15), and is also consistent with the reports of others who have implicated a role for 5-$HT_{1A}$ receptors in the actions of MDMA. For example, 8-OH DPAT produces a hypothermic effect in rats; both single and repeated administration of MDMA increases 5-$HT_{1A}$ receptor density in rat brain frontal cortex, and this increased density is correlated with the potentiation of a hypothermic response to subsequent administration of 8-OH DPAT (2,3). The 5-$HT_{1A}$ receptor antagonist WAY 100,635 also has been shown to reverse the inhibitory effect of MDMA administration on neuronal firing (10). However, even though a 5-$HT_{1A}$ mechanism might contribute to the stimulus actions of MDMA, it is unlikely that MDMA's stimulus effects are solely attributable to this mechanism. Because MDMA has been shown to release 5-HT (10), one possible explanation is that at least a portion of the MDMA stimulus is related to 5-HT release. Indeed, it has been shown that administration of MDMA to fenfluramine-trained rats results in stimulus generalization (21). However, it might also be noted that stimulus generalization failed to occur when

fenfluramine, a 5-HT releasing agent, was administered to rats trained to discriminate 8-OH DPAT from vehicle (11). It has been demonstrated that 5-$HT_2$ and $D_2$ receptor antagonists can at least partially antagonize the MDMA stimulus (15,20). Interestingly, pretreatment of rats with the 5-$HT_2$ receptor antagonist ketanserin or the $D_2$ receptor antagonist haloperidol also blocked MDMA-induced increases in 5-$HT_{1A}$ receptor density and subsequent 8-OH DPAT-induced hypothermia in MDMA-treated rats (3). Furthermore, the MDMA stimulus is antagonized by 5-$HT_3$ receptor antagonists (15). We have previously suggested that MDMA produces its stimulus actions via a complex mechanism (15), and the present results serve only to support this suggestion.

The results of the present investigation might have practical ramifications and aid our understanding of MDMA use by humans. For example, at "raves," MDMA has been taken together with classical hallucinogens to intensify or modify their actions. This process is known as "flipping" or "candy flipping." DOM is a prototypical classical hallucinogen. DOM binds at 5-$HT_2$ receptors but lacks affinity for 5-$HT_{1A}$ receptors; conversely, 8-OH DPAT is a serotonin agonist that binds at 5-$HT_{1A}$ receptors but lacks affinity for 5-$HT_2$ receptors (12). We have previously trained groups of animals to discriminate DOM from vehicle and 8-OH DPAT from vehicle, and have shown that the DOM stimulus fails to generalize to 8-OH DPAT, and that the 8-OH DPAT stimulus fails to generalize to DOM (11,13). However, we have also shown that pretreatment of DOM-trained rats with a small (i.e., 0.05 mg/kg) dose of 8-OH DPAT in combination with the $ED_{50}$ dose of DOM results in stimulus generalization (12). In a separate experiment, this pretreatment left-shifted the dose–response curve to DOM when the animals were administered various doses of DOM (12). It would appear, then, that the administration of the 5-$HT_{1A}$ receptor agonist can enhance the stimulus potency of DOM in DOM-trained animals. Moreover, it was recently demonstrated that the discriminative effects of MDMA and the hallucinogen lysergic acid diethylamide synergize each others actions in rats (22). In the present investigation it is shown that the MDMA stimulus generalizes to the 5-$HT_{1A}$ receptor agonist 8-OH DPAT. When taken together with the previous finding that the serotonin 5-$HT_{1A}$ receptor antagonist NAN-190 partially antagonizes the stimulus effects of MDMA (15), these results suggest that MDMA might behave, at least in part, as a direct- or indirect-acting 5-$HT_{1A}$ receptor agonist. The somewhat higher potency of R(+)8-OH DPAT over S(−)-OH DPAT also supports this concept. Given the above-mentioned potency-enhancing effect of 8-OH DPAT on the action of the hallucinogen DOM in DOM-trained animals, it is possible that the potency-enhancing effect of MDMA observed in "candy flipping" might involve a 5-$HT_{1A}$ mechanism.

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