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Self-injection of *d,l*-3,4-methylenedioxymethamphetamine (MDMA) in the baboon

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Abstract. MDMA (*d,l*-3,4-Methylenedioxymethamphetamine HCl; "ecstasy") self-injection (0.1–3.2 mg/kg/injection) was examined in baboons under conditions in which baseline responding was maintained by intravenous injections of cocaine HCl (0.32 mg/kg/injection). Drug was available under a FR 160-response schedule of intravenous injection. Each drug injection was followed by a 3-h time out allowing a maximum of eight injections per day. MDMA or MDMA vehicle (saline) was substituted for cocaine for a period of 14 or more days followed by a return to the cocaine baseline. MDMA (0.32–3.2 mg/kg/inj) maintained more injections and higher responses rates than were maintained by saline. The maximal number of injections maintained by MDMA and the maximal response rate maintained by MDMA were less than those maintained under baseline conditions with cocaine. The highest dose of MDMA tested maintained a cyclic pattern of self-injection, i.e., days of high numbers of injections intermixed with days of low numbers of injections. At the highest dose of MDMA tested, concurrent food maintained behavior was suppressed to an extent that food intake was also decreased.

Key words: *d,l*-3,4-Methylenedioxymethamphetamine – Drug self-administration – Baboons

Recent controversy on the therapeutic and recreational use of MDMA (*d,l*-3,4-methylenedioxymethamphetamine HCl, "ecstasy") has focused attention on this compound and structurally related phenylisopropylamine compounds (Adler et al. 1985; Klein 1985; Shafer 1985). Reports in the lay press indicate that MDMA may produce both LSD-like and cocaine-like effects. The LSD-like effects are often stated to be milder or less disrupting than the effects of LSD itself (Klein 1985). In one of the few descriptions of the subjective effects of MDMA in man in the scientific literature, Shulgin and Nichols (1978) report that 75–150 mg of "... the drug appears to evoke an easily controlled altered state of consciousness with emotional and sensual overtones. It can be compared in its effects to marijuana, to psilocybin devoid of the hallucinatory component or to low levels of MDA." Greer (1983) reported data suggesting that use of MDMA (50–200 mg) during the course of psychotherapy may be of positive benefit in certain cases. He reported that MDMA produced positive mood changes and enhanced intimacy and communication. The side effects of MDMA were those typical of sympathomimetic drugs (Greer 1983).

In order to further characterize the pharmacology of MDMA the intravenous self-administration of MDMA in the baboon was evaluated using a cocaine substitution procedure. In previous experiments the effects of the related compounds [*d*-amphetamine, *l*-3,4-methylenedioxyamphetamine (*l*-MDA) and 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM)] have been assessed using these procedures (Griffiths et al. 1976, 1979).

Materials and methods

Three male baboons (*Papio anubis*) weighing 21–25 kg served as experimental subjects. Baboon RA had been studied in previous sedative and phenylpropanolamine self-injection experiments and baboon DI had been studied in antidepressant, phenylpropanolamine, and buspirone self-injection experiments. Baboon TA was experimentally naive. Baboons were housed within standard primate squeeze cages, which also served as experimental chambers. These cages were enclosed by sound and light attenuating cubicles (Lukas et al. 1982). Intravenous catheters were implanted using sterile technique in either femoral or internal jugular veins under pentobarbital anesthesia using the methods described in Lukas et al. (1982). Catheters were protected by a harness/tether system, which allowed the baboons virtually unrestricted movement within the cage (Lukas et al. 1982). The infusion system was similar to that described in Findley et al. (1972). Baboons had free access to water through a drinking tube and received daily rations of fruit and vitamin supplements.

A 0.7 × 1.0 m aluminum panel was mounted on one wall of the experimental chamber. A Lindsley lever (Gerbrands, No. G6310) (lower left of panel) with an associated jewel light (approximately 1.5 cm diameter), a leaf lever (lower right of panel) with an associated jewel light, and a food hopper with an associated light (lower left or center of panel) were mounted on the aluminum panel. A 5 × 5 cm translucent panel which could be transilluminated was mounted on the aluminum panel in the upper left corner.

Baboons could respond on the leaf lever under a fixed-

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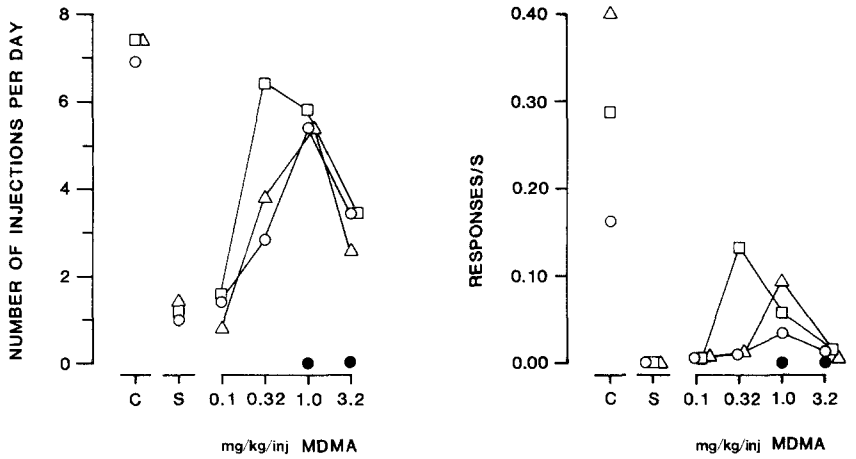

Fig. 1. *Left panel:* Number of injections self-administered per day as a function of MDMA dose. Drug was available under a FR 160-response schedule of intravenous injection followed by a 3-h time-out. Baseline performance was maintained with cocaine hydrochloride (0.32 mg/kg/injection) and 3 consecutive days on which six or more injections of cocaine were self-administered preceded each substitution of MDMA or MDMA vehicle (saline) for a period of 14–18 days. The *vertical* axis represents the mean number injections for the last 5 days of MDMA or saline (above *S*) substitution and for comparative purposes the mean of the means of each of the 3-day periods of cocaine (above *C*) availability that immediately preceded MDMA or saline substitution. The *horizontal* axis represents MDMA dose expressed as the hydrochloride salt on a log scale. Data for each of the three baboons tested are plotted, and different symbols represent different baboons (DI□; RA△; TA○). *Filled symbols* for TA at 1.0 and 3.2 mg/kg/injection MDMA indicate first occasions that this baboon had opportunity to self-inject a drug other than cocaine.
Right panel: Rate of responding for MDMA as a function of MDMA dose. The *vertical* axis represents the mean daily response-rate (fixed-ratio responses on the drug level divided by time available for fixed-ratio responding) for the last 5 days of MDMA or saline (above *S*) substitution and for comparative purposes the mean of the means of each of the 3-day periods of cocaine (above *C*) availability that immediately preceded MDMA or saline substitution. Other details are as in the left panel

ratio 30-response schedule of food pellet (1 g Noyes or Bioserv banana flavored) delivery (i.e., every 30th response delivered a food pellet and produced a brief flash of the hopper light) 24 h per day. The availability of an injection was indicated by a 5-s tone followed by illumination of a jewel light over the Lindsley lever. When the jewel light was illuminated, each response produced a brief feedback tone (approximately 0.1 s). Upon completion of 160 responses on the Lindsley lever following illumination of the jewel light (FR 160), the jewel light over the lever was extinguished, the drug injection was begun, the 5 × 5-cm translucent panel was illuminated for a 1-h period, and a time-out period of 3 h was begun. The schedule of drug availability permitted a maximum of eight injections per day. There was no time limit for completion of the fixed-ratio response requirement. Data were collected each day at approximately 8 a.m. and drug changes were made at this time, if indicated.

The self-injection of MDMA was evaluated using a cocaine substitution procedure (Griffiths et al. 1976). Three days during which 0.32 mg/kg/injection cocaine HCl (dissolved in saline) maintained six or more injections per day preceded the substitution of each dose of MDMA or MDMA vehicle (normal saline). Following substitution of MDMA or saline for approximately 15 days, cocaine was again available. This procedure of replacing cocaine with a dose of MDMA or saline was continued throughout the study. Experiments ran continuously 7 days per week. Drug or vehicle injections were 5 ml and each injection was followed by a 5 ml flush of normal saline. These injections each took about 90 s to complete.

The order and duration of conditions tested (mg/kg/injection MDMA followed by number of days in parentheses) was as follows: RA – 0.1 (15), 1.0 (15), 0.32 (15); 0 (17); 3.2 (18); DI – 1.0 (15), 0 (15), 0.1 (15), 0.32 (15), 3.2 (14); TA – 1.0 (15), 3.2 (16), 0.32 (15), 0.1 (15), 0 (15), 1.0 (18), 3.2 (15). Drug doses are expressed as the salt.

Results

The left panel of Fig. 1 shows mean injections per day for each baboon for the last 5 days of vehicle or MDMA availability and the mean of the means for the 3 days of cocaine availability that preceded vehicle or MDMA availability. As can be seen, 0.32–3.2 mg/kg/injection MDMA maintained responding above vehicle levels. The only exception to this is the initial exposure of baboon TA to the 1.0 and 3.2 mg/kg/injection doses of MDMA; one should note, however, that this was the first opportunity for this baboon to self-inject any drug other than cocaine. In all three baboons, the highest levels of MDMA self-administration were maintained at 0.32 or 1.0 mg/kg/injection, and lower levels were maintained by 0.1 and 3.2 mg/kg/injection of MDMA. The highest levels of MDMA self-administration were less than the maximally obtainable level and less than those maintained by 0.32 mg/kg/injection cocaine HCl.

The right panel of Fig. 1 shows the mean daily rate of responding for each baboon for the last 5 days of vehicle or MDMA availability and the mean of the means for the 3 days of cocaine availability that preceded vehicle or MDMA availability. As can be seen in this panel, doses of 0.32, 1.0, and 3.2 mg/kg/injection MDMA maintained rates of responding higher than those maintained by those maintained by vehicle. Further, 1.0 mg/kg/injection MDMA maintained higher response rates than either 0.32 or 3.2 mg/kg/injection MDMA, except in Baboon DI in

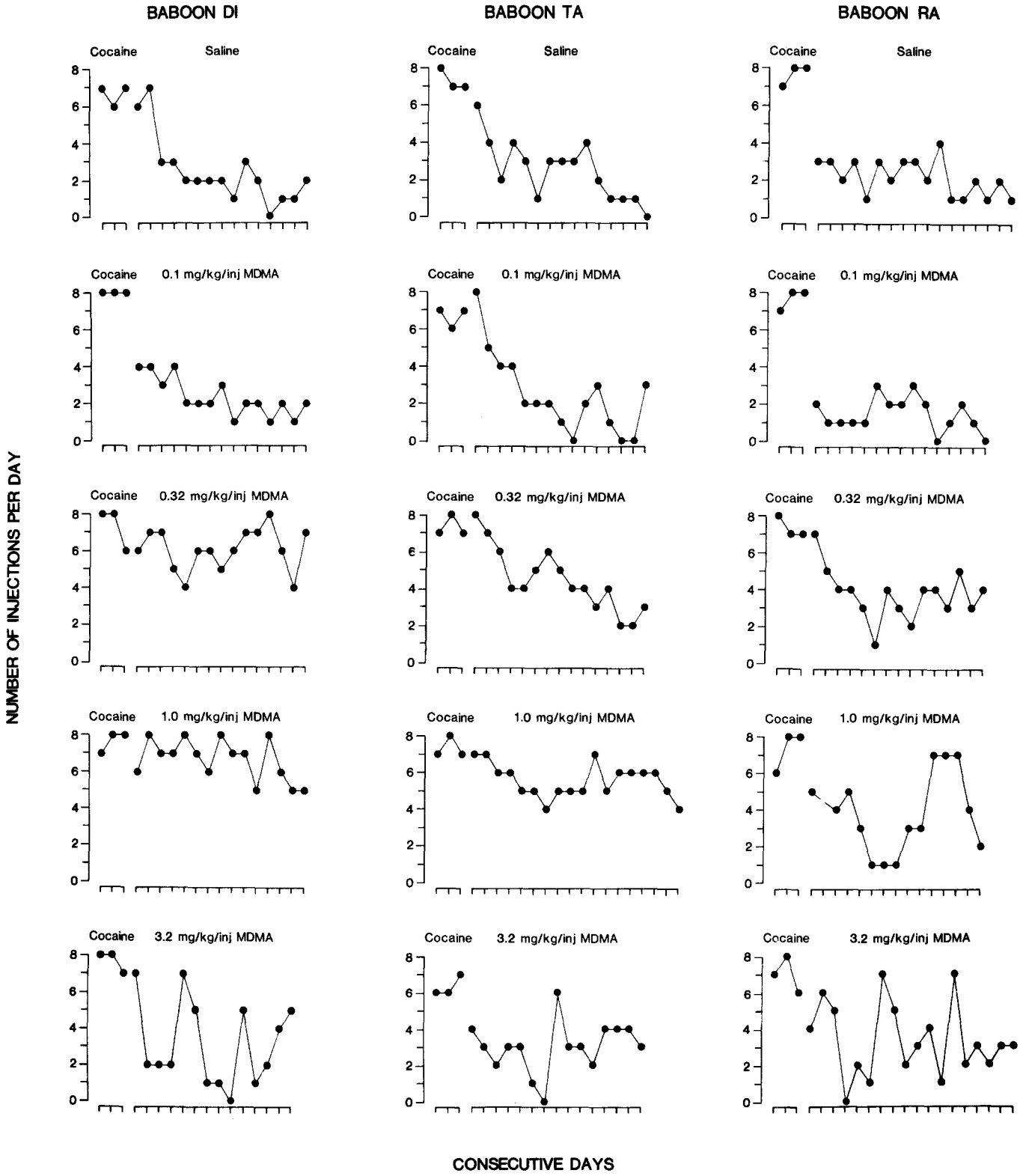

Fig. 2. The number of injections over successive days of MDMA or saline availability for each condition (excluding initial exposure to 1.0 and 3.2 mg/kg/inj MDMA for baboon TA) for each of three baboons. The 3 immediately preceding days of cocaine availability are plotted for comparative purposes. The *vertical* axes are injections per day. The *horizontal* axes are successive days

which 0.32 mg/kg/injection MDMA maintained higher rates. No dose of MDMA maintained rates of responding as high as those maintained by 0.32 mg/kg/injection cocaine.

Figure 2 shows the number of injections per day for each baboon for saline and the four doses of MDMA. As can be seen, saline, 0.1, and 0.32 mg/kg/injection MDMA were associated with a relatively stable number of injections per day during the latter half of the substitution period. At 3.2 mg/kg/injection "cycling" occurred in all three ba-

boons (i.e., days on which high numbers of injections taken were interspersed with days on which low numbers of injections were taken). At 1.0 mg/kg/injection MDMA cycling occurred in one of the three baboons (Baboon RA).

Doses of MDMA of 1.0 mg/kg/injection and below had inconsistent effects on number of food pellets delivered. When 3.2 mg/kg/injection MDMA was available for self-injection, food intake was decreased to near zero levels (data not shown).

During self-injection of cocaine, vehicle, and low doses of MDMA, there were no unusual changes in the gross behavior of the baboons. However, all three baboons engaged in notably unusual behavior while self-injecting high doses of MDMA. Two animals each appeared to track nonexistent visual objects (suggesting hallucinations), were uncharacteristically aggressive toward laboratory personnel, and engaged in repetitive scratching and self-grooming behavior.

Discussion

Response contingent injections of MDMA maintained higher rates of responding than those maintained by response contingent injections of MDMA vehicle, i.e., MDMA served as a reinforcer under these experimental conditions. These results are similar to those obtain previously with *l*-MDA and *d*-amphetamine, but are unlike those obtained with DOM and PMA (paromethoxyamphetamine) (Griffiths et al. 1976, 1979). The present results are consistent with the conclusion that MDMA may have a liability for abuse.

Relevant to an understanding of the pharmacology of MDMA and its abuse liability are the similarities of MDMA to *d*-amphetamine, MDA and DOM. While there are differences between MDMA and amphetamine in subjective effects reported by humans (Shulgin and Nichols 1978), there are also certain similarities. Both MDMA and *d*-amphetamine maintain self-injection behavior above vehicle control levels and high doses of both drugs are associated with a cyclic pattern of self-injection over days (present report; Griffiths et al. 1976). At doses larger than those needed to maintain self-injections, both MDMA and *d*-amphetamine suppressed food intake and food maintained behavior (present report; Griffiths et al. 1976) and produced similar changes in gross behavior such as tracking nonexistent visual objects and repetitive self-grooming (present report and unpublished observations). Both MDMA and amphetamine also can set the occasion for *d,l*-MDA or amphetamine-appropriate responding, but not DOM-appropriate responding, in rat drug discrimination paradigms (Glennon and Young 1984a, b; Glennon et al. 1983).

MDMA has both similarities to and differences from *l*-MDA. MDMA and *l*-MDA are self-injected in baboons (Griffiths et al. 1979; this report), and both set the occasion for *d,l*-MDA appropriate responding in the rat drug discrimination paradigm (Glennon and Young 1984a). On the other hand MDMA, but not *l*-MDA, sets the occasion for amphetamine-appropriate responding in the rat drug discrimination paradigm (Glennon and Young 1984a). Further, consistent with the reputed lesser hallucinogenic effects of MDMA as compared to MDA or LSD (Shulgin and Nichols 1978), *l*-MDA, but not MDMA, sets the occasion for DOM-appropriate responding in the rat drug discrimination paradigm (Glennon et al. 1983; Glennon et al. 1982).

Though both MDMA and DOM can set the occasion for *d-l*-MDA appropriate responding in the rat drug discrimination paradigm (Glennon and Young 1984a, b), most other aspects of the pharmacology of MDMA and DOM are distinctly different. Response contingent injections of MDMA maintain rates of responding above those maintained by vehicle, while response contingent injections of DOM do not (Griffiths et al. 1979; present study). MDMA sets the occasion for amphetamine-, but not DOM-, – appropriate responding in rat-drug discrimination paradigms, while DOM does not set the occasion for amphetamine-appropriate responding (Glennon and Young 1984a, b; Glennon et al. 1983).

The pharmacological properties governing the self-administration of phenylisopropylamine compounds are complex. Unlike other classes of drugs such as opioids, in which the reinforcing properties tend to covary with other pharmacological effects, the effects of phenylisopropylamines on a variety of pharmacological measures do not appear to predict the reinforcing effects of these drugs as measured by a cocaine substitution procedure in primates. Specifically, none of the following pharmacological properties accurately predict the results of self-administration experiments within the phenylisopropylamine class of compounds (Griffiths et al. 1976, 1979): the ability to suppress food intake (cf. Griffiths et al. 1978), the ability to produce rate-dependent effects (Harris et al. 1977, 1978), the ability or inability to set the occasion for amphetamine or DOM-appropriate responding (Glennon and Young 1984a; Glennon et al. 1983; Glennon et al. 1985), and the ability to set the occasion for *d,l*-MDA appropriate responding (Glennon et al. 1984a, b).

Some phenyl substituted phenylisopropylamines, such as MDA, PMA, and MDMA, have pharmacological properties different from those of either *d*-amphetamine or DOM. Therefore, predictions about the abuse liability of these compounds based on their similarities to or differences from classic stimulants like cocaine and amphetamine, or hallucinogens like LSD and DOM may be inappropriate.

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