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# MDMA and memory: the acute and chronic effects of MDMA in pigeons performing under a delayed-matching-to-sample procedure*

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**Abstract.** The purpose of the present study was to examine the acute and chronic effects of (±)3,4-methylenedioxymethamphetamine (MDMA) in pigeons responding under a delayed-matching-to-sample procedure with 0-, 3-, and 6-s delays. In the absence of drug, accuracy (percent correct responses) was inversely related to delay length. When administered pre-chronically, MDMA (0.32–5.6 mg/kg) generally decreased accuracy and response rates at doses of 3.2 mg/kg and above. Although humans report a distinct "hangover" when exposure to MDMA ends, performance of pigeons in the present study did not deteriorate when the chronic regimen ended, indicating an absence of behavioral dependence on the drug. Tolerance developed following chronic exposure to 3.2 mg/kg. In general, greater tolerance occurred at the 0-s delay than at longer delays. Although MDMA is reported to have neurotoxic effects, it does not inevitably produce long-lasting or cumulative behavioral impairment.

**Key words:** (±)3,4-Methylenedioxymethamphetamine (MDMA) – Tolerance – Delayed-matching-to-sample – Pigeons

The drug (±)3,4-methylenedioxymethamphetamine (MDMA) is a synthetic amphetamine analog that reportedly has both stimulant and hallucinogenic properties (Callahan and Appel 1985; Evans and Johanson 1986; Schechter 1986). In the past 5 years, interest has increased in MDMA, largely because of its documented recreational use in humans (Siegel 1986; Peroutka 1987), significant potential for abuse (Lamb and Griffiths 1987), and neurotoxicity to serotonergic systems in rat and nonhuman primate brains (e.g., Stone et al. 1986; Commins et al. 1987; Schmidt 1987; Ricaurte et al. 1988). MDMA also is interesting because of its historic use as an adjunct to psychotherapy due to its reported ability to produce "positive mood changes and enhance intimacy and communication" (Lamb and Griffiths 1987, p 268).

The physiological effects of MDMA have been studied extensively (e.g., Lyon et al. 1986; Commins et al. 1987; Yousif et al. 1990). The behavioral effects of MDMA, however, have not been examined in detail. An exception concerns the ability of the drug to serve as a discriminative stimulus or to substitute for other drugs established as discriminative stimuli. Several studies in this area have appeared. For example, in rats tested under drug-discrimination assays, the subjective effects of MDMA were more mescaline-like than LSD-like (Callahan and Appel 1987). At certain doses, MDMA produced amphetamine-like patterns of responding in rats (Glennon and Young 1984), pigeons (Evans and Johanson 1986), and monkeys (Kamien et al. 1986) trained to discriminate saline from amphetamine.

Few studies have examined the effects of MDMA on schedule-controlled responding. In mice, acute administrations of MDMA decreased response rates maintained under a fixed-ratio 20 (FR 20) schedule of food delivery in generally dose-dependent fashion (Glennon et al. 1987; Rosecrans and Glennon 1987). In pigeons, the drug when given acutely produced dose-dependent decreases in response rates under both components of a multiple FR 30 fixed-interval 3-min (FI 3-min) schedule of food delivery (Nader et al. 1989). Acute administrations of MDMA also decreased rates of responding in monkeys performing under a repeated acquisition procedure, although the drug did not affect learning or performance accuracy (Thompson et al. 1987).

Only two studies have examined how chronic administration influences the behavioral effects of MDMA. In one (Zacny et al. 1990), MDMA initially reduced milk drinking by mice. Tolerance appeared when the drug (2.5 mg/kg, then 5 mg/kg) was administered either 15 min before or 15 min after daily milk-drinking sessions.

In a second study involving chronic exposure, acute administrations of MDMA increased response rates and

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reduced reinforcement rates in rats responding under an interresponse-time-greater-than-72-s (IRT > 72-s) schedule (Li et al. 1989). During the chronic phase, 6 mg/kg MDMA was administered every 12 h for 4 days. Acute dose-response relations were redetermined 4 weeks after chronic exposure. Effects were greater during post-chronic determinations that during pre-chronic determinations (i.e., sensitization occurred).

It is not clear why chronic exposure to MDMA produced tolerance in the milk-drinking task studied by Zacny et al. (1990) and sensitization under the IRT > 72-s schedule examined by Li et al. (1989). Behavioral assays, species, and dosing regimens differed in the two studies, and any of these differences may have accounted for the dissimilar results.

In an attempt to gain further information about the behavioral effects of MDMA, the present study explored the acute and chronic effects of the drug in pigeons responding under a delayed-matching-to-sample (DMTS) procedure. This procedure was employed because it is quite sensitive to the effects of a range of drugs (Thompson 1978) and is commonly considered as an assay of memory (Heise and Milar 1984). It requires subjects to match stimuli (e.g., key colors) separated in time by different delay intervals (e.g., 0, 3, or 6 s) and has provided valuable information concerning the effects of many drugs (Thompson 1986).

## Material and methods

*Subjects.* Four White Carneau pigeons, maintained at 80–85% of their free-feeding body weights, served as subjects. One bird (B4) was experimentally naive. The other three (B5, B6, B7) had histories of responding under a DMTS procedure like that used in the present study and had been acutely exposed to hallucinogenic drugs. These three pigeons were drug free for at least 6 months prior to the start of the present experiment. Each bird was individually housed with unlimited access to grit and water.

*Apparatus.* Four Lehigh Valley Electronics (BRS/LVE, Lehigh Valley, PA) operant conditioning chambers, measuring 32 cm long, 36 cm high, and 35 cm wide, were used. In each chamber, three response keys 2.5 cm in diameter were located 23 cm from the bottom of the intelligence panel approximately 5.5 cm apart. A minimum of 0.2 g pressure was required for key operation. Each key could be illuminated in red or green. An aperture horizontally centered on the front wall 7.5 cm above the floor allowed access to a hopper filled with mixed grain when the hopper was raised. When raised, the hopper was illuminated by a 7-W white bulb. A 7-W bulb (houselight) centrally mounted in the ceiling of the chamber provided ambient illumination. White masking noise was constantly provided. A fan mounted on the back wall of the chamber provided continuous ventilation. A Digital Equipment Corp. (Maynard, MA) PDP8-E minicomputer, using SUPERSKED software (State Systems Inc., Kalamazoo, MI), scheduled experimental events and recorded data.

*Behavioral procedure.* Although three of the subjects had experience under the DMTS procedure, all subjects were exposed to the same training procedures. Prior to the start of the experiment proper, the birds were hopper trained, then exposed to a forward pairing autoshaping procedure similar to that described by Brown and Jenkins (1968). Once pecking on all keys was reliably established during red and green illuminations, the birds were exposed to the DMTS procedure.

Under this procedure, discrete trials were programmed with an 8-s intertrial interval (ITI). Each trial began with a 0.25-s darkening of the chamber, after which the center key was illuminated in red or green (i.e., the sample stimulus was presented). With the exceptions of the 0.25-s periods that preceded sample presentations and time-outs (see below), the chamber was constantly illuminated. The sample color presented on each trial was selected at random with the exception that red and green were presented equally often during each block of 12 trials. A single response to the center key extinguished the sample stimulus and initiated a delay interval of 0, 3, or 6 s. The delay interval arranged on each trial was selected at random, with the exception that each of the three possible delays appeared equally often each session. Random selection ensured that there was no predictive relation between sample color and delay length. At the end of the delay interval, the two side keys were illuminated (i.e., the comparison stimuli were presented) in one of two randomly-determined configurations: red on the left key and green on the right or vice versa. A response to the comparison stimulus that matched the sample stimulus in color resulted in darkening of the side keys and 3-s access to grain, followed by the ITI. Nonmatching responses (errors) were followed by darkening of the chamber for 2 s (timeout). After the timeout, the houselight was illuminated and the ITI initiated. Nonmatching trials were repeated unchanged (i.e., the same sample stimulus, comparison configuration, and delay value were presented until the pigeon responded to the correct comparison stimulus). These correction trials were intended to prevent the pigeon from developing a position preference (in the absence of such a procedure the pigeon could obtain 50% of the available reinforcers by simply responding on one or the other side key).

When the percentage of correct responses [(matching responses/matching responses + nonmatching responses) × 100)] showed no visually evident trend across ten consecutive sessions, the response requirement for extinguishing the sample stimulus was gradually increased to 5, and only every other correct trial was followed by food delivery. Correct trials not followed by food were followed by a 0.5-s flash of the hopper light (a putative conditioned reinforcer) and the ITI. Trials were aborted (terminated) if a subject failed to respond to one of the side-keys within 30 s of presentation of the comparison stimuli, or failed to complete the response requirement on the center key within 30 s. Aborted trials were repeated after an 8-s ITI and were not recorded as incorrect. During the experiment proper, sessions were terminated after 140 trials or 50 min, whichever came first. During determination of acute drug effects, sessions usually were conducted 6 days per week at about the same time each day. During chronic exposure, sessions were conducted daily.

*Pharmacological procedure.* Initial dose-response determination began when (a) each bird had received at least 60 sessions of exposure to the DMTS procedure, and (b) there was no visually evident trend in the percentage of correct responses for each bird for ten consecutive sessions. The acute effects of six doses of MDMA (0.32, 1.0, 1.7, 3.2, 4.2, and 5.6 mg/kg) were determined. MDMA (Sigma Chemical Co., St. Louis, MO) was dissolved in a vehicle of 0.9% saline solution, prepared at an injection volume of 1 ml/kg. Throughout the experiment, drug and vehicle control injections were administered 10 min prior to experimental sessions. Doses and presession injection times were selected on the basis of previous reports (Evans and Johanson 1986; Nader et al. 1989) and pilot data from our laboratory. Each bird received at least two, but no more than three, administrations of every dose. A dose was administered a third time only in the event that the effect of the second administration was markedly different from the first administration. This occurred in four cases. Bird B4 received three administrations of 5.6 mg/kg, B6 received three administrations of 4.2 and 5.6 mg/kg, and B7 received three administrations of 4.2 mg/kg. For each bird, doses were administered in a random order according to a BBCDBBCD design, where B represents baseline sessions, C represents vehicle control sessions, and D represents drug sessions.

Following completion of the acute dose-effect determinations, the chronic effects of MDMA were determined. Here, each subject

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first received at least ten baseline sessions followed by two vehicle control sessions, then chronic exposure to MDMA. The lowest dose that produced obvious behavioral impairment without completely suppressing responding during the acute phase was selected as the chronic dose. Thus, 3.2 mg/kg served as the chronic dose. Following 20 days of daily exposure to 3.2 mg/kg, subjects were exposed to a 4.2 mg/kg challenge dose on a single occasion. Subjects then received five consecutive sessions of exposure to 3.2 mg kg. A 5.6 mg kg challenge dose was then administered on a single occasion. To determine the effects of MDMA withdrawal, subjects then received ten vehicle control sessions followed by 5 days of 3.2 mg kg, then five vehicle control sessions.

## Results

Pre-chronic dose-response curves for accuracy and response rates will be considered initially. Figure 1 shows group performance for overall accuracy at each delay value as a function of dose of MDMA. Data shown are the average percentage of correct responses across the four subjects during pre-chronic control sessions, during acute exposure to each dose, during control sessions immediately prior to the chronic regimen, during the final session of exposure to the chronic dose, and during exposure to the two challenge doses. Figure 2 shows each subject's accuracy at each delay value. MDMA was considered to affect behavior (accuracy or response rate) if performance at a given dose was outside the range of values encompassed by the vehicle control mean ± one standard error. If a subject completed fewer than 30 trials (10 trials at each delay value) during any drug session, responding was considered suppressed below a level necessary to assess accuracy meaningfully, thus data for such sessions are not included. These sessions with no data made it impossible to analyze results via conventional inferential statistics (e.g., an ANOVA followed by planned comparisons), thus no statistical analysis was attempted.

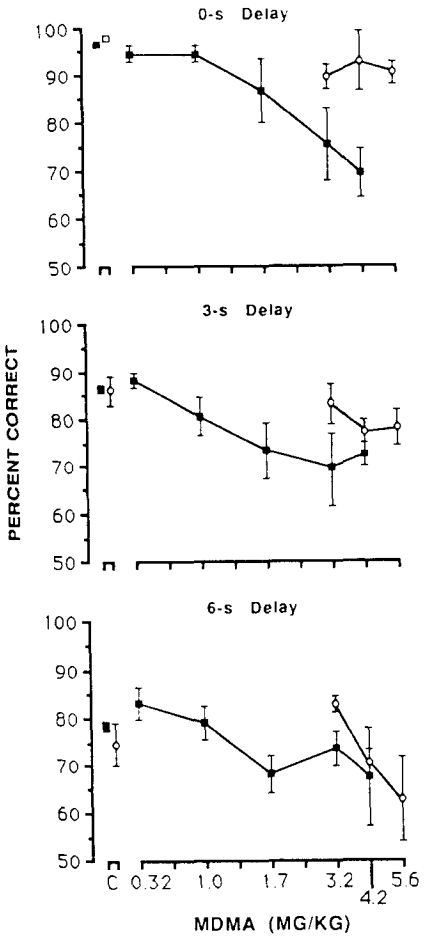


**Fig. 1.** Group data showing the pre- and post-chronic effects of MDMA on the percentage of correct responses at each delay under a DMTS procedure. Each point in the dose-response curve is the mean performance of four birds at every dose determination that did not suppress responding below the minimum trial requirement. The points at *C* indicate the mean for control (saline) sessions. *Vertical lines* indicate standard errors of the mean. *Points* without vertical lines indicate an instance in which the standard error is encompassed by the point. (■) Pre-chronic; (□) post chronic

In the absence of drug, the percentage of correct responses decreased as a function of increasing delay values. For subjects as a group, MDMA at doses above 3.2 mg kg produced dose-dependent decreases in the average percentage of correct responses, but decreases in accuracy did not reach chance levels (i.e., 50%) at any dose. In general, results with individual subjects were similar to those evident in mean group performance, although high doses produced somewhat variable effects across subjects. For instance, 4.2 mg/kg produced significant reductions in accuracy relative to control in B5, whereas B6 was little affected by that same dose.

Figures 3 and 4 show the effects of MDMA on rates of responding (responses/min) to the sample stimulus (i.e., on the center key). Data shown are the average response rates for subjects as a group (Fig. 3) and as individuals (Fig. 4). At doses above 3.2 mg/kg, MDMA produced generally dose-dependent decreases in response rates for subjects as a group. Doses of 3.2 mg/kg or higher also reduced rates below control levels in all individual subjects. Responding of all subjects was completely suppressed at 5.6 mg/kg. MDMA at 4.2 mg/kg completely suppressed responding in B4 at both determinations, and in B6 and B7 at one of two determinations.

In general, tolerance developed to both the accuracy- and rate-reducing effects of MDMA following repeated exposure to 3.2 mg/kg. This effect is readily apparent in Figs 1 and 3, which show that, for subjects as a group: 1) the accuracy- and rate-reducing effects of 3.2 mg/kg were smaller on the final day of chronic exposure than during the pre-chronic dose-response determination, 2) the accuracy- and rate-reducing effects of 4.2 and 5.6 mg/kg were smaller when these doses were given as challenges during the chronic regimen than when they were administered pre-chronically. Although considerable variability is apparent, tolerance to the accuracy- and rate-reducing effects characteristically is evident in the performance of individual subjects. Perhaps the strongest evidence of tolerance concerns the effects of 5.6 mg/kg. This dose completely suppressed responding during initial dose-response determinations, but three of four subjects completed all of the possible trials (i.e., 140) during the session when it was given post-chronically. The exception, bird B7, did not show tolerance to the effects of 5.6 mg/kg (i.e.,

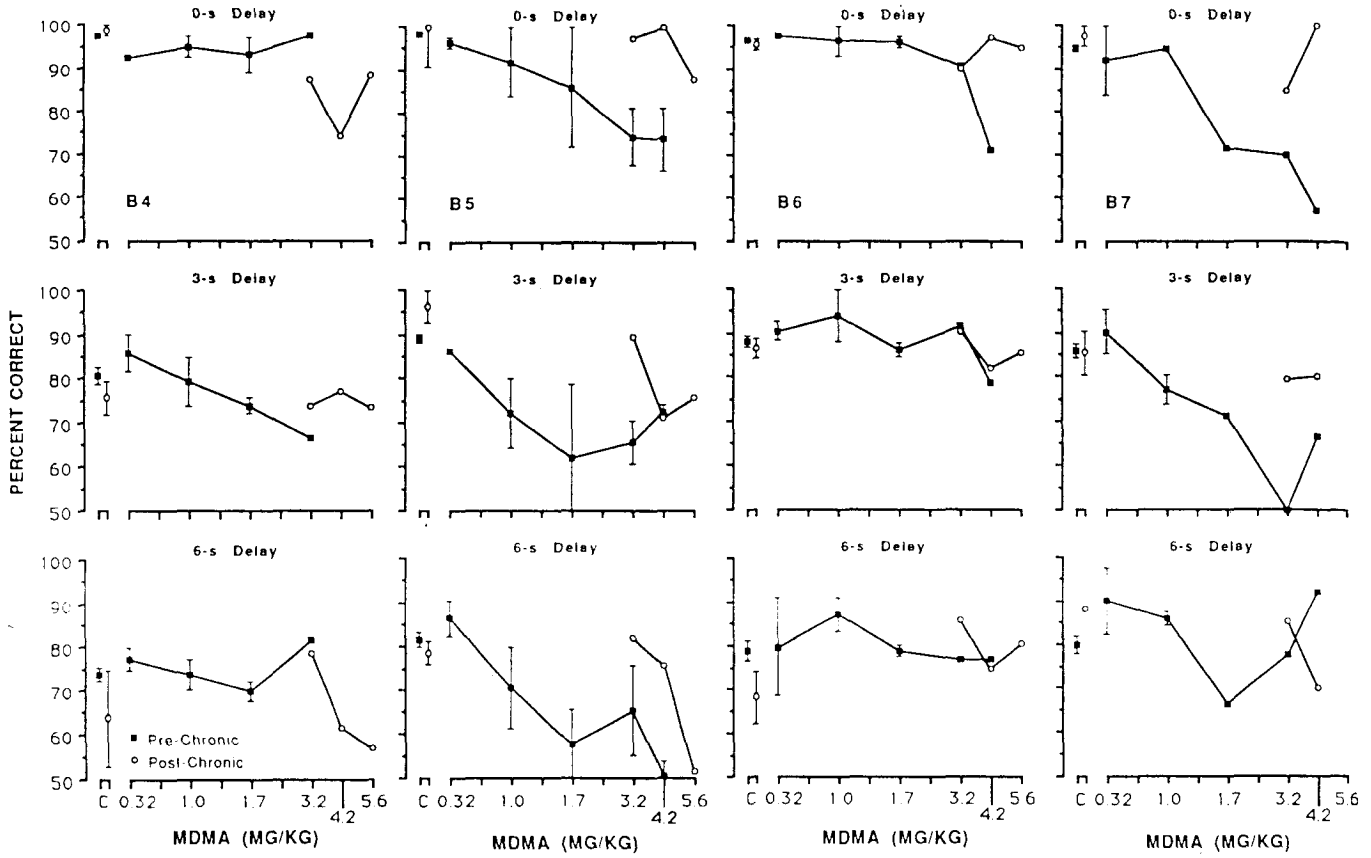


Fig. 2. Individual subject data showing the pre- and post-chronic effects of MDMA on the percentage of correct responses at each delay under a DMTS procedure. Each column of three graphs shows data for a single pigeon. The points at *C* indicate the mean for control (saline) sessions. *Vertical lines* indicate standard errors of the mean. *Points* without vertical lines indicate either a single determination (i.e., where only one administration did not suppress responding below the minimum trial requirement) or an instance in which the standard error is encompassed by the point

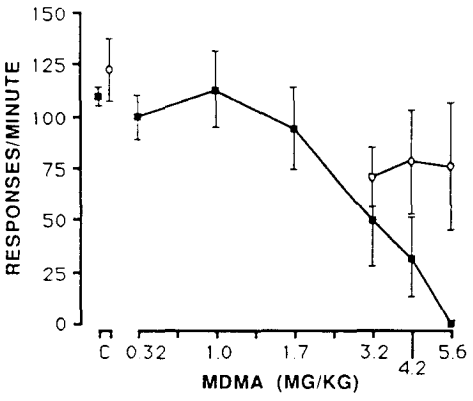


Fig. 3. Group data showing the pre- and post-chronic effects of MDMA on the response rates of pigeons performing under a DMTS procedure. Each point in the dose-response curve is the mean performance for four birds. The points at *C* indicate the mean for control (saline) sessions. *Vertical lines* indicate standard errors of the mean. (■) Pre-chronic; (□) post-chronic

this dose continued to suppress performance completely following chronic exposure).

The magnitude of the tolerance that developed to the accuracy-reducing effects of MDMA appeared to depend on the delay between sample presentation and onset of the comparison stimuli. In general, for three out of four birds, greater tolerance was observed at the 0-s delay than at the 6-s delay. Finally, performance did not deteriorate when the chronic regimen ended, indicating an absence of behavioral dependence on MDMA.

## Discussion

In the present study, MDMA produced dose-dependent decreases in both accuracy and response rates under the DMTS procedure. The rate-reducing effects shown here are consistent with results reported with mice responding under a FR 20 schedule (Glennon et al. 1987; Rosecrans and Glennon 1987) and in pigeons responding under a multiple FR 30 FI 3-min schedule (Nader et al. 1989). They also agree with results reported by Thompson et al. (1987), who demonstrated that acute administrations of MDMA decreased rates of responding in monkeys performing under a repeated acquisition procedure. The accuracy-reducing effects shown here are inconsistent with the Thompson et al. (1987) findings, which indicated that MDMA did not affect learning or performance accuracy. Why MDMA reduced accuracy under the DMTS procedure in the present study and not the repeated acquisition procedure used by Thompson et al. (1987) is not obvious.

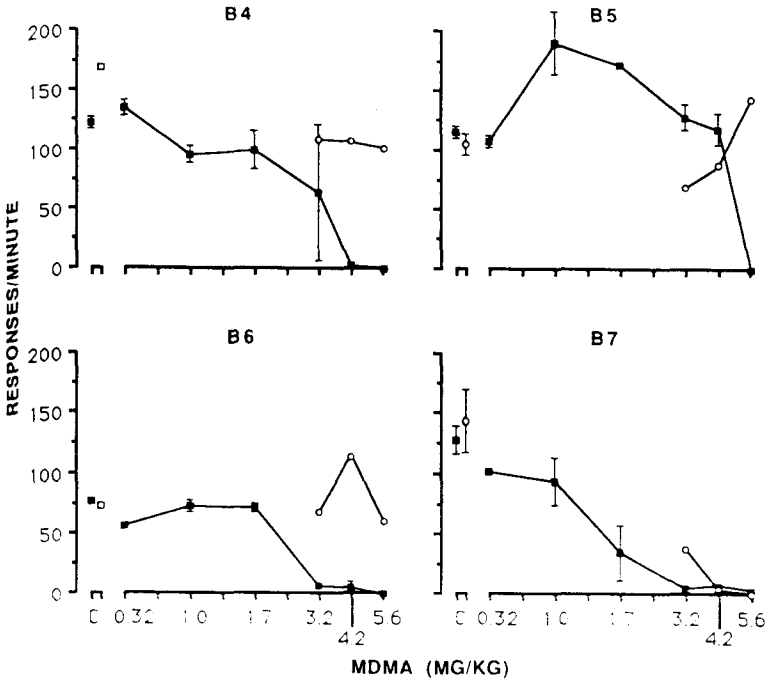


**Fig. 4.** Individual subject data showing the pre- and post-chronic effects of MDMA on response rates of pigeons performing under a DMTS procedure. Each graph represents data from a single pigeon. The points at *C* indicate the mean for control (saline) sessions. *Vertical lines* indicate standard errors of the mean. *Points* without vertical lines indicate either a single determination (i.e., where only one administration did not suppress responding below the minimum trial requirement) or an instance in which the standard error is encompassed by the point. (■) Pre-chronic; ( ) post-chronic

Differences in the behavioral assays, species, and dosing regimens employed in the two studies could account for the disparate results.

The results of the present study also show that tolerance developed to both the accuracy- and rate-reducing effects of MDMA. This finding is consistent with the results of a prior study, which demonstrated tolerance to MDMA-induced reductions in milk drinking by mice (Zacny et al. 1990). The present results are inconsistent with the results of a prior study in which sensitization was observed following repeated administration of MDMA under an IRT > 72-s schedule of food delivery (Li et al. 1989). Interestingly, in all studies that have examined possible tolerance to the behavioral effects of MDMA, the effect of the drug when initially administered was reinforcement loss, thus the difference in findings cannot be explained in terms of the reinforcement-loss hypothesis (Schuster et al. 1966) or related concepts (see Wolgin 1989). The fact that tolerance developed to MDMA in two of three studies is of interest, given that the drug reportedly is a neurotoxin to serotonergic and to a lesser extent, dopaminergic systems in rodent and primate brains (Stone et al. 1986; Commins et al. 1987; Schmidt 1987; Ricaurte et al. 1988). Apparently, the neurotoxic effects of MDMA are not necessarily associated with long-lasting or cumulative behavioral impairment.

In the present study, the magnitude of tolerance that developed to the accuracy-reducing effects of MDMA appeared to be a function of delay length. This relation is consistent with the results of a prior study that examined the effects of cocaine on DMTS performance in pigeons (Branch and Dearing 1982) and is compatible with a reinforcement-density analysis of tolerance (Wolgin 1989). Accuracy (percent correct responses) in the present study was directly related to the number of reinforcers obtained: 50% of correct responses were followed by food delivery, the remainder by a putative conditioned reinforcer (i.e., flash of the hopper light). The difference in accuracy under control and pre-chronic drug conditions was greater at the 0-s delay than at the 6-s delay. Hence more reinforcers were lost due to the effects of the drug when the delay was 0 s. The larger proportional loss at the 0-s delay may have contributed to the greater tolerance observed at that delay. An alternative analysis is that stimulus control was greater at the 0-s delay than at longer delays, and this variable may have affected the development of tolerance. Several studies indicate that the degree of stimulus control in the absence of drug often modulates acute drug effects, and a recent report suggests that it may also influence the development of tolerance (Rees et al. 1987). The present findings are consistent with this observation.

Previous reports have suggested that, in humans, MDMA produces a withdrawl syndrome characterized by drowsiness, muscle aches, depression, and impairment of concentration (Barnes 1988). Therefore, it is plausible that one would observe behavioral impairment in nonhumans upon termination of chronic exposure to MDMA. This did not occur in the present study. Performance during the first and subsequent control sessions following chronic exposure was close to pre-chronic baseline levels. This finding is inconsistent with reports that "the drug causes a distinct hangover and by the second day its negative side effects are pronounced" in humans (Barnes 1988, p 864).

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