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# Investigation of MDMA-Related Agents in Rats Trained to Discriminate MDMA From Saline

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GLENNON, R. A. AND R. HIGGS. *Investigation of MDMA-related agents in rats trained to discriminate MDMA from saline.* PHARMACOL BIOCHEM BEHAV **43**(3) 759-763, 1992.—To determine whether metabolite-related analogs of *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDMA) produce stimulus effects similar to those of the parent compound, and to determine the structural requirements associated with the MDMA stimulus, several MDMA analogs were examined in tests of stimulus generalization using rats trained to discriminate 1.5 mg/kg MDMA from saline. Although several of the analogs produced up to 50-60% MDMA-appropriate responding, none [with the exception of *N*-methyl-1-(4-methoxyphenyl)-2-aminopropane (PMMA)] resulted in stimulus generalization. The partial generalization, coupled with the possible reduced ability of certain of the agents to penetrate the blood-brain barrier relative to MDMA, suggests that these agents are not behaviorally inactive. PMMA, although not a metabolite of MDMA, is closely related in chemical structure to MDMA and its metabolites; PMMA produces >80% MDMA-appropriate responding and is approximately three times more potent ($ED_{50}$ = 0.2 mg/kg) than MDMA itself ($ED_{50}$ = 0.76 mg/kg). PMMA is a newer scheduled substance with an as yet unknown mechanism of action; however, on the basis of the stimulus generalization observed PMMA may share some behavioral and mechanistic similarity with MDMA. These results also indicate that an intact methylenedioxy ring, such as that found in MDMA but absent in PMMA, is not a prerequisite for MDMA-like activity and further support the notion that ring-opened MDMA metabolites may produce effects that contribute to the actions of MDMA.

MDMA MDMA metabolites Drug discrimination Methamphetamine PMMA

*N*-METHYL-1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDMA) is a Schedule I substance with potential, although controversial, therapeutic application in psychotherapy (16); it is also associated with widespread abuse and is available on the clandestine market under a variety of names, of which "Ecstasy" is perhaps the most common. As part of our investigations of the mechanisms of action and structure-activity relationships of phenylisopropylamines, we first examined MDMA and MDMA-related agents in the late 1970s and early 1980s (12). Subsequently, using a drug discrimination paradigm we trained rats to discriminate MDMA from saline to further investigate the stimulus effects of these agents (6). Considerable progress has been made in the past decade [see Glennon (6) and Nichols and Oberlender (17) for recent reviews], but the mechanism of action of MDMA as a discriminative stimulus has yet to be elucidated.

Although MDMA is an analog of the phenylisopropylamine amphetamine or, more accurately, *N*-monomethylamphetamine (i.e., methamphetamine), it is evident that MDMA is not a simple amphetamine-like agent. In tests of stimulus generalization, racemic MDMA and S(+)MDMA, but not R(−)MDMA, produce amphetamine-like stimulus effects (i.e., >80% amphetamine-appropriate responding) (6). However, unlike the amphetamine stimulus the MDMA stimulus cannot be completely antagonized by the dopamine antagonist haloperidol (8,19), and in animals trained to discriminate MDMA from saline, administration of (+)amphetamine typically results only in partial (50-65% generalization (6,19). Furthermore, the MDMA stimulus generalizes to other agents (e.g., MDE or the *N*-ethyl homolog of MDMA) that do not produce amphetamine-like stimulus effects (10). Thus, MDMA and amphetamine may share some behavioral similarity, but MDMA is clearly capable of producing an additional non-amphetamine-like effect.

It has been suggested that certain effects of MDMA may be related to the formation of an active metabolite. We, and others, previously identified several metabolites of MDMA in the rat (1,2,4,5,14,15,21); these include α-methyldopamine, *N*-monomethyl-1-(3-hydroxy-4-methoxyphenyl)-2-aminopropane (3-OH-PMMA), *N*-monomethyl-1-(4-hydroxy-

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3-methoxyphenyl)-2-aminopropane (4-OH-MMMA), and its *N*-desmethyl analog 1-(4-hydroxy-3-methyoxyphenyl)-2-aminopropane (4-OH-MMA). See Fig. 1 for the structures of these metabolites and other agents described in this study. These metabolites may be formed from a common intermediate: *N*-monomethyl α-methyldopamine (21). To determine if they might produce any MDMA-like effects, we proposed to examine the stimulus effects of several of these metabolites in MDMA-trained animals. In as much as α-methyldopamine and *N*-monomethyl α-methyldopamine are catechol derivatives that will not likely penetrate the blood–brain barrier, we were not surprised to find, in a preliminary study, that *N*-monomethyl α-methyldopamine produces only saline-like effects. Likewise, *N*-monomethyl α-methyldopamine and α-methyldopamine also fail to produce amphetamine-like effects in rats trained to discriminate (+)amphetamine from saline (6). While this article was in preparation, Yeh and Hsu (20) reported that several catechol metabolites of MDMA, unlike MDMA itself, are ineffective as locomotor stimulants in rats; they, too, attributed this inactivity to the inability of these agents to penetrate the blood–brain barrier. Consequently, we opted to evaluate several of the MDMA metabolites as their more lipophilic *O*-methyl ethers; 1-(3,4-dimethoxyphenyl)-2-aminopropane (3,4-DMA) is the *O*-methyl ether of 4-OH MMA, and *N*-Me 3,4-DMA may be viewed as the common *O*-methyl ether of both 3-OH PMMA and 4-OH MMMA. Although there is no reason to believe that the ethers themselves are metabolites of MDMA, they could be formed in vivo via a process of *O*-methylation. Furthermore, there is no evidence to suggest that *O*-alkyl derivatives should be inherently inactive (i.e., MDMA itself is an *O*-alkylated compound). These *O*-methyl ethers, then, represent derivatives of actual metabolites that should more readily penetrate the blood–brain barrier than the metabolites themselves. In the present study, we also examine 3-OH-PMMA and several additional structurally related agents. Thus, the purpose of this investigation was to examine the structural requirements associated with the MDMA stimulus by examining MDMA-related analogs that bear a close structural resemblance to some of the metabolites of MDMA.

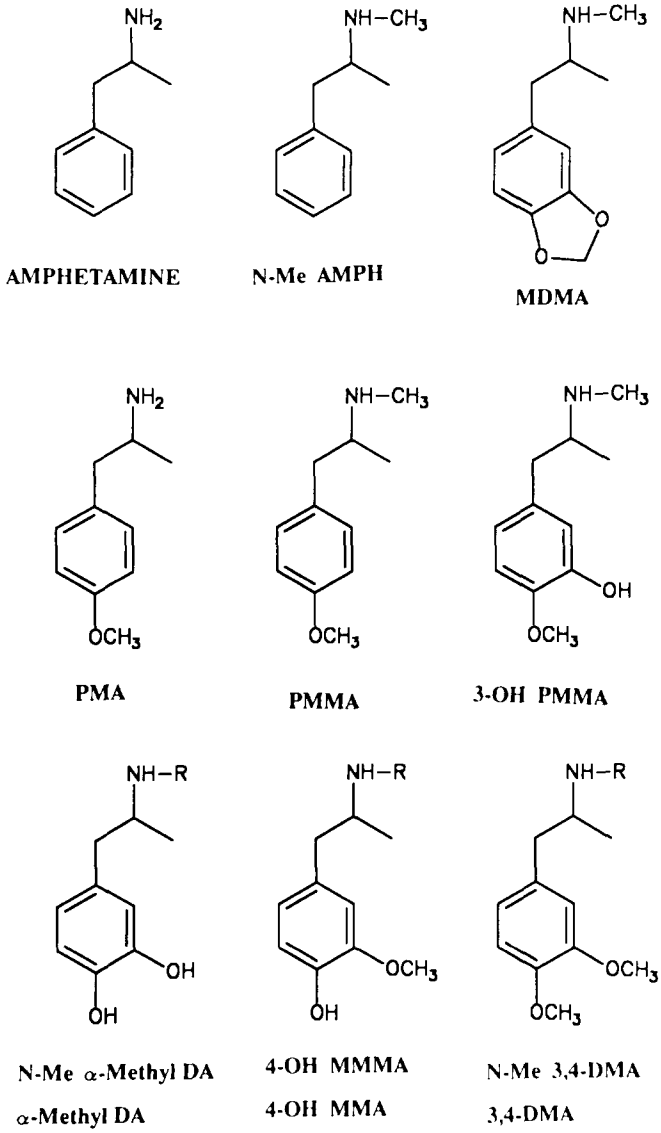


FIG. 1. Chemical structures of MDMA, MDMA metabolites, and related agents described in this study: amphetamine, methamphetamine (*N*-Me AMPH), MDMA, PMA, PMMA, and 3-OH-PMMA. For the bottom three agents, the *R* group can be either methyl of hydrogen. Where $R = CH_3$, the agents are *N*-monomethyl α-methyldopamine (*N*-Me α-methyl DA), 4-OH MMMA, and *N*-monomethyl 3,4-DMA (*N*-Me 3,4-DMA); where *R* = H, the agents are α-methyldopamine (α-methyl DA), 4-OH-MMA, and 3,4-DMA, respectively.

## METHOD

### *Drug Discrimination Studies*

Six male Sprague-Dawley rats, weighing approximately 250–300 g at the beginning of the study, were trained to discriminate 1.5 mg/kg MDMA from 1.0 ml/kg sterile 0.9% saline exactly as we previously reported (10). During the course of the study, animals' body weights were maintained at approximately 80% of their free-feeding body weights by carefully monitoring their diets. In brief, using standard two-lever operant chambers (Coulbourn Instruments Model E10-10) animals were first trained to lever press for sweetened milk reward and were then trained to respond on one lever after administration of MDMA and on the opposite lever after administration of saline using a variable-interval 15-s schedule of reinforcement. For three animals, the right lever was reinforced for MDMA and the left lever for saline; the situation was reversed for the remaining three animals. All injections were via the intraperitoneal route 15 min prior to testing. Training sessions of 15 min duration were conducted 5 days per week. Animals' discrimination learning was assessed weekly under each condition during a 2.5-min nonreinforced (i.e., extinction) session, followed by a 12.5-min training session. Data collected during the extinction sessions included percent of total responses on the MDMA-appropriate lever and response rate (responses per min). Once animals consistently made >80% of their responses on the MDMA-appropriate lever after administration of 1.5 mg/kg MDMA, and <20% of their responses on the same lever following administration of 1.0 ml/kg 0.9% saline, stimulus generalization studies were initiated. For greater detail regarding this protocol, see Glennon and Misenheimer (10).

Stimulus generalization studies were conducted to determine if the MDMA stimulus would generalize (transfer) to doses of several MDMA-related agents. Discrimination train-

ing continued, as described above, except test sessions were interposed among the training sessions. That is, once per week animals were administered a dose of drug and allowed to respond under extinction conditions for 2.5 min, whereupon they were immediately returned to their individual home cages. Where stimulus generalization occurred, $ED_{50}$ values were calculated by the method of Finney (3). In these studies, the $ED_{50}$ dose represents the dose of an agent at which animals would be expected to make 50% of their responses on the MDMA-appropriate lever. Animals making $<5$ total responses during the entire 2.5-min extinction session were reported as being disrupted.

### *Drugs*

MDMA HCl was obtained from NIDA. 3-OH-PMMA, 3,4-DMA, *N*-Me 3,4-DMA, PMA, and PMMA were examined as their HCl salts; we previously reported their synthesis (9,13,21). (+)*N*-Monomethylamphetamine (i.e., methamphetamine) HCl ((+)Me AMPH) was previously synthesized in our laboratories.

## RESULTS

Administration of (+)Me AMPH resulted in partial generalization (maximum 60% MDMA-appropriate responding) in MDMA-trained rats (Table 1). 3,4-DMA produced what appears to be a biphasic effect; accordingly, very small dose increments were subsequently examined. At 1.9 mg/kg, 3,4-DMA produced 67% MDMA-appropriate responding; slightly higher doses (2.1 and 2.3 mg/kg) elicited a saline-like effect, and still higher doses (3.0 and 3.2 mg/kg) again resulted in 57–59% drug-appropriate responding. Because of the disruption of behavior and the decrease in response rates at 4 mg/kg, higher doses were not investigated. *N*-Me 3,4-DMA elicited a maximum of 60% MDMA-appropriate responding, with disruption of behavior at slightly higher doses (Table 1). PMA also produced a maximum response of approximately 50–60% MDMA-appropriate responding; higher doses resulted in disruption of behavior (Table 1). It might be noted that at 0.5 mg/kg PMA two of five animals that responded made $>80\%$ of their responses on the MDMA-appropriate lever and the one that responded at 0.6 mg/kg made 80% of its responses on the same lever. Because there is some evidence that PMA may have a rapid onset of action (11), the 0.3-mg/kg dose of PMA was also examined using a shorter (5 rather than 15 min) presession injection interval; however, the results were not different than those obtained with the 15-min interval. The MDMA metabolite 3-OH-PMMA elicited a maximum 52% MDMA-appropriate responding (at 0.2 mg/kg). At 0.4 mg/kg, 3-OH- PMMA produced 33% drug-appropriate responding; one of four animals responding made 100% of its responses on the MDMA-appropriate lever. PMMA produced 86% MDMA-appropriate responding at 0.3 mg/kg ($ED_{50}$ = 0.2 mg/kg) and disruption of behavior at 0.5 mg/kg.

## DISCUSSION

We and others previously demonstrated that MDMA produces amphetamine-like effects in (+)amphetamine-trained rats (6). We also argued that MDMA is not a simple amphetamine-like agent because administration of (+)amphetamine to MDMA-trained animals typically results only in partial generalization [i.e., 49% MDMA-appropriate responding (6)]. Schechter reported as much as 62.5% MDMA-appropriate responding (19). In one study, however, it was shown that an MDMA stimulus generalizes to (+)amphetamine (18). The *N*-monomethyl analog of (+)amphetamine, *N*-Me AMPH, also produces partial generalization (Table 1). The MDMA metabolite 3-OH-PMMA likewise produces partial (maximum 52%) generalization. These results suggest that 3-OH-PMMA and MDMA share some aspects of their stimulus effects but that 3-OH-PMMA, like amphetamine and *N*-Me AMPH, may produce other effects that disrupt animals' behavior. At this time, it is impossible to discount the possibility that the disruptive effects are peripherally mediated. Alternatively, it is also possible that 3-OH-PMMA is more MDMA like than amphetamine and *N*-Me AMPH but, due to its polar hydroxyl group, it does not penetrate the blood-brain barrier as readily (or completely) as do the two amphetamine analogs. Consequently, we examined 3,4-DMA and its *N*-monomethyl derivative *N*-Me 3,4-DMA where the polar hydroxyl group has been *O*-methylated to decrease polarity. Both compounds continue to produce partial ($\geq 60\%$) generalization. Finally, we examined two analogs where the polar hydroxyl group has been removed. The deshydroxy analog of 3-OH-PMMA (i.e., the 3-desmethoxy analog of *N*-Me 3,4-DMA) is PMMA, and the 3-desmethoxy analog of 3,4-DMA is PMA. PMA is a Schedule I substance that has been previously shown to produce (+)amphetamine-like stimulus effects (11). PMMA, a more recently scheduled agent [see Glennon et al. (19) for additional information], does not produce (+)amphetamine-like stimulus effects (9). In MDMA-trained rats, PMA produces partial (50–55%) stimulus generalization: however, several animals made $>80\%$ of their responses on the MDMA-appropriate lever. PMMA, the *N*-monomethyl analog of PMA, results in complete stimulus generalization and is three times more potent than MDMA.

The present results are difficult to interpret and several explanations are possible; these will be discussed.

1. MDMA metabolites do not readily penetrate the blood-brain barrier and consequently produce erratic effects. It is conceded that certain metabolites may not readily penetrate the blood-brain barrier when administered systemically; this is especially likely for catechols and, to a lesser extent, for the monophenolic derivative 3-OH-PMMA. However, this is not true for the nonhydroxylated analogs, and is also inconsistent with the partial generalization obtained even with 3-OH-PMMA.
2. MDMA metabolites and related derivatives behave like amphetamine and *N*-Me AMPH to disrupt animals' behavior. Although we previously demonstrated that *N*-Me AMPH and PMA produce amphetamine-like stimulus effects (11), administration of 3,4-DMA (11), *N*-methyl 3,4-DMA (13), and PMMA (9) (at doses higher than those used in the present study) to amphetamine-trained animals produces a maximum of only 10% amphetamine-appropriate responding. Thus, it is unlikely that the stimulus effects observed, at least for the latter three agents, can be considered amphetamine like.
3. The metabolite/metabolite analogs are incapable of producing MDMA-like effects because they lack an intact methylenedioxy ring. The MDMA stimulus generalizes to PMMA, which lacks the intact methylenedioxy ring, and PMMA is approximately three times more potent than MDMA. The presence of a methylenedioxy ring does not appear necessary for an agent to produce MDMA-like stimulus effects.

TABLE 1
RESULTS OF STIMULUS GENERALIZATION STUDIES

| Agent | Dose (mg/kg) | n* | % Drug-Appropriate Responding† | Response Rate (Responses per min)† |
|---|---|---|---|---|
| MDMA | 1.5 | 6/6 | 90 (3) | 9.9 (2.1) |
| | | | $ED_{50}$ = 0.76 mg/kg‡ | |
| Saline (1 ml/kg) | | 6/6 | 8 (3) | 10.4 (1.6) |
| (+)Me AMPH | 0.2 | 5/5 | 22 (10) | 20.6 (1.4) |
| | 0.5 | 3/4 | 50 (16) | 7.8 (2.0) |
| | 0.8 | 4/5 | 60 (10) | 6.4 (1.7) |
| | 0.9 | 4/5 | 34 (16) | 3.6 (1.3) |
| | 1.0 | 2/5 | –§ | |
| 3,4-DMA | 0.1 | 3/3 | 39 (11) | 14.8 (2.4) |
| | 0.7 | 3/3 | 49 (10) | 9.6 (2.8) |
| | 1.5 | 6/6 | 52 (12) | 8.4 (2.2) |
| | 1.7 | 4/5 | 65 (14) | 6.4 (1.2) |
| | 1.9 | 4/5 | 67 (12) | 6.0 (1.6) |
| | 2.1 | 4/4 | 25 (6) | 12.2 (1.6) |
| | 2.3 | 4/4 | 19 (3) | 8.0 (0.4) |
| | 2.6 | 4/4 | 48 (10) | 7.1 (2.2) |
| | 3.0 | 2/4 | 57 (11) | 7.6 (2.4) |
| | 3.2 | 2/4 | 59 (9) | 8.6 (1.4) |
| | 3.6 | 3/4 | 38 (8) | 6.6 (2.1) |
| | 4.0 | 2/4 | 44 (10) | 3.1 (0.4) |
| *N*-Me 3,4-DMA | 0.01 | 3/6 | 34 (12) | 4.1 (1.5) |
| | 0.03 | 4/6 | 60 (23) | 5.7 (2.4) |
| | 0.05 | 0/3 | –§ | |
| | 0.1 | 0/3 | –§ | |
| | 0.3 | 0/3 | –§ | |
| PMA | 0.05 | 3/3 | 34 (14) | 13.4 (4.6) |
| | 0.2 | 3/3 | 47 (18) | 8.6 (2.1) |
| | 0.3 | 3/3 | 55 (13) | 4.3 (1.3) |
| | 0.5 | 5/6 | 50 (20) | 5.1 (1.2) |
| | 0.6 | 1/6 | –§ | |
| | 0.7 | 0/3 | –§ | |
| PMA (5 min) | 0.3 | 5/6 | 56 (10) | 5.5 (1.6) |
| 3-OH-PMMA | 0.02 | 4/4 | 20 (5) | 8.8 (3.1) |
| | 0.05 | 3/4 | 45 (13) | 2.6 (0.2) |
| | 0.1 | 2/3 | 48 (33) | 2.8 (0.1) |
| | 0.2 | 3/4 | 52 (25) | 6.7 (4.1) |
| | 0.4 | 4/6 | 33 (28) | 5.2 (1.7) |
| | 0.5 | 0/4 | –§ | |
| PMMA | 0.05 | 3/4 | 4 (2) | 8.0 (1.0) |
| | 0.2 | 3/3 | 40 (10) | 8.8 (1.9) |
| | 0.3 | 3/3 | 86 (10) | 8.7 |
| | 0.5 | 1/3 | –§ | |
| | | | $ED_{50}$ = 0.2 (0.10–0.36) mg/kg# | |

*Number of animals responding/number of animals receiving drug.
†Data collected during the 2.5-min extinction session. Numbers in parentheses are SEM.
‡$ED_{50}$ value previously reported (6).
§Disruption of behavior (i.e., majority of animals failed to make >5 responses during the entire 2.5-min extinction session).
#$ED_{50}$ value followed by 95% confidence limits.

The results of the present study suggest that the MDMA metabolite 3-OH-PMMA, and certain structurally related agents, may be capable of producing MDMA-like effects but may simply have difficulty penetrating the blood-brain barrier when administered systemically. On the basis of the observed partial generalization, it is also possible that 3-OH-PMMA may contribute to some of the behavioral effects seen upon administration of MDMA; alternatively, the partial generalization may reflect a similarity in the peripheral components of these agents with the peripheral effects of MDMA. To

further investigate these possibilities, it will be necessary to conduct additional studies using routes of administration that bypass the blood–brain barrier. Another significant finding originating from these studies is that the presence of an intact methylenedioxy ring is not a requirement for the production of MDMA-like stimulus effects. In fact, it was these preliminary results with PMMA (7) that prompted the present examination of the ring-opened MDMA metabolites. PMMA itself is a scheduled substance about which relatively little is known; although it is the 4-methoxy analog of *N*-Me AMPH, it does not produce amphetamine-like stimulus effects in rats (9). The present results suggest it may behave more like MDMA than amphetamine. It is evident from this investigation that the methylenedioxy group can no longer be viewed as a prerequisite for MDMA-like effects and that ring-opened MDMA metabolites and ring-opened analogs of MDMA deserve additional investigation.

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