Pharmacology Biochemistry and Behavior, Vol. 59, No. 2, pp. 265–270, 1998

0091-3057/98 $19.00 + .00

ELSEVIER

PII S0091-3057(97)00415-2

MDMA-Like Stimulus Effects of Hallucinogens in Male Fawn–Hooded Rats

MARTIN D. SCHECHTER

Department of Pharmacology, Northeastern Ohio Universities College of Medicine, P.O. Box 95, Rootstown, OH 44272-0095

Received 14 December 1996; Revised 10 April 1997; Accepted 23 April 1997

SCHECHTER, M. D. *MDMA-like stimulus effects of hallucinogens in male Fawn–Hooded rats.* PHARMACOL BIOCHEM BEHAV **59**(2) 265–270, 1998.—A two-lever, food-motivated, operant technique was employed to train the purportedly serotonergically dysfunctional Fawn–Hooded (FH) rat to discriminate 1.5 mg/kg MDMA. Once all 10 male subjects learned the MDMA-vehicle discrimination at criterion performance level, doses different than the training dose were used to generate a dose–response discrimination gradient. The ED_{50} value of MDMA was shown to be 0.136 mg/kg, not significantly different from that of previously trained Sprague–Dawley male rats. Thus, the Fawn–Hooded rat appears to not differ in its sensitivity to lower doses of MDMA. Testing for MDMA-like stimulus generalizations with other drugs indicated that the MDMA derivative MDE produced generalization at a dose of 2.25 mg/kg and allowed for an ED_{50} value of 0.496 mg/kg. Like MDE, the testing of α-ethyltryptamine was shown to produce MDMA-like responding. Lastly, a dose of 0.12 mg/kg LSD produced 90% MDMA-lever selection. In contrast to MDMA generalizations to these three drugs, testing of cocaine at doses of 2.5–10 mg/kg and mescaline at 8–14 mg/kg did not produce MDMA-like discriminative effects. The results of this testing in the presumably serotonergically dysfunctional Fawn–Hooded rat would indicate that this line not only can discriminate MDMA as well as heterogenous-bred lines, but also shows the same discriminative generalizations and nongeneralizations from MDMA to serotonergic and dopaminergic agents. © 1998 Elsevier Science Inc.

Drug discrimination MDMA Generalization MDE Cocaine α-Ethyltryptamine LSD Mescaline Fawn–Hooded rat

IN a recent monograph on the subject of drug discrimination, a premier investigator in this area of behavioral psychopharmacology suggested that this paradigm is "a simply and easy-to-understand theory (presence vs. absence), which (allows for) the results of the paradigm (to) appear simple, plausible, and interpretable" (30). This statement is evidenced by more than 1,200 publications to date that attest to the fact that this paradigm has been well demonstrated in its utility to study psychoactive drugs (37) since the first drug, alcohol, was shown in 1951 to produce this effect (8). Between the years of 1986 and 1989, three laboratories were involved in using the discriminative stimulus properties of MDMA (3,4-methylenedioxymethamphetamine; "ecstasy"; "XTC") to produce differential responding in rats (14,15,28,33). The chemical structure of MDMA resembles both the psychostimulant methamphetamine and the hallucinogen mescaline. It is, thus, not surprising that behavioral (34), as well as more recent in vivo microdialysis studies (19), indicate that MDMA may act upon both serotonin and dopamine neural systems. It is likely that these dual mechanisms have allowed at least one investigator's laboratory to posit MDMA as a new class of psychoactive agent that was labelled an "entactogen" (26–28) producing a "generalized feeling that all is right and good with the world" (39), whereas others have used the term "empathogen," allowing "a feeling of emotional closeness to others (and to one's self) coupled with a breakdown of personal communication barriers" (39).

Although discrimination of MDMA has been trained in commercially available, heterogenous rat lines (14,15,28,33), the Fawn–Hooded (FH) rat has never been used for this purpose. This strain of inbred rat has a serotonergic storage defect (21) that allows for alterations in its CNS serotonergic system that may be considered dysfunctional when compared to this neurotransmitter activity in the brain of other rat

Requests for reprints should be addressed to Martin D. Schechter, Department of Pharmacology, Northeastern Ohio Universities College of Medicine, P.O. Box 95, Rootstown, OH 44272-0095.

strains (2,3,18,40). When FH rats are given a choice between tap water and 10% ethanol, they will drink excessive amounts of ethanol (29,32). Thus, the FH rat may represent a model for the study of serotonergic mediation of alcoholism as this increased drinking behavior can be reduced by (the 5-HT releasing drug) MDMA (31). Although more recent experiments designed to determine whether the FH is an acceptable model of volitional ethanol intake have been more negative (25), the rat line's brain alteration in serotonergic function has never been disputed. In drug discrimination experiments, FH rats have been trained to discriminate fenfluramine and they were shown not to differ in their ability to discriminate this serotonin-releasing drug when compared to other rat lines (35).

The present work, therefore, intended to employ the serotonergically dysfunctional FH rat to discriminate the interoceptive cueing effects of MDMA based solely upon the presence or absence of MDMA. Once this was accomplished, other putative serotonergically mediated hallucinogens, such as the MDMA analog MDE ("Eve"), LSD and α-ethyltryptamine, were to be tested to see if generalization from the MDMA-elicited stimulus cue to other drugs occurs in this rat strain. Likewise, because of the purported dopaminergic activity of MDMA, cocaine and mescaline were also to be tested in the MDMA-trained FH rats.

METHOD

Subjects

The subjects used for this study were 10 male FH rats born in our Vivarium facility. The parentage of these rats originated from the University of East Carolina School of Medicine (males), whereas the females originally came from the National Cancer Institute. The male progeny used herein were experimentally naive and approximately 250–270 days old at the beginning of experimentation. They were individually housed in galvanized hanging cages with free access to tap water except during experimental sessions. The ambient temperature was 20–22°C and the animals were maintained on a 12 L:12 D cycle with lights on at 0600 h. The animals weight was adjusted by daily rationing of approximately 16 g/day of commercial rat chow so as to maintain them at 85–90% of their free-feeding weights to facilitate motivation of operant performance for food reward. Behavioral measurements were conducted in a room separate from the animal colony.

Apparatus

The experimental equipment consisted of 12 identical standard rodent operant chambers (Lafayette Instrument Corp., Lafayette, IN) each equipped with two operant levers located 7 cm apart and 7 cm above a grid floor. A food-pellet receptacle was located 2 cm above the floor equidistant between the two levers and was capable of receiving a single 45 mg food pellet (Noyes Co., Lancaster, NH). The test chamber was housed in a sound-attenuating cubicle equipped with an exhaust fan and a 9-W houselight. Solid-state programming equipment (Med Associates, St. Albans, VT) was used to control and record the session and was located in an adjacent room to preclude any possible external cueing (noise) effects.

Drug Discrimination Training

The drug discrimination procedure consisted of training rats to press one of two available levers in the operant chamber while under the influence of the MDMA drug state and to press the second equivalent lever in the nondrug state, i.e., after saline vehicle injection. Thus, each of the two stimuli was associated with responding on a particular lever while training consisted of two phases. In the first phase, lever pressing behavior was shaped by placing the food-deprived rat into the operant chamber and delivering a food pellet whenever the exploratory nature of the rat bordered in the close proximity of the assigned training lever. The rats were soon trained, by the technique of successive approximations, to press one lever for reinforcement on a graduated (1 to 10) fixed-ratio (FR) schedule. Rats were initially administered an intraperitoneal (IP) injection of vehicle (1 ml/kg, 0.9% sodium chloride in distilled water) and, 20 min later, were placed into the operant chamber and, upon pressing the designated "saline-correct lever," they received food reinforcement on an FR 1 schedule, i.e., each press resulted in delivery of one food pellet. The food reinforcement schedule was gradually increased, over 8 days, until the rats were pressing the vehicle-appropriate lever on an FR 10 schedule, thus delivering one reinforcement pellet per 10 lever presses.

After FR 10 responding on the first lever was established, the rats were administered an equal volume of the training dose, i.e., 1 ml/kg (bodyweight) of 1.5 mg/ml MDMA IP. Twenty minutes after injection, they were required to press the lever, opposite to the one that they learned to press after vehicle, on an FR 1 schedule to receive reinforcement. The training continued in daily 15-min sessions proceeding from FR 1 through FR 10 until the MDMA-appropriate lever was pressed on an FR 10; this required 6 days of training. To minimize effects due to any possible position preference, the rats were divided into two subgroups. For one subgroup, responding on the lever to the left of the food pellet receptacle following MDMA injection was reinforced, whereas the other half of the animals were reinforced with food after responding on the lever to the right of the food receptacle. Responses on the opposite lever, in each case, were reinforced with food pellets after vehicle injection.

After the rats were pressing both levers on an FR 10 schedule, the second phase of training, i.e., discrimination training, began and utilized a sequence of MDMA (M) and vehicle (V) administrations in the following order: M-V-V-M-M; V-M-M-V-V. Thus, in each 2-week period, the rats received five MDMA and five vehicle administration/training sessions. The number of responses on each lever before obtaining the first food pellet was recorded and the first lever pressed 10 times was designated as the "selected" lever. The rats were then allowed to continue lever-pressing until 400 responses on the correct lever were made and, thus, 40 food reinforcements (on the FR 10 schedule) were obtained. The rats remained on this training schedule until each animal was able to attain criterion performance. This occurred when the rats correctly "selected" the appropriate lever according to the drug or nondrug state imposed on that day in 8 of 10 consecutive sessions.

Drug-Response Experiments to MDMA Doses

Once the training criterion was achieved by all the rats, they were tested with doses of MDMA different from the 1.5 mg/kg training dose. This allowed a dose–response relationship to be observed as a performance gradient to discriminative responding. During this series of experiments, and in the following generalization tests (below), MDMA-vehicle discrimination testing was maintained by administering either the training dose of MDMA or its vehicle every second day. On interspersed days, rats were placed into the experimental chamber 20 min following novel doses of MDMA and were allowed to lever press un-

til 10 presses were accumulated on either of the two levers. The animals were then immediately removed from the experimental chamber to preclude reinforcement/training at an MDMA dose other than that to which they were trained. The lever with 10 presses accumulated first was designated as the "selected" lever. Each MDMA test dose was administered in random order on two occasions with each test session preceded by one vehicle and one MDMA maintenance session. In this way, the animal's experience on days preceding test days was counterbalanced with respect to any possible aftereffects that may have been produced by the training condition. The doses of MDMA chosen for testing were 0.0315, 0.0625, 0.25, 0.75, plus one dose higher than the training dose at 2.0 mg/kg.

Generalization of the MDMA Interoceptive Stimulus to Other Drugs

Following the dose–response experiments using different doses of MDMA, other drugs chosen for either their serotonergic, albeit hallucinatory, activity or their dopaminergic activity were tested in these MDMA-trained animals to indicate the possibility of a MDMA-like discriminative effect. This generalization, or transfer of discriminative stimuli, was said to occur if 80% or greater MDMA lever selection was made in testing, because this percentage was the 8/10 criterion originally employed in training the MDMA vs. vehicle performance level in these rats. All drugs were tested on two occasions, each with one session following an MDMA maintenance and one session following a vehicle maintenance session. If, at any time, an individual rat was seen to drop below the 8 of 10 state-appropriate lever selections during these maintenance sessions, the animal's lever selection during the interspersed generalization experiment series was dropped from the data. This occurred in one animal during mescaline testing, two animals during MDE, and cocaine trials and to a third animal during α-ethyltryptamine tests (below).

Measurements and Statistical Analysis

Data are presented as quantal measurements, i.e., the percentage of rats that made their first-choice selection on the MDMA-correct lever during testing. The dose–response quantal data were subjected to analysis by a computer-generated (38) program of the procedure of Litchfield and Wilcoxon (23) that employs log-dose vs. probit measurements and allows for ED_{50} values with 95% confidence limits to be calculated. This methodology was employed for all drugs seen to generalize from MDMA as defined as a novel drug that produced 80% or greater selection on the MDMA lever.

Drugs

The drugs employed (abbreviation; dose-range tested; source) were: *d,l* 3,4-methylenedioxymethamphetamine (MDMA; 0.0315–2.0 mg/kg; National Institute on Drug Abuse or NIDA), *d*-lysergic acid diethylamide tartrate (LSD; 0.02–0.12 mg/kg; NIDA), 3,4,5 trimethoxybenzeneethanamine sulfate (mescaline; 8–14 mg/kg; NIDA), 3,4-methylenedioxy-N-ethylamphetamine (MDE; 0.375–2.25 mg/kg; NIDA), 2β-carbomethoxy-3β-benzoyloxytropane (*l*-cocaine; 2.5–10 mg/kg; NIDA), α-ethyl-1H-indole-3-ethanamide hydrochloride (α-ethyltryptamine or α-EtT; 1.25–5.0 mg/kg; Research Biochemicals International, Natick, MA). All drugs were dissolved in 0.9% saline immediately before administration, with the dose calculated as the salt, each administered at a constant IP volume of 1 ml/kg and tested in extinction 20 min postadministration.

RESULTS

After all the rats attained criterion performance, they were tested with one higher and four lower doses of MDMA and showed a typical dose–response relationship (inverted closed triangles, Fig. 1). The ED_{50} value (95% confidence limits) was calculated (38) to be 0.136 (0.098–0.188) mg/kg. The administration of LSD at doses of 0.02 to 0.12 mg/kg was observed to generally produce a dose-responsive effect on the MDMA lever with the highest dose producing greater than 80% MDMA-appropriate responding and the analysis indicating an ED_{50} value of LSD equal to 0.039 (0.0231–0.0687) mg/kg. The last representation (closed squares) in Fig. 1 is that of mescaline in which 1 of the 10 animals did not maintain maintenance days criterion levels and the data reflects an $n = 9$. Results indicate that, at doses of 8, 10, 12, and 14 mg/kg, the largest percent MDMA-lever selection (55.5%) occurred at 12 mg/kg and no dose produced complete MDMA-like responding. Higher doses were precluded from testing because of behavioral disruption seen with one trial of 16 mg/kg mescaline.

The dose–response results after MDMA are represented once again (as inverted closed triangles) in Fig. 2 which also indicates that MDE, in the eight rats that maintained criterion performance, tested at doses of 0.375, 0.75, 1.5, and 2.25 mg/kg produced a dose-responsive effect upon the MDMA lever with the highest dose producing 81.3% MDMA-lever selections; an ED_{50} value of 0.496 (0.376–0.654) mg/kg was calculated (38). This same number of rats was tested with three

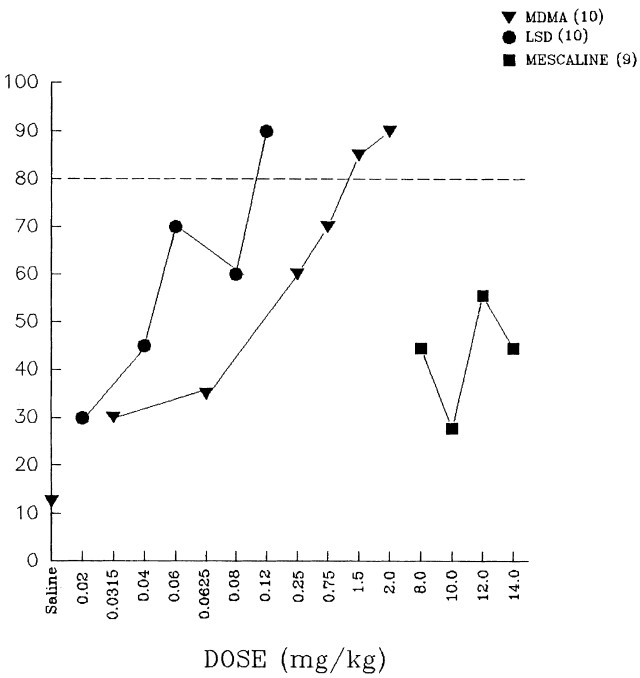

FIG. 1. Generalization from 1.5 mg/kg MDMA/saline trained male Fawn–Hooded rats to MDMA, LSD, and mescaline. Abscissa: doses (mg/kg) of drugs tested on two occasions each, once following an 1.5 mg/kg MDMA and once following a vehicle maintenance day session; Ordinate: percent of rats (n = 10,9) accumulating 10 responses first on the designated MDMA appropriate lever during test sessions. Dotted line at 80% indicates level to adjudge generalization from MDMA responding.

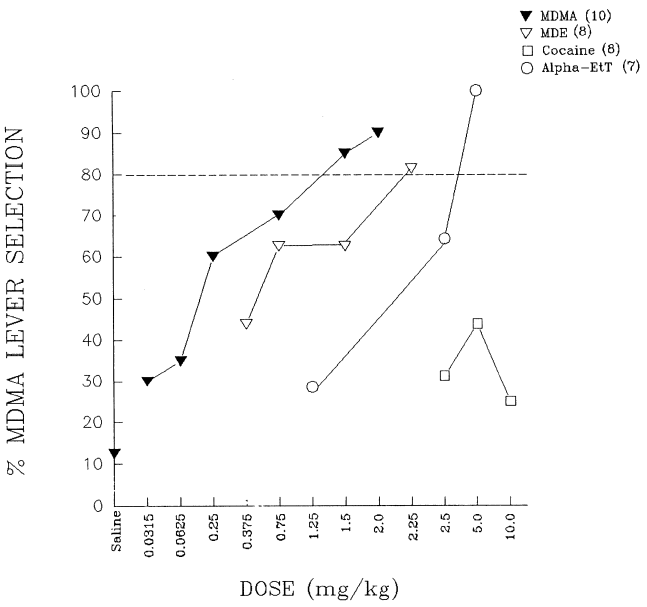

FIG. 2. Generalization from MDMA discriminative performance (as in Fig. 1) after various doses of MDE, α-ethyltryptamine and cocaine with 80% MDMA lever selection indicating generalization. Abscissa and ordinate as in Fig. 1.

doses of cocaine and the MDMA selections never exceeded 40% and actually decreased at the highest dose. Lastly, α-ethyltryptamine (α-EtT) was tested in seven rats and produced a dose–response relationship where the highest dose (5 mg/kg) elicited 100% of MDMA-like responding. The ED_{50} value for α-EtT was 1.822 (1.630–2.038) mg/kg.

DISCUSSION

The Fawn–Hooded (FH) strain of rats was originally derived from the Wistar rat line and it possesses a complete absence (11) or a greatly diminished (1) ability to bind ^{3}H-imipramine in both platelets and in brain tissue. These factors serve as indirect markers of serotonergic function and indicate that the FH rat has a genetic 5-HT storage abnormality. This diminished 5-HT function may suggest why research has shown these animals resemble the alcohol-preferring strain of rats in that they consume large amounts of ethanol when given free access to food, water, and ethanol. It has, therefore, been suggested that they "seem to be a good model for the study of relationships between the serotonergic system and alcohol behavior" (10). The present study intended to use these serotonergically dysfunctional rats to test if they are capable of learning to discriminate the purportedly serotonergically mediated drug MDMA. Previous work from this laboratory indicated that the FH rat shows a diminished ability to recognize the interoceptive stimuli produced by ethanol (36), but not those produced by another serotonergically active drug fenfluramine (5). The first time a group of Sprague–Dawley rats was trained in this laboratory with MDMA as a drug capable of controlling differential responding in a drug discrimination paradigm was over a decade ago (33); discriminative training was at the same training dose, with the same apparatus, and by the same personnel. The ED_{50} value in the male Sprague–Dawley rat was shown to be 0.27 (0.16–0.47) mg/kg. Analysis (38) indicates that when this ED_{50} value is compared with the FH rat (present study) results are not statistically different. Thus, the FH male rat appears to have a slightly greater, but not statistically different, sensitivity to lower doses of MDMA.

The administration of MDE, the n-ethyl derivative of MDMA, was seen to produce a generalization at a dose of 2.25 mg/kg (Fig. 2) and allowed for an ED_{50} value of 0.496 (0.376–0.654) mg/kg. Previously, MDMA was shown to generalize to MDE with an ED_{50} value for the former of 0.76 mg/kg and for the latter of 0.73 mg/kg (14). Thus, it appears that in rats trained to MDMA, MDE generalizes substitutes for it and this generalization appears symmetrical as work previously done in this laboratory (5) using rats trained to discriminate 2.0 mg/kg MDE indicated an ED_{50} value of 0.75 mg/kg and a generalization to MDMA with an ED_{50} value of 0.62 mg/kg.

Like MDE, the testing of the compound α-ethyltryptamine (α-Et) was shown to produce MDMA-like responding. This Schedule I drug has been reported to be capable of producing MDMA-like effects both in rats (22) and human (12) subjects. Drug discrimination studies using the same training dose of MDMA have also shown that α-EtT produces MDMA-like effects in a dose–response manner with an ED_{50} value for MDMA equal to 0.76 mg/kg and for α-EtT equal to 3.5 mg/kg (13). This generalization is of interest in light of the fact that α-EtT is a tryptamine derivative like LSD and, thus, is more closely related to serotonin, whereas MDMA structurally resembles phenethylamines.

LSD produced MDMA-like discrimination in (generally) a dose-responsive manner with the dose of 0.12 mg/kg producing 90% MDMA lever selection. A previous study using a training dose of 1.25 mg/kg MDMA, and then increasing it to 1.75 mg/kg after a 5-week period, allowed for a maximum of 78% of the animals selecting the MDMA lever at a dose of 0.16 mg/kg LSD (28). In addition, when the MDMA analog, MDA, was used in a dose of 1.5 mg/kg in Sprague–Dawley animal discrimination training, the administration of LSD produced generalization with 0.075 mg/kg producing 86% of responses on the MDA-appropriate lever and generated an ED_{50} value of 0.058 mg/kg (16). LSD has also been shown to generalize to the α_2-adrenergic agent yohimbine (7,24) and to the nonhallucinogenic compound quipazine (9), as well as to the dopaminergic ergot derivative lisuride (20). These results make the nature of the discriminative stimulus cueing properties of LSD a very complex and hard-to-pinpoint entity (24). Even though MDMA generalized to LSD, this was not the case when four doses of the hallucinogen mescaline were tested. This is especially interesting because rats trained to discriminate mescaline generalized to both isomers of MDMA (6). The other drug tested was cocaine and, much like amphetamine (14), it did not produce MDMA-like responses at the doses tested. A higher dose tested in a single trial produced behavioral disruption in that more than half the rats did not respond. This observation, therefore, precluded the dose from being retested.

The results of these tests in serotonergically dysfunctional FH rats would indicate that they not only discriminate MDMA as well as heterogenous-bred rats, but also show the same generalizations and nongeneralizations to other serotonergic and dopaminergic agents. Regarding the results of these generalization studies, the most probable explanation for the ability of MDMA to generalize to LSD and α-ethyltryptamine resides in the reports that have MDMA stimulating the release of 5-HT from rat brain and supports the hypothesis that it acts as an indirect serotonin agonist (27). This

pronounced increase in synaptic 5-HT by MDMA has recently been reviewed and shown to be the result of an interaction both upon release and on the 5-HT transporter (19). Thus, MDMA-induced release of serotonin may, indeed, be mediated through an interaction with the 5-HT uptake site located in the axonal terminal. The inability of both cocaine and mescaline to produce MDMA-like responding in the FH rat replicates results in other studies (4) and continues to suggest that the major role of discriminative stimulus control by MDMA is not produced by dopaminergic neurons.

This work continues to add to the growing number of studies regarding the behavioral effects of MDMA, which was first synthesized over 80 years ago and has only recently received prominence as an illegal recreation drug of abuse with neurotoxic capabilities after chronic administration in humans. Continued investigation as to its exact CNS mechanism of action will allow pharmacotherapy for the increasing number of reported hyperthermic, "serotonergic syndrome" and sudden deaths that have been occurring in abusers (17).

ACKNOWLEDGEMENTS

The author would like to, as always, express his sincere thanks to Mrs. Denise McBurney who conducted both the present and the cited (reference 33) 1987 experimentation and to Mrs. Sheila Formick and Ms. Martha Hilgert for their tenacious word processing skills.

REFERENCES

1. Arora, R. C.; Tong, C.; Jackson, H.; Stoff, D.; Meltzer, H. Y.: Serotonin uptake in imipramine binding in blood platelets and brain of Fawn–Hooded and Sprague–Dawley rats. Life Sci. 33:437–442; 1983.
2. Aulakh, C. S.; Hill, J. L.; Lesch, K. P.; Murphy, D. L.: Functional subsensitivity of 5-hydroxytryptamine$_1$c or α_2 adrenergic heteroreceptors mediating clonidine-induced growth hormone release in the Fawn–Hooded rat strain relative to the Wistar rat strain. J. Pharmacol. Exp. Ther. 262:1038–1043; 1992.
3. Aulakh, C. S.; Wozniak, K. M.; Hill, J. L.; Devane, C. L.; Tolliver, T. J.; Murphy, D. L.: Differential neuroendocrine responses to the 5-HT agonist m-chlorophenypiperazine in Fawn–Hooded rats relative to Wistar and Sprague–Dawley rats. Neuroendocrinology 48:401–406; 1988.
4. Baker, L. E.; Broadbent, J.; Michael, E. K.; Matthews, P. K.; Metosh, C. A.; Saunders, R. B.; West, W. B.; Appel, J. B.: Assessment of the discriminative stimulus effects of the optical isomers of ecstasy (3,4-methylenedioxymethamphetamine; MDMA). Behav. Pharmacol. 6:263–275; 1995.
5. Boja, J. W.; Schechter, M. D.: Behavioral effects of N-ethyl-methylenedioxyamphetamine (MDE; "Eve"). Pharmacol. Biochem. Behav. 28:153–156; 1987.
6. Callahan, P. M.; Appel, J. B.: Differences in the stimulus properties of 3,4-methylenedioxyamphatamine and 3,4 methylenedioxymethamphetamine in animals trained to discriminate hallucinogens from saline. J. Pharmacol. Exp. Ther. 246:866–870; 1988.
7. Colpaert, F. C.: Cross-generalization between LSD and yohimbine in the rat. Eur. J. Pharmacol. 102:73–77; 1984.
8. Conger, J. J.: The effects of alcohol on conflict behavior in the albino rat. Stud. Alcohol 12:1–29; 1951.
9. Cunningham, K. A.; Appel, J. B.: Neuropharmacological reassessment of the discriminative stimulus properties of *d*-lysergic acid diethylamide (LSD). Psychopharmacology (Berlin) 91:67–73; 1987.
10. Daoust, M.; Sompagnon, P.; LeGrand, E.; Boucly, P.: Ethanol intake and ^{3}H-serotonin uptake: I: A study in Fawn–Hooded rats. Life Sci. 48:1969–1976; 1991.
11. Dumbrill-Ross, A.; Tang, S. W.: Absence of high-affinity [^{3}H]-imipramine binding in platelets and cerebral cortex of Fawn–Hooded rats. Eur. J. Pharmacol. 72:137–138; 1981.
12. Fed. Reg. 58:13533, March 12; 1993.
13. Glennon, R. A.: MDMA-like stimulus effects of α-ethyltryptamine and the α-ethyl homolog of DOM. Pharmacol. Biochem. Behav. 46:459–462; 1993.
14. Glennon, R. A.; Misenhemer, B. R.: Stimulus effects of N-monoethyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDE) and N-deoxy-1-(3,4-methylenedioxyphenyl)-2-aminopropane (N-OH MDA) in rats to discriminate MDMA from saline. Pharmacol. Biochem. Behav. 33:909–912; 1989.
15. Glennon, R. A.; Titeler, M.; Lyon, R. A.; Yousif, M.: MDMA ("Ecstacy"): Drug discrimination and brain binding properties. Soc. Neurosci. Abstr. 12:919; 1986.
16. Glennon, R. A.; Young, R.: MDA—An agent that produces stimulus effects similar to those of 3,4-DMA, LSD and cocaine. Eur. J. Pharmacol. 99:249–250; 1984.
17. Green, R. A.; Cross, A. J.; Goodwin, G. M.: Review of the pharmacology and clinical pharmacology of 3,4 methylenedioxymethamphetamine (MDMA or "Ecstacy"). Psychopharmacology (Berlin) 119:247–260; 1995.
18. Gudelsky, G. A.; Koenig, J. I.; Meltzer, H. Y.: Altered responses to serotonin agents in Fawn–Hooded rats. Pharmacol. Biochem. Behav. 22:489–492; 1985.
19. Gudelsky, G. A.; Nash, J. F.: Carrier-mediated release of serotonin by 3,4-methylenedioxymethamphetamine: Implications for serotonin-dopamine interactions. J. Neurochem. 66:243–249; 1996.
20. Holohean, A. M.; White, F. J.; Appel, J. B.: Dopaminergic and serotonergic mediation of the discriminable effects of ergot alkaloids. Eur. J. Pharmacol. 81:595–602; 1982.
21. Kirchmaier, C. M.; Meyer, M.; Spangenberg, P.; Heller, R.; Haroske, D.; Breddin, H. K.; Till, U.: Platelet membrane defects in Fawn–Hooded bleeder rats. Thromb. Res. 57:353–360; 1990.
22. Krebs, K. M.; Geyer, M. A.: Behavioral characterization of alpha-ethyltryptamine, a tryptamine derivative with MDMA-like properties in rats. Psychopharmacology (Berlin) 113:284–287; 1993.
23. Litchfield, J. T.; Wilcoxon, F.: A simplified method of evaluating dose–effect experiments. J. Pharmacol. Exp. Ther. 96:99–106; 1949.
24. Marona-Lewicka, D.; Nichols, D. E.: Complex stimulus properties of LSD: A drug discrimination study with α_2-adrenoceptor agonists and antagonists. Psychopharmacology (Berlin) 120:384–391; 1995.
25. McMillan, B. A.; Williams, H. L.: Volitional consumption of ethanol by Fawn–Hooded rats: Effects of alternative solutions and drug treatments. Alcohol 12:345–350;1995.
26. Nichols, D. E.; Hoffman, A. J.; Oberlender, R. A.; Jacob, P., III; Shulgin, A. T.: Derivatives of 1-(1,3-benzodioxol-5-yl)-2-butanamine: Representatives of a novel therapeutic class. J. Med. Chem. 29:2009–2015; 1986.
27. Nichols, D. E.; Lloyd, D. J.; Hoffman, A. J.; Nichols, M. B.; Yim, G. K. W.: Effects of certain hallucinogenic amphetamine analogs on the release of [^{3}H] serotonin from rat brain synaptosomes. J. Med. Chem. 25:530–535; 1982.
28. Oberlender, R.; Nichols, D. E.: Drug discrimination studies with MDMA and amphetamine. Psychopharmacology (Berlin) 95:71–76; 1988.
29. Overstreet, D. J.; Kampov-Polevoy, A. B.; Rezvani, A. H.; Murrelle, L.; Haliks, J. A.; Genowski, D. S.: Saccharin intake predicts ethanol intake in genetically heterogenous rats as well as different rat strains. Alcohol. Clin. Exp. Res. 17:366–369; 1993.
30. Overton, D. A.: A historical prospective on drug discrimination. In: Glennon, R. A.; Jäbe, T. U. C.; Frankenheim, J., eds. Drug discrimination: Applications to drug abuse research. National Institute on Drug Abuse Research Monograph #116. Rockville, MD: U.S. Dept. Health Human Services; 1991:5–24.
31. Rezvani, A. H.; Garges, P. L.; Miller, D. B.; Gordon, C. J.: Attenuation of alcohol consumption by MDMA (Ecstacy) in two

strains of alcohol-preferring rats. Pharmacol. Biochem. Behav. 43:103–110; 1992.
32. Rezvani, A. H.; Overstreet, D. J.; Genowski, D. S.: Genetic serotonin deficiency in alcohol preference in the Fawn–Hooded rats. Alcohol Alcohol. 25:573–575; 1990.
33. Schechter, M. D.: MDMA as a discriminative stimulus: Isomeric comparisons. Pharmacol. Biochem. Behav. 27:41–44; 1987.
34. Schechter, M. D.: Serotonergic-dopaminergic mediation of 3,4-methylenedioxymethamphetamine (MDMA; "ecstacy"). Pharmacol. Biochem. Behav. 31:817–824; 1989.
35. Schechter, M. D.: Serotonergic mediation of fenfluramine discrimination stimuli in Fawn–Hooded rats. Life Sci. 60:PL83–90;1997.
36. Schechter, M. D.; Meehan, S. M.: Ethanol discrimination in Fawn–Hooded rats is compromised when compared with other strains. Alcohol 10:77–81; 1993.
37. Stolerman, I. P.; Shine, P. J.; Samele, C.; Rasul, F.: The drug discrimination database, 1951–1988. Rockville, MD: NIDA Administrative Document; 1989.
38. Tallarida, R. J.; Murray, R. B.: Manual of pharmacologic calculations for computer pPrograms. New York: Springer Verlag; 1981.
39. Taylor, J. M.: MDMA frequently asked-questions; http:\www.damicon.fidrugs mdmaFAQ-MDMA.html. Jan 20, 1996.
40. Wang, P.; Aulakh, C. S.; Hill, J. L.; Murphy, D. L.: Fawn–Hooded rats are subsensitive to the food intake suppressant effects of a 5-HT agonist. Psychopharmacology (Berlin) 94:558–562; 1988.