Pharmacology Biochemistry and Behavior, Vol. 57, Nos. 1/2, pp. 173–177, 1997

0091-3057/97 $17.00 + .00

PII S0091-3057(96)00302-4

MDMA and *d*-Amphetamine Produce Comparable Effects in Pigeons Performing under a Multiple Fixed-Ratio Interresponse-Time-Greater-than-*t* Schedule of Food Delivery

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Received 26 January 1995; Accepted 8 May 1996

LeSAGE, M., AND A. POLING. *MDMA and* d*-amphetamine produce comparable effects in pigeons performing under a multiple fixed-ratio interresponse-time-greater-than-*t *schedule of food delivery.* PHARMACOL BIOCHEM BEHAV **57** (1/2) 173–177, 1997.—The purpose of this study was to gain further information about the behavioral effects of (±) 3,4-methylenedioxymethamphetamine (MDMA) on schedule-controlled responding. MDMA (0.32, 0.56, 1.0, 3.2, 5.6, and 10 mg/kg) and *d*-amphetamine (0.32, 0.56, 1.0, 3.2, 5.6, and 10 mg/kg) were administered to pigeons performing under a multiple fixed-ratio 30 (FR 30) interresponse-time-greater-than-15-s (IRT>15-s) schedule of food delivery. In general, both drugs had no significant effect on response rates under the IRT>15-s component at doses that decreased rates under the FR component. Results of the present experiment indicate that under some conditions MDMA and *d*-amphetamine produce similar, and rate-dependent, effects. © 1997 Elsevier Science Inc.

d-Amphetamine Interresponse-time-greater-than-*t* schedule Fixed-ratio schedule Multiple schedule Rate-dependent drug effects Pigeons

THE drug (±)3,4-methylenedioxymethamphetamine (MDMA or "Ecstasy") is a synthetic amphetamine analog that reportedly has both stimulant and hallucinogenic properties (2,4,25). MDMA is an interesting drug because of its documented recreational use in humans (21,27,28), significant potential for abuse (13), neurotoxicity to serotonergic systems in rat and nonhuman primate brains (3,23,26,29), and acute clinical toxicity in humans (10).

Because MDMA structurally resembles amphetamine and produces similar discriminative effects (2,4,25), it is of interest to compare other effects of the two compounds. In previous studies involving operant behavior, both drugs have been shown to decrease response rates under fixed-ratio schedules (8,22,24), increase response rates and reduce reinforcement rates under interresponse-time-greater-than-*t* (IRT>*t*) schedules (7,15), and decrease response rates under conditional-discrimination procedures (5,6,14,30,31). These findings suggest that MDMA and amphetamine affect schedule-controlled responding in comparable fashion.

Data reported by Nader, Hoffman, and Barrett (18) suggest, however, that under certain conditions the effects of MDMA and amphetamine on schedule-controlled behavior differ. In their study, pigeons performed under a multiple fixed-ratio 30 (FR 30) fixed-interval 3-min (FI 3-min) schedule of food delivery. In the absence of drug, rates were typically high under the FR 30 component and relatively low under the FI 3-min component. When administered acutely, MDMA produced dose-dependent decreases in rate of responding under both components of the schedule. Thus, drug effects were not dependent on baseline rate of responding. Although Nader et al. did not examine amphetamine in their study, they noted that MDMA's effects "differed from the prototypic CNS stimulant effects typically reported for *d*-amphetamine and its stereoisomers in which FI responding is increased at doses

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that only decrease FR responding" (18). If this conclusion is accepted, the effects of amphetamine, but not those of MDMA, are rate-dependent. But empirical support for the conclusion is equivocal.

Consider the findings reported by Miczek and Haney (17). In their study, the effects of *d*-amphetamine, MDMA, and PCP were examined in mice exposed to two variants of a multiple schedule. In one experiment, mice were exposed to a multiple FR 30 FI 10-min schedule of milk delivery. Under this schedule, *d*-amphetamine significantly increased response rates under the FI component, but reduced response rates under the FR component. MDMA also increased the rate of FI responding and decreased the rate of FR responding. Although MDMA's rate-increasing effects were not statistically significant for subjects as a group, Miczek and Haney noted that "five out of six MDMA-treated mice showed elevations in FI response rates at the 0.3, 1.0, or 3.0 mg/kg doses of 20-90% above control level" (17).

These findings were replicated in a third experiment in which *d*-amphetamine and MDMA were given to mice exposed to the same multiple FR 30 FI 10-min schedule of milk delivery, but with a 5-min observational period at the midpoint of the session to assess drug effects on aggressive behavior. Results were similar to those obtained in the first experiment: Both drugs increased response rates under the FI component, but decreased rates under the FR component. Again, *d*-amphetamine's rate-increasing effects were statistically significant, but MDMA's were not. However, rate-dependency plots of local rates under the FI revealed that both drugs increased the low local rates at the beginning of the interval at a dose (3.0 mg/kg) that decreased high local rates at the end of the interval. Moreover, this rate-dependent effect was more clear with MDMA than with *d*-amphetamine.

In contrast to the findings of Nader et al. (18), the data reported by Miczek and Haney (17) suggest that MDMA may produce rate-dependent effects similar to those of amphetamine. The purpose of the present study was to gain further information about the behavioral effects of MDMA on schedule-controlled responding. To explore further the acute effects of MDMA on different baseline rates of responding, the drug was administered to pigeons performing under a multiple FR 30 IRT>15-s schedule of food delivery. The acute effects of *d*-amphetamine also were determined in the same subjects to allow a direct comparison of the effects of amphetamine and MDMA on schedule-controlled responding. We anticipated that in the absence of drug the FR 30 schedule would generate substantially higher response rates than the IRT>15-s schedule, and that *d*-amphetamine and perhaps MDMA would at some doses decrease response rates under the former schedule while increasing them under the latter schedule.

METHODS

Subjects

Five White Carneau pigeons, maintained at 80% of their free-feeding weight, served as subjects. All birds had histories of exposure to acute administrations of cocaine under a progressive-ratio schedule of food delivery (12), but were drug free for at least six months prior to the start of the present experiment. Each bird was individually housed with unlimited access to grit and water in a light- (16 h light, 8 h dark each day), temperature- (22–24°C), and humidity-controlled (60–70%) colony area.

Apparatus

Four Lehigh Valley Electronics operant conditioning chambers, measuring 32 cm high, 36 cm wide, and 35 cm deep, were used. In each chamber, three response keys 2.5 cm in diameter were located 23 cm from the bottom of the front wall, approximately 5.5 cm apart. Only the center key was used in the present study. That key could be illuminated in white or red. An aperture horizontally centered in the front wall 7.5 cm above the chamber floor allowed access to a hopper filled with Purina Pigeon Grain (Ralston-Purina, St. Louis) when the hopper was raised. When raised, the hopper was illuminated by a 7-W white bulb. A 7-W white bulb (houselight) located behind a translucent diffusing panel centered on the chamber's ceiling provided ambient illumination. An exhaust fan provided ventilation and masking noise. Additional masking noise was provided via speakers mounted inside each chamber. Control of experimental events and data recording were accomplished through use of an IBM-compatible computer using MED-PC software and interfacing (Med Associates, St. Albans, VT).

Behavioral Procedure

All subjects required retraining and were first autoshaped (1) to peck the center key when lighted white or red. Once pecking was established under this procedure, all subjects were exposed to a multiple FR IRT> *t* schedule of food delivery. Under the FR component, every nth response was followed by 3-s access to grain. Under the IRT> *t* component, 3-s access to grain followed the first response emitted at least *t* s after the immediately preceding response. The center key was illuminated in white during the FR component and in red during the IRT> *t* component. During each session, the first component was selected at random after which components alternated regularly (i.e., following each food delivery). During initial exposure to the multiple schedule, the FR value was 1 and the IRT> *t* value was 1 s. Over several sessions, the FR value was incremented gradually to 30 and the IRT> *t* value to 15 s. These values remained in effect for the remainder of the study.

Pharmacological Procedure

Acute dose-response determinations began after each bird had received at least 30 sessions of exposure to the multiple FR 30 IRT>15-s schedule and response rates under both components of the schedule showed no visually-evident trend across 10 consecutive sessions. The acute effects of six doses of MDMA (0.32, 0.56, 1.0, 3.2, 5.6, and 10 mg/kg) and *d*-amphetamine (0.32, 0.56, 1.0, 3.2, 5.6, and 10 mg/kg) were determined. Each dose of each drug was administered at least twice (range 2–6) in a mixed order that differed across subjects. Not all doses were administered to each subject, because different doses completely suppressed responding in different birds. Drug was administered on Tuesdays and Fridays. Vehicle was administered on Thursdays. Baseline sessions, prior to which no injections were given, were conducted on Sundays, Mondays, and Wednesdays. Three randomly-selected birds were first exposed to MDMA; the other two birds were first exposed to *d*-amphetamine. Following dose-response determinations for one drug, each bird was exposed to baseline conditions (no injections) for at least 10 sessions and until response rates stabilized. When rates stabilized, dose-response determinations began for the second drug.

Both drugs were prepared in a vehicle of 0.85% isotonic

saline solution at an injection volume of 1 ml/kg and injected intramuscularly (IM) into the pectoral muscle 10 min prior to experimental sessions. During this 10-min interval, birds remained in the darkened experimental chamber. Doses and presession injection times were selected based on prior reports (4,14,18). MDMA was obtained from the National Institute on Drug Abuse (Baltimore, MD), *d*-amphetamine from Sigma Chemical Co. (St. Louis, MO).

Statistical Procedure

Response rates under the two schedules were analyzed statistically via repeated measures ANOVA, followed by multiple comparisons (via Fisher's PLSD tests) between rates during vehicle and drug sessions. The ANOVA was computed using the mean response rates of individual subjects during exposure to vehicle and each dose of drug. Because some subjects were not exposed to 5.6 and 10 mg/kg doses, rate estimates (of 0 responses per min) were used for those birds. Such estimates are reasonable in that a lower dose (3.2 mg/kg) produced complete suppression of behavior in these birds.

RESULTS

In the absence of drug, all birds responded at relatively high rates during the FR 30 component and relatively low rates during the IRT>15-s component. Mean group control rates under both schedules during vehicle control sessions immediately prior to *d*-amphetamine injections are shown in Fig. 1. This figure also shows mean group response rates at all *d*-amphetamine doses. Statistical analysis indicated a significant overall effect under both the FR 30 ($F = 22.41$, df = 6, 24, $p = 0.0001$) and the IRT>15-s ($F = 4.33$, df = 6, 24, $p = 0.004$) schedules. Multiple comparisons revealed that rates under the FR 30 were significantly ($p < 0.05$) below the control level at doses of 1.0 mg/kg and above. Only the highest dose of *d*-amphetamine (10 mg/kg) significantly affected (reduced) response rate under the IRT>15-s schedule relative to the control level.

Figure 1 shows the effects of MDMA on response rate. Statistical analysis indicated a significant overall effect of MDMA under both the FR 30 ($F = 10.8$, df = 6, 24, $p = 0.0001$) and the IRT>15-s ($F = 16.01$, df = 6, 24, $p = 0.0001$) schedules. Rates under the FR 30 were significantly ($p < 0.05$) below the control mean at MDMA doses of 1.0 mg/kg and above. Under the IRT>15-s schedule, rates were significantly ($p < 0.05$) below control at doses of 5.6 and 10 mg/kg.

Figure 2 shows the effects of *d*-amphetamine and MDMA on mean overall rate of reinforcement (food deliveries per session), expressed as a percentage of the control reinforcement rate. Because the FR 30 and IRT>15-s schedules alternated after each reinforcement, reinforcement rate data are not presented separately for the two schedules. Analysis of variance revealed that *d*-amphetamine ($F = 22.39$, df = 6, 24, $p = 0.001$) and MDMA ($F = 25.21$, df = 6, 24, $p = 0.0001$) significantly affected reinforcement rate. Multiple comparisons tests revealed that both drugs significantly ($p < 0.05$) reduced the rate of reinforcement relative to the control mean at doses of 3.2 mg/kg and above.

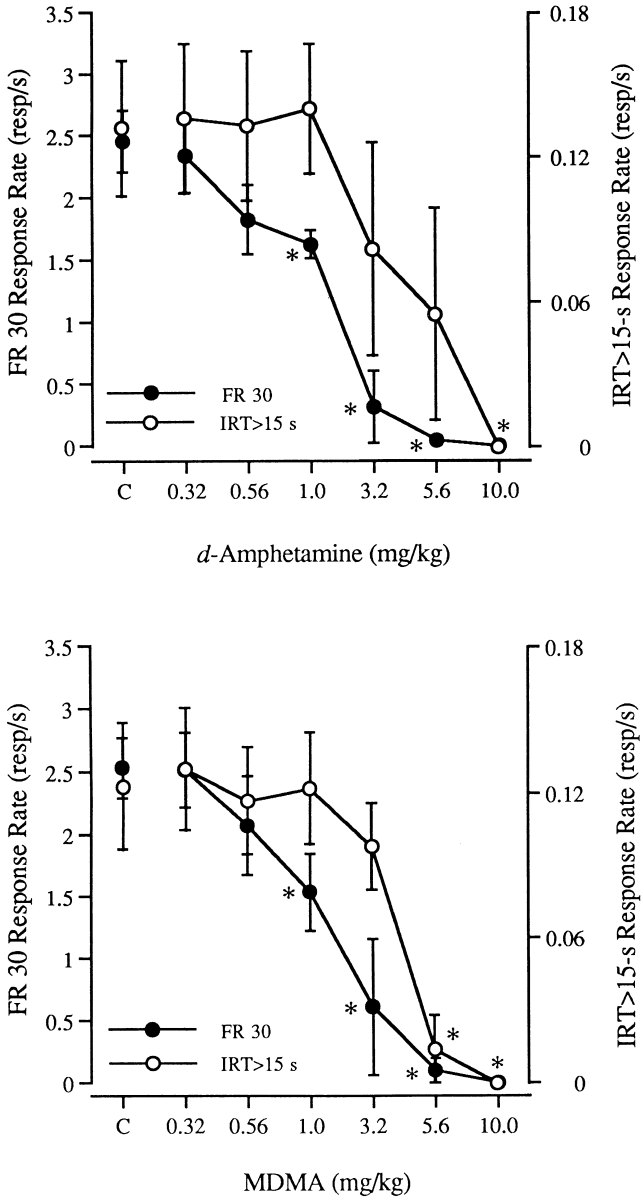

FIG. 1. Acute effects of *d*-amphetamine and MDMA on the mean rate of responding of five pigeons performing under a multiple FR 30 IRT>15-s schedule of food delivery. Vertical lines indicate standard errors of the mean. Asterisks (*) indicate drug data that differ significantly ($p > 0.05$) from control data. Note that the y-axes (rates) are scaled differently for the FR 30 (left axis) and the IRT>15-s (right axis) schedules.

DISCUSSION

The purpose of the present study was to explore the acute effects of MDMA on the different baseline rates of responding engendered by a multiple FR 30 IRT>15-s schedule of food delivery and to compare directly those effects with the effects of *d*-amphetamine. Response rates under the IRT>15-s component generally were less disrupted by MDMA and *d*-amphetamine than rates under the FR 30 component. Interestingly, both drugs significantly reduced FR responding at a dose (1.0 mg/kg) that did not significantly affect responding under the IRT>15-s schedule, or rate of reinforcement. Significant rate reductions under the FR 30 schedule, but not under the IRT>15-s schedule, also were evident at higher doses of both drugs (3.2 and 5.6 mg/kg *d*-amphetamine and 3.2 mg/kg

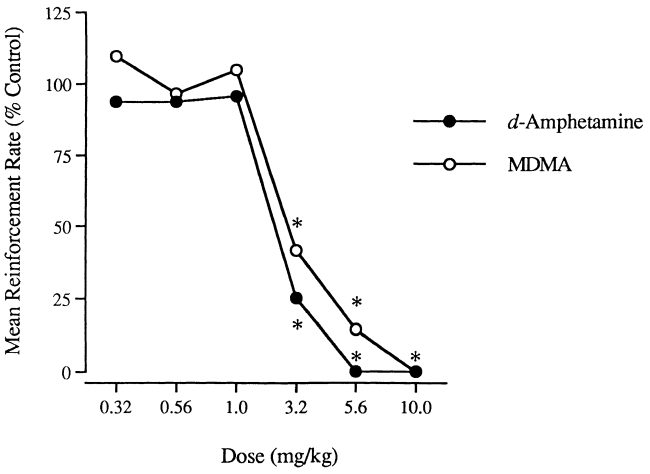

FIG. 2. Acute effects of *d*-amphetamine and MDMA on the rate of reinforcement (food deliveries per session) of five pigeons performing under a multiple FR 30 IRT>15-s schedule of food delivery. Each data point represents the mean rate of reinforcement during exposure to the indicated drug and dose, expressed as a percentage of the control rate. Control reinforcement rate was 35.7 food deliveries per session for *d*-amphetamine, 36.4 food deliveries per session for MDMA.

MDMA), and these doses significantly reduced reinforcement rate.

Despite similarities in the effects of amphetamine and MDMA under several procedures, Nader et al. (18) suggested that the behavioral effects of the drugs differ insofar as amphetamine has rate-dependent effects, but MDMA does not. The present data are not consistent with this analysis. Both drugs appeared to produce similar rate-dependent effects in that, although both drugs only produced decreases in response rate under both schedules, the higher rates maintained under the FR schedule were decreased more than the lower rates maintained under the IRT>15-s schedule.

That neither drug increased the low-rate responding maintained under the IRT>15-s schedule was unexpected. Amphetamine-induced increases in low-rate behavior have been observed in several studies (7,9,15,16,17) and MDMA-induced rate increases in low-rate responding also have been observed (15,17). Given that prior studies have shown that a history of exposure to ratio schedules modulates the effects of amphetamine under fixed-interval schedules (32), it is possible that the birds' history of exposure to PR schedules altered drug effects under the IRT>15-s schedule, but without testing behaviorally-naive subjects it is impossible to determine how, or if, the PR history influenced the present findings. However, the present results are consistent with those of a prior study (11) in which *d*-amphetamine generally reduced the responding of experimentally-naive pigeons performing under an IRT>20-s schedule. They also are consistent with the findings of Nader et al. (18), who found that MDMA reduced both low-rate and high-rate operant responding. The birds used in that study were reported to have a history of exposure to benzodiazepines, but their schedule histories (if any) were not specified.

Although they share some common actions with hallucinogens (e.g., mescaline) and stimulants (e.g., amphetamine) MDMA and related compounds (MDA, MBDB) have been considered to represent a unique drug class, the "entactogens" (19,20). The extent to which drugs from the three classes produce comparable behavioral effects is of interest, in part, to evaluate the utility of the distinction (20). Although the present data suggest that MDMA and *d*-amphetamine produce comparable rate-dependent effects under some circumstances, future research is required before strong general conclusions can be reached concerning the extent to which these drugs affect schedule-controlled responding in similar fashion, and the degree to which baseline response rates modulate the effects of MDMA. Given that many variables may affect drug effects on schedule-controlled behavior (e.g., species, dose, subjects' history, schedule values), within-subjects comparisons of the two drugs are likely to yield more informative results than between subjects comparisons, especially when the latter comparisons are based on subjects tested in different laboratories.

ACKNOWLEDGEMENT

The authors would like to thank the National Institute on Drug Abuse for supplying MDMA. The reported research was partially supported by NIDA grant DA07869-01A4.

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