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# Effect of 8-hydroxy-2-(*N*,*N*-di-*n*-propylamino)tetralin and MDMA on the discriminative stimulus effects of the classical hallucinogen DOM in rats

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ABSTRACT

Co-administration of the 5-$HT_{1A}$ serotonin receptor agonist (±)8-hydroxy-2-(*N*,*N*-di-*n*-propylamino)tetralin [(±)8-OH DPAT] enhances the discriminative stimulus effects of the classical hallucinogen 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) in rats. In the present investigation, using Sprague–Dawley rats trained to discriminate DOM (1.0 mg/kg) from saline vehicle under a VI-15 s schedule of reinforcement, it was shown that the stimulus-enhancing actions of 8-OH DPAT are related more to its R(+)-isomer than to its S(−)-enantiomer, and that the (±)- and R(+)8-OH DPAT-induced effects are antagonized by the 5-$HT_{1A}$ receptor antagonist NAN-190. (±)8-OH DPAT and its isomers substitute in rats trained to discriminate the designer drug *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDMA; methylenedioxymethamphetamine) from vehicle indicating some similarity of effect. On this basis, it was hypothesized that MDMA might be capable of enhancing the DOM stimulus. Co-administration of MDMA with low (i.e., 0.1 and 0.3 mg/kg) doses of DOM resulted in greater DOM-appropriate responding than engendered by administration of DOM alone. As such, the present findings are the first to demonstrate an MDMA-induced enhancing effect on the discriminative stimulus actions of a classical hallucinogen. The results also suggest that a 5-$HT_{1A}$ serotonin receptor mechanism might contribute to this phenomenon.



## 1. Introduction

MDMA or *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane (methylenedioxymethamphetamine; "Ecstasy"), a so-called designer drug popular with the "rave" culture, is a ring-substituted phenylisopropylamine that produces empathogenic and amphetamine-like subjective effects in humans (e.g. Tancer and Johanson, 2001; Vollenweider et al., 1998). Studies with human volunteers have shown that the overall psychological (i.e., empathogenic) effects of MDMA are largely dependent on carrier-mediated release of serotonin (5-HT) whereas the stimulant-like euphoric actions are related, at least in part, to indirect stimulation of dopamine receptors (Liechti and Vollenweider, 2001; Vollenweider et al., 1998). The mild perceptual effects induced by MDMA might involve stimulation of 5-$HT_2$ serotonin receptors (Liechti and Vollenweider, 2001; Vollenweider et al., 1998).

There are anecdotal reports that a combination of a classical hallucinogen (Glennon, 1991) and MDMA produces a heightened psychoactive response in humans; use of the drug combination is referred to as "flipping" or "candy flipping". That is, when the two agents are co-ingested, their combined "effect" seems greater than that of either agent taken alone. It also has been shown in drug discrimination studies with rats trained to discriminate MDMA that co-administration of MDMA and the classical hallucinogen lysergic acid diethylamide (LSD) produces enhanced MDMA-appropriate responding (Schechter, 1998a). To date, however, few investigations have addressed this interesting phenomenon, and it has yet to be demonstrated in a laboratory setting that MDMA can actually enhance the effects of a hallucinogen.

Some time ago it was demonstrated that the discriminative stimulus effects of the phenylisopropylamine classical hallucinogen 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM), a 5-$HT_{2A}$ serotonin receptor agonist, are altered following pretreatment of the animals with the 5-$HT_{1A}$ receptor agonist (±)8-hydroxy-2-(*N*,*N*-di-*n*-propylamino)tetralin (racemic 8-OH DPAT) (Glennon, 1991). That is, even though DOM does not bind at 5-$HT_{1A}$ receptors, nor does (±)8-OH DPAT bind at 5-$HT_{2A}$ receptors, and despite the failure of DOM and (±)8-OH DPAT to substitute for one another in tests of stimulus generalization in rats regardless of which is used as training drug (Arnt, 1989; Glennon, 1986; Glennon and Hauck, 1985; Glennon et al., 1991), pretreatment of DOM-trained rats with low doses of (±)8-OH DPAT shifted the DOM dose–response curve to the left (Glennon, 1991). Others have shown that (±)8-OH DPAT also enhances DOM-induced muscle contraction in rats (Fone et al., 1991).

Glennon and Young (2000) demonstrated that an MDMA stimulus generalizes to (±)8-OH DPAT indicating that the MDMA stimulus

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might involve, to some extent, a 5-$HT_{1A}$ agonist component of action. Because MDMA does not bind at 5-$HT_{1A}$ serotonin receptors ($K_i$> 10,000 nM; Khorana et al., 2004), it would seem unlikely that MDMA-stimulus generalization to (±)8-OH DPAT results from a direct interaction of MDMA with this receptor population. MDMA, however, has been shown to act as a 5-HT releasing agent (Gartside et al., 1997; Johnson et al., 1986; Rudnick and Wall, 1992), and some of the released 5-HT might activate 5-$HT_{1A}$ receptors (i.e., MDMA might act, at least in part, by indirectly activating 5-$HT_{1A}$ receptors). There is additional evidence that 5-$HT_{1A}$ receptors could be involved in various pharmacological actions of MDMA. The 5-$HT_{1A}$ receptor antagonist NAN-190 (Glennon et al., 1988b; Rydelek-Fitzgerald et al., 1990; Sharif et al., 2004), for example, partially antagonized the stimulus actions of MDMA in MDMA-trained rats (Glennon et al., 1992), and attenuated MDMA-induced spontaneous tail-flick behavior in rodents (Millan and Colpaert, 1991). Another 5-$HT_{1A}$ receptor antagonist, WAY100,635, reversed the effect of MDMA on neuronal firing (Gartside et al., 1997), and single and repeated administration of MDMA increased 5-$HT_{1A}$ receptor density in rat brain frontal cortex (Aguirre et al., 1998). Others (Bishop et al., 2006) have suggested that indirect activation of 5-$HT_{1A}$ receptors by MDMA-induced release of 5-HT might account for certain involuntary motor behaviors in rats. Furthermore, stimulation of 5-$HT_{1A}$ receptors by MDMA-induced 5-HT release also has been implicated as a mechanism underlying certain aspects of rat social interactions (Morely et al., 2005; Thompson et al., 2007), and chronic exposure to MDMA results in neuroadaptive alterations in rat 5-$HT_{1A}$ receptor sensitivity (Crawford et al., 2006; Granoff and Ashby, 2001; Piper et al., 2006).

The present study was undertaken to confirm and extend some of the above drug discrimination findings using rats trained to discriminate DOM from saline vehicle, and to determine if MDMA might modulate the discriminative stimulus potency of DOM. For example, (±)8-OH DPAT has been shown to enhance the discriminative stimulus effects of DOM. Here, that effect was re-examined and extended to an evaluation of the optical isomers of 8-OH DPAT. In addition, if the stimulus-enhancing effect of 8-OH DPAT on the DOM stimulus is mediated via a 5-$HT_{1A}$ receptor mechanism, it should be possible to attenuate the effect by pretreatment of the animals with a 5-$HT_{1A}$ receptor antagonist. Furthermore, the relationships that exist between the stimulus effects of DOM, 8-OH DPAT, and MDMA as described above led to the hypothesis that the 5-$HT_{1A}$ receptor-activating component of MDMA might enhance the actions of DOM in DOM-trained animals when administered in combination. Such a demonstration, when combined with earlier findings might provide, to some extent, a possible explanation for “candy flipping”.

## 2. Materials and methods

### 2.1. Drug discrimination studies

Six male Sprague–Dawley rats (Charles River Laboratories), weighing 250–300 g at the beginning of the study, were trained to discriminate (15-min presession injection interval) 1.0 mg/kg of DOM from saline vehicle (sterile 0.9% saline) under a variable interval 15-s schedule of reinforcement for appetitive reward (i.e., sweetened condensed milk) using standard two-lever Coulbourn Instruments operant equipment as previously described (Glennon et al., 1983; Young et al., 1980). Animal studies were conducted under an approved Institutional Animal Care and Use Committee protocol.

In brief, animals were food-restricted to maintain their body weights at approximately 80% of their expected free-feeding weight, but were allowed access to water *ad libitum* in their individual home cages. Daily training sessions were conducted with the training dose of DOM or saline. For half the animals, the right lever was designated as the drug-appropriate lever, whereas the situation was reversed for the remainder of the animals. Learning was assessed every fifth day during an initial 2.5-min non-reinforced (extinction) session followed by a 12.5-min training session. Data collected during the extinction session included number of responses on the drug-appropriate lever (expressed as a percent of total responses) and response rate (i.e., responses per minute). Animals were not used in the subsequent stimulus generalization or combination studies until they consistently made ≥80% of their responses on the drug-appropriate lever after administration of training drug and ≤20% of their responses on the same drug-appropriate lever after administration of saline for several weeks. During the stimulus generalization (i.e., substitution) and drug combination phases of the study, maintenance of the DOM/saline discrimination was insured by continuation of the training sessions on a daily basis (except on a generalization test day). On one of the two days before a generalization test, half the animals would receive the training dose of DOM and the remainder would receive saline; after a 2.5-min extinction session, training was continued for 12.5 min. Animals not meeting the original training criteria 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 non-reinforcement conditions. An odd number of training sessions (usually 5) separated any two generalization test sessions. Doses of test drugs were administered in a random order. DOM was always administered 15 min prior to testing. In the stimulus generalization studies, (±)8-OH DPAT and its isomers were also administered 15 min prior to testing. In the combination studies, (±)8-OH DPAT, R(−)8-OH DPAT, S(+)8-OH DPAT, and MDMA were administered by separate intraperitoneal injection immediately preceding administration of DOM, and where NAN-190 was employed it was administered 30 min prior to testing.

### 2.2. Data analysis

Stimulus generalization and antagonism data (42 dose or dose combination groups) were analyzed by one-way analysis of variance (statistically significant $F$ value set at $p \leq 0.05$) and followed by Newman–Keuls multiple post-hoc tests ($p \leq 0.05$) to determine statistical significance between dose groups. The data also were characterized by additional criteria. In substitution and antagonism tests, animals that did not respond were labeled as disrupted; such data cannot be assigned a numerical value and, therefore, cannot be included in the statistical analysis. Moreover, animals that made fewer than 5 total responses during the 2.5- min extinction session also were characterized as being disrupted because they failed to meet the (training) testing criteria and also were excluded from statistical analysis. Lastly, data for a particular dose (or dose combination) were not statistically analyzed or plotted if >50% of the animals were disrupted following administration of that dose (or dose combination); such data would be described as disruption because the main effect of the drug was to disrupt a majority of the animals. Thus, percent drug-appropriate responding and response rate data are presented that refer only to ≥50% of the animals that made ≥5 responses during extinction sessions (Young and Glennon, 1986). Response rate data (i.e. responses/min) were evaluated by Dunnett's $t$-test ($p<0.05$) for comparison of a control group (i.e. mean response rate after saline) versus dose(s) of training drug, experimental dose groups, or dose combinations.

*Complete Stimulus Generalization (or no Stimulus Antagonism)* was considered to have occurred if no statistical difference occurred between percent DOM-appropriate responding of the training dose of training drug versus dose of test drug (or drug combination) and the group mean was ≥80% DOM-appropriate responding. Thus, stimulus generalization (or no antagonism) was determined by a more stringent and conservative standard than simply lack of statistical significance between the results produced by training dose versus test dose (or dose combination). Where complete stimulus generalization

occurred, potency comparisons were made between the training drug and the test agent via calculation of the effective dose 50% ($ED_{50}$) as determined from the dose–response data by the method of Finney (1952). The $ED_{50}$ dose represents the calculated drug dose where animals would be expected to make 50% of their responses on the drug-appropriate lever. Results of generalization tests that fell ≤79% DOM-appropriate responding were characterized as partial generalization (or partial antagonism) as defined below.

*Partial Generalization (or Partial Antagonism).* In drug discrimination studies, the administration of the training dose of training drug or vehicle during *initial training sessions* typically results in the animals dividing their responses equally (i.e. characterized as random responding, 50% drug-appropriate responding after injection of drug or vehicle, or responding that is not appropriate for either training treatment) on the levers. However, as training progresses with drug and vehicle, the animals gradually learn to respond on the drug-designated lever when given drug (i.e. percent of responses on the drug-designated lever is high and percent of responses on the vehicle-designated lever is low) and respond on the vehicle-designated lever when given vehicle (i.e. percent of responses on the drug-designated lever is low and percent of responses on the vehicle-designated lever is high). When the discrimination is learned, the well-trained animals exhibit particular tendencies for responding on each lever. Early drug discrimination studies firmly established the specificity of the training dose of a training drug such that (behaviorally active) doses of drugs from other drug classes produced responding primarily on the saline-appropriate lever and *not* 50% drug-lever responding. In other words, doses of test drugs that produce effects that are clearly dissimilar from both saline and drug (discrimination training) conditions produce responding predominantly, if not exclusively, on the saline-appropriate lever (e.g., see Balster and Ford, 1978; Colpaert, 1978; Colpaert et al., 1979; Krimmer and Barry, 1977; Lal et al., 1977; Shannon and Holtzman, 1977; Silverman and Ho, 1977). For example, Shannon and Holtzman (1977) trained animals to discriminate 3.0 mg/kg of morphine from saline and found that test doses of mescaline between 3.0 and 100 mg/kg produced a maximum of 0% morphine-appropriate responding; such doses (up to 100 mg/kg) of mescaline are clearly not inert. Thus, animals do not respond along a general continuum of "drugged versus not-drugged" states, such that "random (i.e., 50%)" drug-appropriate responding occurs when a dose(s) of test drug is administered that is known to produce a pharmacological effect(s) that is clearly different from that produced by the training stimulus and vehicle. On the contrary, drug discrimination data are typically interpreted to indicate that responding on the drug-appropriate lever occurs only when there is some degree of similarity between the (learned) stimulus effect in comparison to the effect of the test dose of the challenge drug. As such, animals respond according to "training drug effect" versus "no-drug/different drug effect" states. In the current study, therefore, partial generalization (or partial antagonism) was considered to have occurred when a challenge drug (or drug combination) produced percent drug-lever responding that was between those of the treatment conditions (i.e. technically 21% to 79% but usually between 40% and 70%).

*No Generalization (or Stimulus Antagonism)* was considered to have occurred if no statistical difference occurred between percent DOM-appropriate responding of the vehicle versus dose of test drug and the group mean was ≤20% DOM-appropriate responding. Thus, a determination of no stimulus generalization (or stimulus antagonism) was determined by a more stringent and conservative standard than simply lack of statistical significance between the results produced by vehicle versus a test dose (or dose combination).

### 2.3. Drugs

Racemic 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane HCl (DOM) and *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane HCl (MDMA) were obtained as gifts from the National Institute on Drug Abuse. (±)8-Hydroxy-2-(*N*,*N*-di-*n*-propylamino)tetralin (racemic 8-OH DPAT) and its two individual optical isomers were purchased as their HBr salts from Research Biochemicals, Inc. (Natick, MA). NAN-190, or 1-(2-methoxypenyl)-4-[4-(2-phthalimido)-butyl] piperazine HBr, was synthesized as previously described (Glennon et al., 1988a). All drug doses were administered via intraperitoneal injection (1 ml/kg); doses refer to the weight of the salts. Solutions in sterile 0.9% saline were freshly prepared each day.

## 3. Results

A group of rats ($n=6$) was trained to discriminate 1.0 mg/kg of DOM from saline vehicle (Fig. 1) such that, once trained, the animals made ≥80% of their responses on the drug-appropriate lever following administration of the DOM training dose, and ≤20% of their responses on this same lever following administration of saline vehicle. The rats learned the DOM versus saline discrimination over the same period of time as rats trained previously (Glennon et al., 1983; Young et al., 1980). Thus, the DOM versus saline discrimination was learned by the animals after 30 training sessions and remained stable for an additional 10 training sessions before substitution tests were initiated. The stimulus generalization and stimulus antagonism data were subjected to statistical evaluation and found to be statistically significant ($F(41,172)=11.78$, $p<0.0001$).

Administration of lower DOM doses to the trained animals resulted in a dose-related decrease in percent DOM-appropriate responding (DOM $ED_{50}=0.3$ mg/kg; 95% CL = 0.2–0.5 mg/kg). The animals' response rates were not substantially different under the different conditions

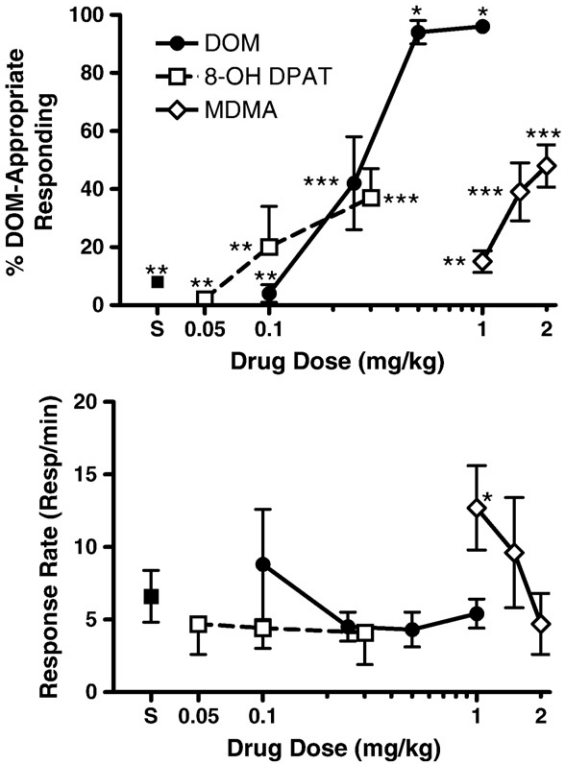


**Fig. 1.** Results (group mean ± SEM) of stimulus generalization studies conducted with DOM, (±)8-OH DPAT, and MDMA in rats ($n=6$) trained to discriminate 1.0 mg/kg of DOM from saline vehicle (upper panel). The animals' response rates are shown in the lower panel. S = responses following administration of saline vehicle. One asterisk indicates a statistically significant difference from the response of saline vehicle. Two asterisks indicate a statistically significant difference from the response of DOM (1.0 mg/kg). Three asterisks indicate a statistically significant difference from the response of saline vehicle and DOM (1.0 mg/kg).

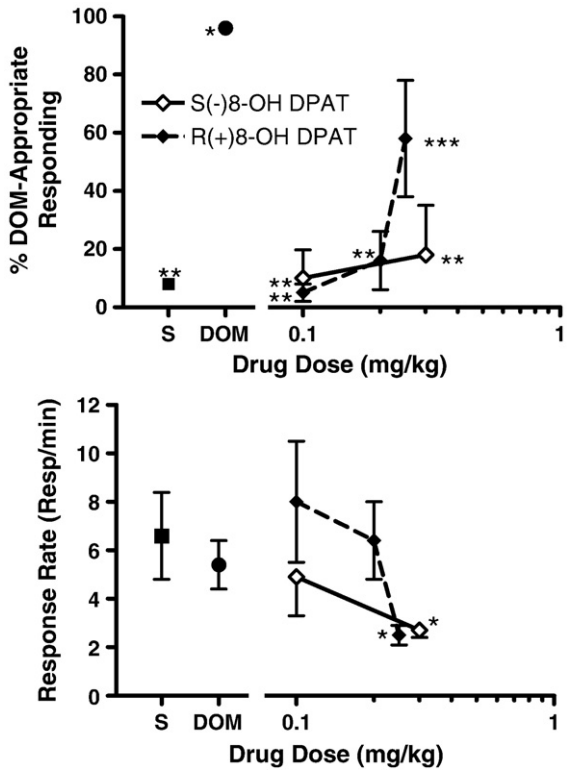


**Fig. 2.** Results (group mean±SEM) of stimulus generalization studies with the optical isomers of 8-OH DPAT in rats ($n$=6) trained to discriminate 1.0 mg/kg of DOM from saline vehicle (upper panel), and animals' response rates (lower panel). DOM=responses following 1.0 mg/kg of DOM, and S=responses following administration of saline vehicle. One asterisk indicates a statistically significant difference from the response of saline vehicle. Two asterisks indicate a statistically significant difference from the response of DOM (1.0 mg/kg). Three asterisks indicate a statistically significant difference from the response of saline vehicle and DOM (1.0 mg/kg).

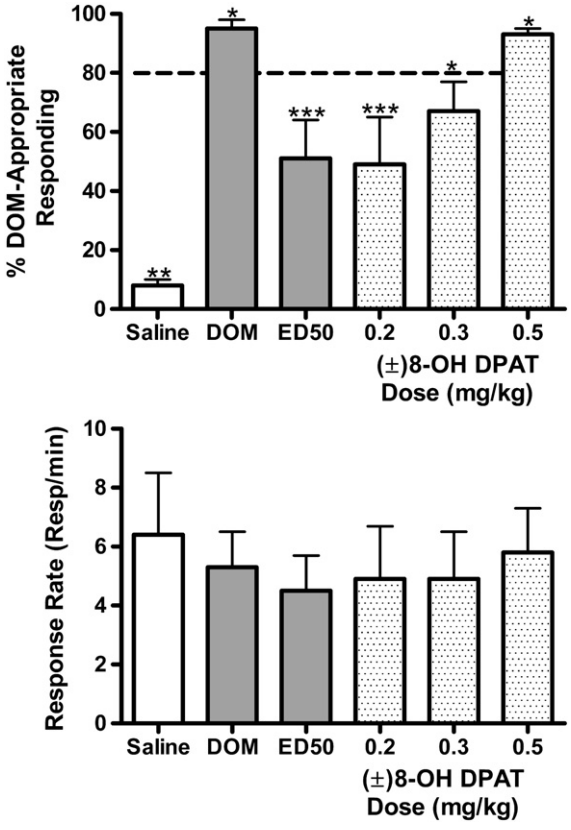


**Fig. 3.** Results (group mean±SEM) of (±)8-OH DPAT doses given in combination with the $ED_{50}$ dose of DOM to rats ($n$=5) trained to discriminate 1.0 mg/kg of DOM from saline vehicle (upper panel). One asterisk indicates a statistically significant difference from the response of saline vehicle. The animals' response rates are shown in the lower panel. DOM=responses following 1.0 mg/kg of DOM, ED50=responses following administration of the $ED_{50}$ dose (i.e., 0.3 mg/kg) of DOM, and S=responses following administration of saline vehicle. Two asterisks indicate a statistically significant difference from the response of DOM (1.0 mg/kg). Three asterisks indicate a statistically significant difference from the response of saline vehicle and DOM (1.0 mg/kg).

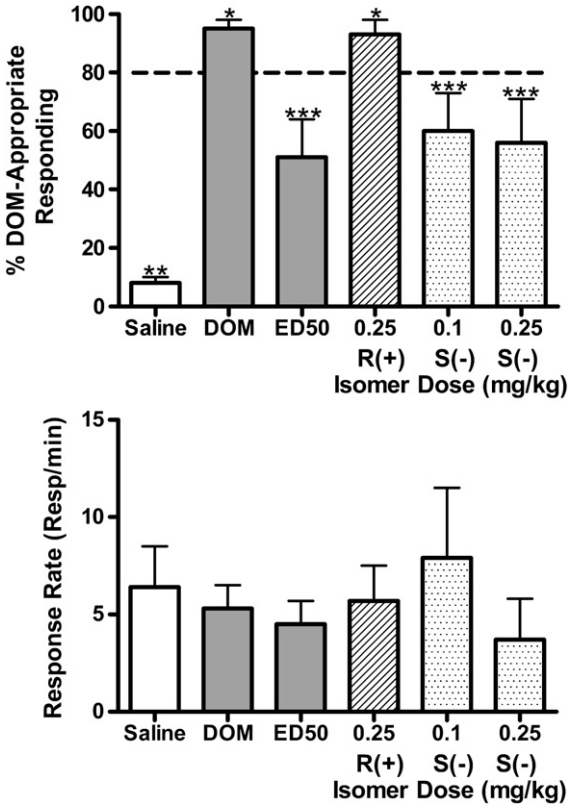


**Fig. 4.** Results (group mean±SEM) of selected R(+)- and S(−)8-OH DPAT doses given in combination with the $ED_{50}$ dose of DOM to rats ($n$=5) trained to discriminate 1.0 mg/kg of DOM from saline vehicle (upper panel). The animals' response rates are shown in the lower panel. DOM=responses following 1.0 mg/kg of DOM, ED50=responses following administration of the $ED_{50}$ dose (i.e., 0.3 mg/kg) of DOM, and S=responses following administration of saline vehicle. One asterisk indicates a statistically significant difference from the response of saline vehicle. Two asterisks indicate a statistically significant difference from the response of DOM (1.0 mg/kg). Three asterisks indicate a statistically significant difference from the response of saline vehicle and DOM (1.0 mg/kg).

(Fig. 1). Tests of stimulus generalization with racemic 8-OH DPAT doses showed that a dose of 0.3 mg/kg produced 37% DOM-appropriate responding (Fig. 1), with one of the six animals failing to respond. Administration of 0.4 mg/kg of (±)8-OH DPAT (data not shown) resulted in behavioral disruption with all animals failing to respond.

Tests of stimulus generalization were conducted with the individual optical isomers of 8-OH DPAT (Fig. 2). Administered S(−) 8-OH DPAT doses of 0.1 and 0.3 mg/kg, the animals failed to make >20% of their responses on the DOM-appropriate lever. At these doses, two of the six animals failed to respond. Following administration of 0.3 mg/kg of S(−)8-OH DPAT, animals' response rate was significantly ($p$<0.05) less than the saline vehicle rate. Administration of 0.5 mg/kg of this isomer resulted in five of the six animals failing to make ≥5 total responses during the entire 2.5-min extinction session. The R(+)-isomer engendered a maximum of 58% DOM-appropriate responding (at 0.25 mg/kg) with two of the six animals failing to respond. Following administration of 0.25 mg/kg of R(+)8-OH DPAT, animals' response rate was significantly ($p$<0.05) less than the saline vehicle

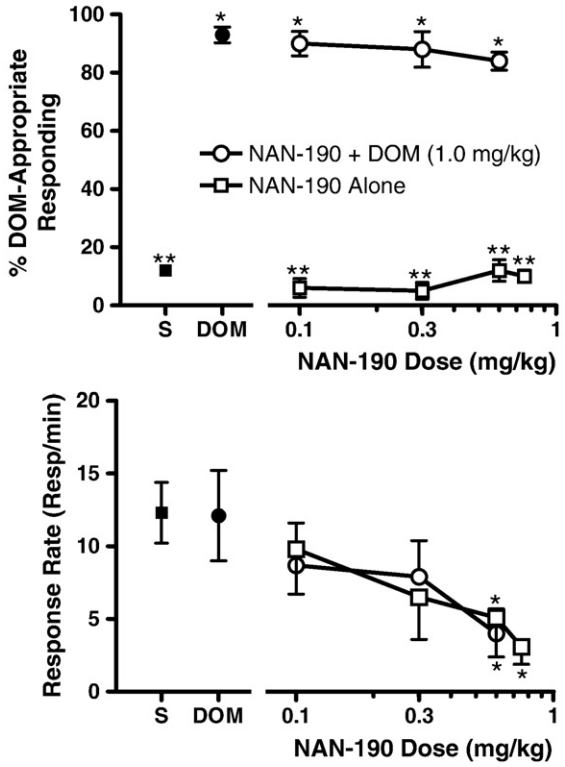


**Fig. 5.** Results (group mean ± SEM) of NAN-190 doses given alone (open squares) or in combination with 1.0 mg/kg of DOM (open circles) to rats ($n$=6) trained to discriminate 1.0 mg/kg of DOM from saline vehicle (upper panel). The animals' response rates are shown in the lower panel. DOM=responses following 1.0 mg/kg of DOM, and S=responses following administration of saline vehicle. One asterisk indicates a statistically significant difference from the response of saline vehicle. Two asterisks indicate a statistically significant difference from the response of DOM (1.0 mg/kg).

rate. Administration of a higher dose (i.e., 0.3 mg/kg) of this isomer resulted in disruption of behavior in the majority of the animals.

MDMA was examined in rats trained to discriminate DOM from saline vehicle (Fig. 1). The animals displayed a maximum of 48% DOM-appropriate responding at a dose of 2.0 mg/kg, and all but one animal was disrupted following an MDMA dose of 2.5 mg/kg. The animals' response rate was increased significantly ($p<0.05$) after administration of 1.0 mg/kg of MDMA; however, as the dose of MDMA was increased response rate decreased and only four of six animals responded following 1.5 mg/kg, and three of six animals responded following 2.0 mg/kg.

Administration of the calculated $ED_{50}$ dose of DOM (i.e., 0.3 mg/kg) to the DOM-trained animals ($n$=6) resulted in their making 51% of their responses on the DOM-appropriate lever (Fig. 3). Administration of the calculated $ED_{50}$ dose of DOM ($n$=5) in combination with doses of racemic 8-OH DPAT (0.2 mg/kg to 0.5 mg/kg) produced dose-related substitution such that following 0.5 mg/kg of (±)8-OH DPAT and 0.3 mg/kg of DOM the animals made ≥80% of their responses on the DOM-appropriate lever. Administration of the $ED_{50}$ dose of DOM with 0.25 mg/kg of R(+)8-OH DPAT also resulted in the animals ($n$=5) making ≥80% of their responses on the DOM-appropriate lever, whereas in combination with 0.25 mg/kg of S(−)8-OH DPAT, the animals ($n$=5) made only 56% of their responses on this same lever (Fig. 4). A lower (i.e., 0.1 mg/kg) dose of S(−)8-OH DPAT in combination with the $ED_{50}$ dose of DOM elicited 60% DOM-appropriate responding (Fig. 4), whereas administration of a higher dose (i.e., 0.3 mg/kg) disrupted the lever-pressing behavior of four of the five animals (data not shown).

In a separate experiment, doses of the 5-$HT_{1A}$ receptor antagonist NAN-190 failed to substitute for DOM in DOM-trained animals; administered alone, NAN-190 (0.1–0.75 mg/kg) produced a maximum of 12% DOM-appropriate responding (Fig. 5). Following administration of 0.6 or 0.75 mg/kg of NAN-190, animals' response rate was significantly ($p<0.05$) less than the saline vehicle rate. Administered in combination with the training dose of DOM (Fig. 5), NAN-190 (0.1–0.6 mg/kg) failed to antagonize the DOM stimulus and the animals' response rate was significantly ($p<0.05$) reduced after the administration of the training dose of DOM and 0.6 mg/kg of NAN-190. Following administration of 0.75 mg/kg of NAN-190 in combination with the training dose of DOM, none of the six animals responded during the entire 2.5-min extinction session.

At a dose of 0.1 mg/kg NAN-190 failed to antagonize the stimulus-enhancing effect of (±)8-OH DPAT or R(+)8-OH DPAT when administered in combination with the $ED_{50}$ dose of DOM (Fig. 6). However, at a dose of 0.3 mg/kg, NAN-190 in combination with either 0.5 mg/kg of (±)8-OH DPAT or 0.25 mg/kg of R(+)8-OH DPAT plus the $ED_{50}$ dose of DOM reduced drug-appropriate responding to 54% and 51%, respectively; for a control response, the $ED_{50}$ dose was administered and produced 48% DOM-appropriate responding. Following administration of 0.3 mg/kg of NAN-190 and 0.25 mg/kg of R(+)8-OH DPAT, animals response rate was significantly ($p<0.05$) less than that of the saline vehicle rate.

Fig. 7 shows the effect of MDMA doses when administered in combination with the $ED_{50}$ dose of DOM ($n$=6 animals per dose combination). Administration of 0.3, 0.5, and 1.0 mg/kg of MDMA in combination with 0.3 mg/kg of DOM resulted in progressively

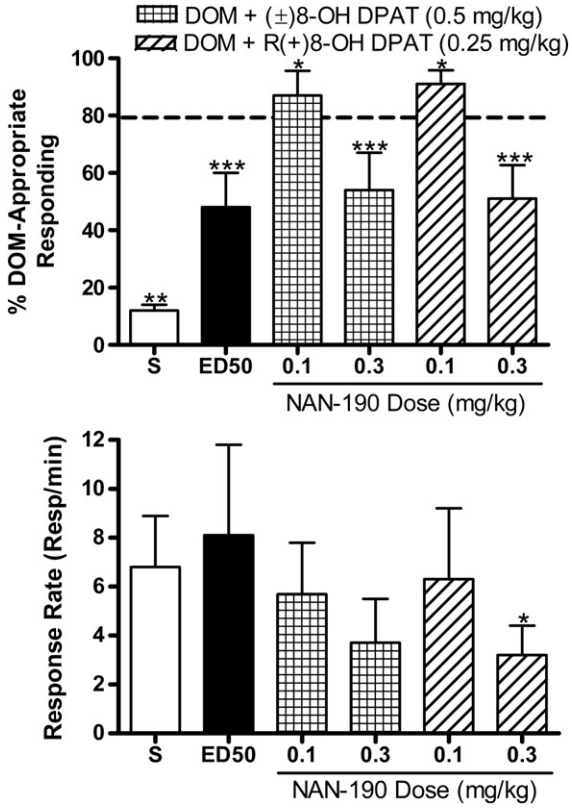


**Fig. 6.** Results (group mean ± SEM) of NAN-190 doses (0.1 and 0.3 mg/kg) administered to animals receiving a combination of the $ED_{50}$ dose of DOM plus either 0.5 mg/kg of (±)8-OH DPAT or 0.25 mg/kg of R(+)8-OH DPAT to rats ($n$=6) trained to discriminate 1.0 mg/kg of DOM from saline vehicle (upper panel). The animals' response rates are shown in the lower panel. ED50=responses following administration of the $ED_{50}$ dose (i.e., 0.3 mg/kg) of DOM, and S=responses following administration of saline vehicle. One asterisk indicates a statistically significant difference from the response of saline vehicle. Two asterisks indicate a statistically significant difference from the response of DOM (1.0 mg/kg; control percent=98% (±1); responses/min=5.3 (±0.8). Three asterisks indicate a statistically significant difference from the response of saline vehicle and DOM (1.0 mg/kg).

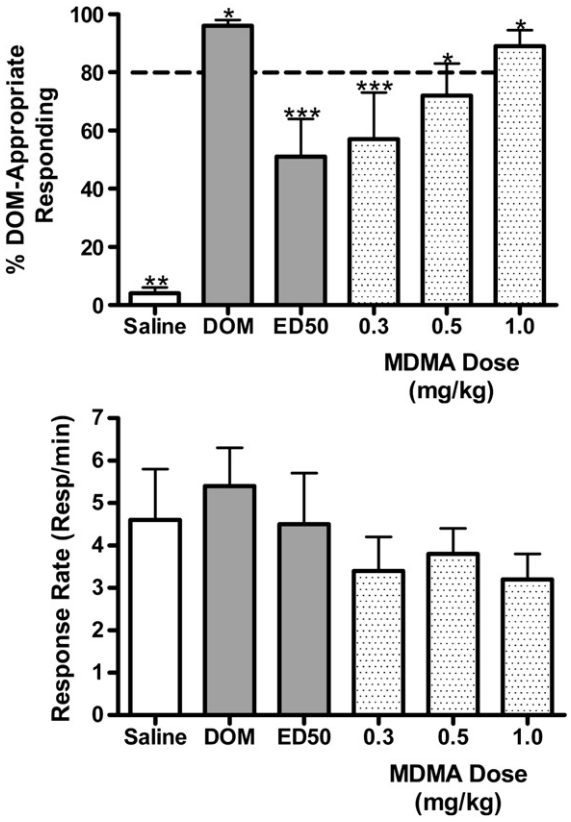


**Fig. 7.** Results (group mean ± SEM) of MDMA doses given in combination with the $ED_{50}$ dose of DOM to rats ($n=6$) trained to discriminate 1.0 mg/kg of DOM from saline vehicle (upper panel). The animals' response rates are shown in the lower panel. DOM = responses following 1.0 mg/kg of DOM, ED50 = responses following administration of the $ED_{50}$ dose (i.e., 0.3 mg/kg) of DOM, and S = responses following administration of saline vehicle. One asterisk indicates a statistically significant difference from the response of saline vehicle. Two asterisks indicate a statistically significant difference from the response of DOM (1.0 mg/kg). Three asterisks indicate a statistically significant difference from the response of saline vehicle and DOM (1.0 mg/kg).

increased DOM-appropriate responding such that following 1.0 mg/kg of MDMA in combination with the $ED_{50}$ dose of DOM the animals made ≥80% of their responses on the DOM-appropriate lever. One of six, and three of six, animals were disrupted at the two highest MDMA doses evaluated in combination with DOM.

A final study examined the effect of MDMA doses administered in combination with a dose of DOM (0.1 mg/kg) lower than the $ED_{50}$ dose (Fig. 8; $n=6$). By itself, administration of 0.1 mg/kg of DOM produced only 4% DOM-appropriate responding. However, in combination with MDMA doses of 0.5 to 1.0 mg/kg, the animals made from 41% to 68% of their responses on the DOM-appropriate lever. Administration of 1.2 mg/kg of MDMA in combination with 0.1 mg/kg of DOM resulted in behavioral disruption with all animals failing to respond during the 2.5-min extinction session.

## 4. Discussion

DOM and (±)8-OH DPAT each serve as discriminative stimuli in rats, but the agents do not substitute for one another in tests of stimulus generalization regardless of which is used as training drug (reviewed: Glennon, 1988). However, when these agents are administered in combination, the stimulus effects of DOM are enhanced by pretreatment of the animals with low doses of (±)8-OH DPAT (Glennon, 1991). In the present investigation, some of these findings were replicated and extended. For example, it was confirmed that a DOM stimulus fails to generalize to (±)8-OH DPAT (Fig. 1). Examination of the individual optical isomers of 8-OH DPAT (Fig. 2) revealed that although the R(+)-isomer results in partial generalization, neither 8-OH DPAT isomer engendered ≥80% DOM-appropriate responding. Clearly, then, neither racemic 8-OH DPAT nor either of its individual isomers fully substitutes for DOM.

In the present investigation, it was confirmed that racemic 8-OH DPAT enhances the discriminative stimulus effect of a DOM dose lower than that of the DOM training dose. Administration of 0.5 mg/kg of (±)8-OH DPAT in combination with the $ED_{50}$ dose of DOM resulted in the animals responding as they did following administration of the training dose of DOM (Fig. 3). Because (±)8-OH DPAT is composed of an equivalent amount of each isomer, it was hypothesized that half the (±)8-OH DPAT dose (i.e., a 0.25 mg/kg dose) of one of the two optical isomers should be capable of mimicking the actions of the racemate. As shown in Fig. 4, a combination of the $ED_{50}$ dose of DOM plus 0.25 mg/kg of R(+)8-OH DPAT, but not S(−)8-OH DPAT, resulted in stimulus generalization. Taken together, the above results show that at the doses evaluated neither (±)8-OH DPAT nor its optical isomers substitute for a DOM stimulus, but that (±)8-OH DPAT and its R(+)-isomer enhance the stimulus effects of the $ED_{50}$ dose of DOM in DOM-trained animals. Because the R(+)-isomer of 8-OH DPAT produced an effect similar to that of (±)8-OH DPAT, but at half the dose of the racemate, it would seem that this isomer is the more responsible of the two for the effects produced by the racemate. Also, because R(+)8-OH DPAT, by itself, produced 58% DOM-appropriate responding when administered to the DOM-trained animals at a dose of 0.25 mg/kg, the apparent stimulus-enhancing effect of 0.25 mg/kg of this isomer when administered in combination with the $ED_{50}$ dose of DOM might simply reflect an additive effect of the individual

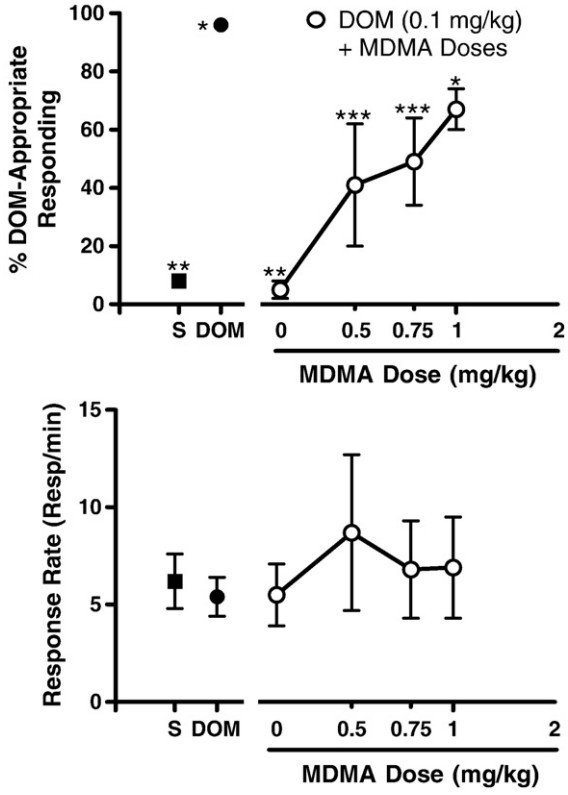


**Fig. 8.** Results (group mean ± SEM) of MDMA doses given in combination with a very low dose (i.e., 0.1 mg/kg) of DOM to rats ($n=6$) trained to discriminate 1.0 mg/kg of DOM from saline vehicle (upper panel). The animals' response rates are shown in the lower panel. DOM = responses following 1.0 mg/kg of DOM, and S = responses following administration of saline vehicle. One asterisk indicates a statistically significant difference from the response of saline vehicle. Two asterisks indicate a statistically significant difference from the response of DOM (1.0 mg/kg). Three asterisks indicate a statistically significant difference from the response of saline vehicle and DOM (1.0 mg/kg).

components rather than representing a synergistic effect. This will require further investigation. Although both isomers of 8-OH DPAT bind with nearly comparable affinity at 5-$HT_{1A}$ receptors, R(+)8-OH DPAT is a 5-$HT_{1A}$ receptor full agonist (adenylate cyclase assay) whereas S(−)8-OH DPAT possesses only 50% of the efficacy of its R(+)-enantiomer (Cornfield et al., 1991; Hacksell et al., 1993); hence, enhancement of the DOM stimulus by R(+)8-OH DPAT might be interpreted as evidence for a 5-$HT_{1A}$ receptor-mediated agonist effect.

As further support for 5-$HT_{1A}$ receptor involvement in the actions of 8-OH DPAT, the effect of the 5-$HT_{1A}$ receptor antagonist NAN-190 was examined. NAN-190 has been previously demonstrated to antagonize the discriminative stimulus effects of (±)8-OH DPAT in rats and, in fact, was the first such agent shown to successfully do so (Glennon et al., 1988b). In the present investigation, NAN-190 neither substituted for, nor antagonized, the stimulus effects of DOM (Fig. 5). Yet, NAN-190 was able to reduce both the (±)8-OH DPAT-enhanced and R(+)8-OH DPAT-enhanced stimulus actions of the $ED_{50}$ dose of DOM to levels expected for the DOM dose alone (Fig. 6). That is, NAN-190 essentially abolished the DOM potency-enhancing effects of racemic 8-OH DPAT and its more effective R(+)-optical isomer.

Even though (±)8-OH DPAT is widely used as a 5-$HT_{1A}$ agonist, it binds at 5-$HT_7$ receptors and (±)- and R(+)8-OH DPAT have been shown to display 5-$HT_7$ receptor agonist action (e.g. Krobert et al., 2001; Lovenberg et al., 1993; Wood et al., 2000). Furthermore, some actions previously ascribed to a 5-$HT_{1A}$ mechanism, because they were produced by (±)8-OH DPAT, are now considered to be 5-$HT_{1A}$- and/or 5-$HT_7$ receptor-mediated (Bonaventure et al., 2004; Faure et al., 2006; Hedlund et al., 2004; Meneses, 2004). Because R(+)8-OH DPAT (its antipode has not yet been examined) has been shown to be a 5-$HT_7$ receptor partial agonist (Krobert et al., 2001), and since NAN-190 displays low affinity ($K_i$>1000 nM) for 5-$HT_7$ receptors (Shen et al., 1993), it seems likely that the observed actions of 8-OH DPAT in the present study involve a 5-$HT_{1A}$ rather than a 5-$HT_7$ receptor mechanism.

Another aspect of this investigation was to examine the effect of MDMA in combination with DOM in rats trained to discriminate DOM from vehicle. Previous studies have demonstrated that MDMA-stimulus generalization occurs to (±)8-OH DPAT, and that (±)8-OH DPAT enhances the stimulus actions of DOM (Glennon, 1991; Glennon and Young, 2000). However, DOM and MDMA failed to substitute for one another in tests of stimulus generalization regardless of which was employed as training drug (Glennon et al., 1982, 1986; Glennon, 1989; Nichols and Oberlender, 1989). As shown in Fig. 1, MDMA failed to substitute for a DOM stimulus. That is, MDMA produced a maximum of 48% DOM-appropriate responding at 2.0 mg/kg and behavioral disruption at 2.5 mg/kg. These findings are consistent with what was earlier reported [(52% at 2.0 mg/kg and behavioral disruption at 2.5 mg/kg (Glennon et al., 1982)]. Nonetheless, the current hypothesis was that MDMA might enhance the stimulus action of DOM. Fig. 7 shows that MDMA enhances the stimulus effects of DOM in DOM-trained animals. It is unlikely that the results reflect an additive effect of the two agents because 1.0 mg/kg of MDMA, by itself, produces saline-appropriate responding in DOM-trained animals (Fig. 1). Supportive of this concept are the results shown in Fig. 8. At a dose of 0.1 mg/kg, DOM elicits only 4% DOM-appropriate responding; however, a combination of this dose of DOM and 1.0 mg/kg of MDMA (i.e., an MDMA dose that, by itself, produces only 15% DOM-appropriate responding) produced 68% DOM-appropriate responding. Although stimulus generalization did not occur (i.e., a higher MDMA dose in combination with 0.1 mg/kg of DOM resulted in behavioral disruption), a substantial degree of partial generalization was observed.

The results obtained here are not inconsistent with findings that LSD enhances the stimulus effects of MDMA (Schechter, 1998a). However, there are some important distinctions between the two studies. One difference is that rather than the stimulus effects of MDMA being enhanced by a hallucinogenic agent (Schechter, 1998a), the present investigation demonstrates that the stimulus effects of a hallucinogenic agent (i.e., DOM) were enhanced by MDMA. Furthermore, the Schechter study employed a strain of rat (Fawn-Hooded) different from that used here (Sprague–Dawley), and it has been demonstrated that MDMA-stimulus generalization occurs to LSD in serotonergically dysfunctional Fawn-Hooded rats (Schechter, 1998b) but not in Sprague–Dawley rats (Nichols and Oberlender, 1989). Also, LSD is a potent, but non-selective serotonin receptor ligand with 5-$HT_{1A}$ agonist action of its own (i.e., inhibition of cAMP accumulation) whereas, in contrast, DOM lacks significant 5-$HT_{1A}$ receptor affinity and agonist action (Pauwels et al., 1993). Hence, the present investigation is the first to demonstrate that MDMA can enhance the discriminative stimulus effects of a classical hallucinogen when the agents are administered together.

MDMA does not bind at 5-$HT_{1A}$ receptors but can act, at least in part, by indirectly activating 5-$HT_{1A}$ receptors via 5-HT release (see Introduction). The stimulus actions of DOM are enhanced by administration of the 5-$HT_{1A}$ receptor agonist (±)8-OH DPAT (Glennon, 1991) as are the discriminative stimulus effects of LSD (Reissig et al., 2005). If MDMA possesses, to some degree, an indirect 5-$HT_{1A}$ component of action, then MDMA might be able to enhance the stimulus actions of DOM much in the same manner seen upon co-administration of 8-OH DPAT with DOM. Taken together, the present investigation a) confirmed that (±)8-OH DPAT failed to substitute for, but enhances, the stimulus effects of DOM in rats trained to discriminate 1.0 mg/kg of DOM from saline vehicle, b) showed that this enhancement is more apparent with the higher-efficacy 5-$HT_{1A}$ receptor agonist R(+)8-OH DPAT than with its lower-efficacy S(−)-enantiomer, c) showed that the stimulus-enhancing effects of 8-OH DPAT are antagonized by the 5-$HT_{1A}$ receptor antagonist NAN-190, and d) demonstrated that MDMA, an agent to which (±)8-OH DPAT substitutes when MDMA is used as training drug in rats, also enhances the stimulus actions of DOM. As such, the present findings support anecdotal reports that MDMA can enhance the actions of a classical hallucinogen, and further suggest that the stimulus-enhancing effect might involve a combined 5-$HT_2$/5-$HT_{1A}$ receptor mechanism when these agents are administered together.

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