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MDMA produces stimulant-like conditioned locomotor activity*

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Abstract. Daily administration of a drug in a distinctive environment establishes contingencies that support Pavlovian conditioning. Environmental cues that are paired with the drug injection and that predict the onset of drug action can become conditioned stimuli. Ultimately, the conditioned stimuli come to predict the availability of drug and develop the potential to engender conditioned drug responses. Various psychostimulant drugs can produce conditioned locomotion when tested in the presence of environmental cues that were repeatedly associated with the drug experience. The ability of amphetamine and cocaine to produce conditioned locomotion was demonstrated in the present study. Stimulant-like properties of methylenedioxymethamphetamine (MDMA) have been reported in locomotor paradigms, drug discrimination procedures, and human subjective questionnaires. MDMA (5 mg/kg), paired for 5 days to a distinct environment signalled by the presence of a distinct odor, produced enhanced locomotion during a test probe with the odor alone indicating that MDMA can also produce conditioned locomotion. The observation that the stimulus properties of MDMA can also become associated with environmental cues supports the hypothesis that some of the behavioral effects of MDMA resemble those of other classical psychostimulants such as amphetamine and cocaine.

Key words: Conditioned locomotion – MDMA – Amphetamine – Cocaine – Rat

Previous studies have established that daily administration of indirect sympathomimetics, such as amphetamine (AMPH) and cocaine, in a distinctive environment can impart stimulant-like activity on the environment (Tilson and Rech 1973; Post et al. 1981; Beninger and Hahn 1983). In these cases, locomotor hyperactivity is thought to be classically conditioned through the repeated pairing of the unconditioned locomotor drug effect with a previously neutral stimulus, the testing environment (Pickens and Crowder 1967). Similarly, the stereotyped behaviors frequently associated with higher doses of stimulants have been reported to be under the stimulus control of classical conditioning (Borberg 1974; Bridger et al. 1982). Thus, the repeated administration of a drug to an animal in a distinctive test environment allows for conditioning contingencies because the pharmacological stimulus, unconditioned stimulus, is almost always preceded by a set of cues, conditioned stimulus, consistently present when the drug is administered.

Methylenedioxymethamphetamine (MDMA) is a substituted phenylisopropylamine that results from N-monomethylation of methylenedioxyamphetamine (MDA). Biochemically MDMA has been found to release [^{3}H]serotonin and to a lesser extent [^{3}H]dopamine from superfused rat brain slices (Johnson et al. 1986; Schmidt et al. 1987) and to potently inhibit [^{3}H]serotonin uptake into synaptosomes (Steele et al. 1987). Pronounced stereoselectivity was observed with MDMA in its ability to inhibit synaptosomal uptake of [^{3}H]dopamine (Steele et al. 1987) and release of [^{3}H]dopamine from rat caudate nucleus slices (Johnson et al. 1986) but no significant stereoselectivity was observed in inhibiting synaptosomal uptake of [^{3}H]norepinephrine (Steele et al. 1987). Behaviorally, MDMA has been shown to have stimulus properties which resemble AMPH in drug discrimination paradigms (Gennon and Young 1984; Oberlender and Nichols 1988). Stimulus generalization to the indirect acting dopamine agonist *l*-cathinone and the serotonergic agent fenfluramine have also been reported (Schechter 1986). Potential for abuse liability has been demonstrated in animal models of self-administration (Beardsley et al. 1986; Lamb and Griffiths 1987) and self-stimulation (Hubner et al. 1988). MDMA and its ethyl analog, MDE, tended to decrease prepulse inhibition in an acoustic startle procedure in a manner similar to the dopaminergic stimulants AMPH and apomorphine (Mansbach et al. 1989). Also like AMPH, MDMA produced an overall increase in acoustic startle magnitude.

Qualitative differences in the subjective effects of MDMA versus other psychoactive amphetamines have resulted in claims for potential usefulness in psychotherapy (Grinspoon and Bakalar 1986) as well as widespread street use (Peroutka 1987; Barnes 1988; Peroutka et al. 1988). MDMA has been described as producing feelings of closeness (Peroutka et al. 1988), facilitating self-insight and heightening empathy (Beck and Morgan 1986). The psychopharmacology of MDMA suggests that this drug may possess stimulant-like and hallucinogen-like effects combined with a novel action termed "entactogenic" (enabling the therapist or patient to reach inside and deal with painful emotional issues that are not ordinarily accessible) by Nichols (1986). A neurotoxic potential has also been associated with MDMA. In rats, significant reductions of tryptophan hydroxylase, serotonin, and its primary metabolite have been reported following single or multiple doses of

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MDMA (Stone et al. 1986; Mokler et al. 1987; Schmidt 1987). Similar neurochemical deficits and structural damage to serotonergic nerve fibers, induced by MDMA, have also been assessed in non-human primates (Ricaurte et al. 1988).

The ability of MDMA to stimulate locomotion has been reported (Braun et al. 1980; Gold and Koob 1988) and recently compared with the behavioral profiles of classic stimulants and hallucinogens (Gold et al. 1988a). The dose-related increase in locomotion produced by MDMA is similar in amount to doses of AMPH which do not produce stereotypy; however, some qualitative differences were observed (Gold et al. 1988a). For example, the duration of the locomotor hyperactivity is quite prolonged and has a time course which seems to coincide with reports of subjective effects in humans (Shulgin and Nichols 1978; Beck and Morgan 1986). In order to better characterize the psychostimulant actions of MDMA, rats were tested in a conditioned locomotion protocol with MDMA and the results compared with AMPH- and cocaine-induced conditioned locomotor responses.

Materials and methods

Subjects. Sixty-four male, albino Wistar rats (220–270 g at the start of the studies, Charles River, Kingston) were used as subjects. Rats were housed in groups of three with free access to food and water and maintained in a temperature controlled environment under a normal 12-h light cycle. All experiments were conducted during the light phase of this cycle. Before behavioral testing, rats were briefly handled by the experimenter (5 min).

Behavioral apparatus. Locomotor activity was measured in a bank of 16 wire cages, each cage 20 cm high $\times$ 25 cm wide $\times$ 36 cm long, with two horizontal infrared beams across the long axis 2 cm above the floor. Total photocell beam interruptions and crossovers were recorded by a computer every 10 min.

Drugs. $\pm$3,4-Methylenedioxymethamphetamine HCl (National Institute on Drug Abuse, Rockville, MD) and *d*-amphetamine sulfate (Sigma, St. Louis, MO) were mixed in saline and injected subcutaneously (SC) at the back of the neck, in a volume of 1 ml/kg body weight. Cocaine hydrochloride (Mallinckrodt Inc, St. Louis, MO) was mixed in saline and injected intraperitoneally (IP) in a volume of 1 ml/kg body weight.

Conditioned locomotion protocol. The conditioned locomotion protocol has been described previously (Gold et al. 1988b). Before day 1, each rat was habituated to the photocell cages overnight. Each day, eight rats were injected with the test drug and eight received saline immediately before being placed in the photocell cages. Small dishes of peanut butter were placed under every other cage and functioned as part of the conditioned stimulus complex by enhancing the saliency of the testing environment. At the conclusion of each session the rats were returned to their home cages. At this time each group was injected with the alternative drug solution, either saline or the test drug, to control for repeated drug exposure. Drug conditioning occurred on days 1–5. On day 6, all rats were injected with saline, placed in the photocell cages, and tested for a conditioned locomotor response.

In four separate experiments the conditioned locomotion protocol was repeated with AMPH 0.5 mg/kg (SC), cocaine 7.5 and 15 mg/kg (IP) or MDMA 5 mg/kg (SC) injected as the training drug (days 1–5). The experimental sessions for AMPH and MDMA lasted 120 min. Cocaine, a shorter acting drug, was tested for only 60 min. On day 6, all rats were injected with saline, placed in the photocell cages and tested for a conditioned locomotor response.

Data analysis. Ten minute totals for locomotor activity were subjected to a two-way analysis of variance (ANOVA) with repeated measures on the second factor, time.

Results

Daily injection of AMPH produced an unconditioned locomotor activation, measured by an increase in photocell beam interruptions, in the rats injected with AMPH immediately before the experimental session. Repeated daily injection of this dose of AMPH produced a statistically significant conditioned locomotor activation measured on the conditioning test day (day 6) when compared with subjects that received saline in the same environment [Fig. 1, upper left panel, main effect of drug, $F(1,14)=12.8$].

Similarly, daily injection of cocaine (7.5 and 15 mg/kg) produced an unconditioned locomotor activation, measured by an increase in photocell beam interruptions, in the rats injected with cocaine immediately before the experimental session (Fig. 1, lower left and upper right panels). Repeated daily injection of these doses of cocaine produced statistically significant conditioned locomotor activation measured on the conditioning test day (day 6) when compared with subjects that received saline in the same environment [Fig. 1, 7.5 mg/kg:$F(1,14)=8.8$; 15 mg/kg:$F(1,14)=17.5$]. Extinction of the conditioned response was then examined following the 15 mg/kg dose of cocaine by presenting the conditioned stimuli without the presence of the unconditioned stimulus. The conditioned response was evident not only on day 6 (reported above and in Fig. 1), but on days 7 [saline group $=405\pm51$, cocaine group $=731\pm61$; $F(1,14)=16.9$] and 8 [saline group $=550\pm45$, cocaine group 776 ± 53; $F(1,14)=10.6$]. On day 9 the two groups were no longer significantly different.

Daily injection of MDMA 5 mg/kg also produced an unconditioned locomotor hyperactivity measured by an increase in photocell beam interruptions (see Fig. 1, lower right panel). As with AMPH and cocaine, repeated daily injection of this dose of MDMA produced a statistically significant conditioned locomotor activation when compared to subjects who received saline in the same environment [see Fig. 1, $F(1,14)=7.8$]. The context-dependency of the conditioned response was demonstrated in that control rats who received the same exposure to the drug, on the same days but in a different environment, did not exhibit the conditioned response in the test cages. The time course of the unconditioned and conditioned locomotion was examined by comparing 10 min means for the drug- and saline-treated animals (Fig. 2). Although there was a significant main effect of drug for day 1 [$F(1,14)=13.6$], day 5 [$F(1,14)=5.8$] and day 6 (reported above), the time course of locomotor activity was significantly different only on day 1 [$F(11,154)=7.9$] and day 6 [$F(11,154)=4.7$; drug $\times$ time interactions]. It is also very interesting to note that the standard errors of the means were larger on day 5 than

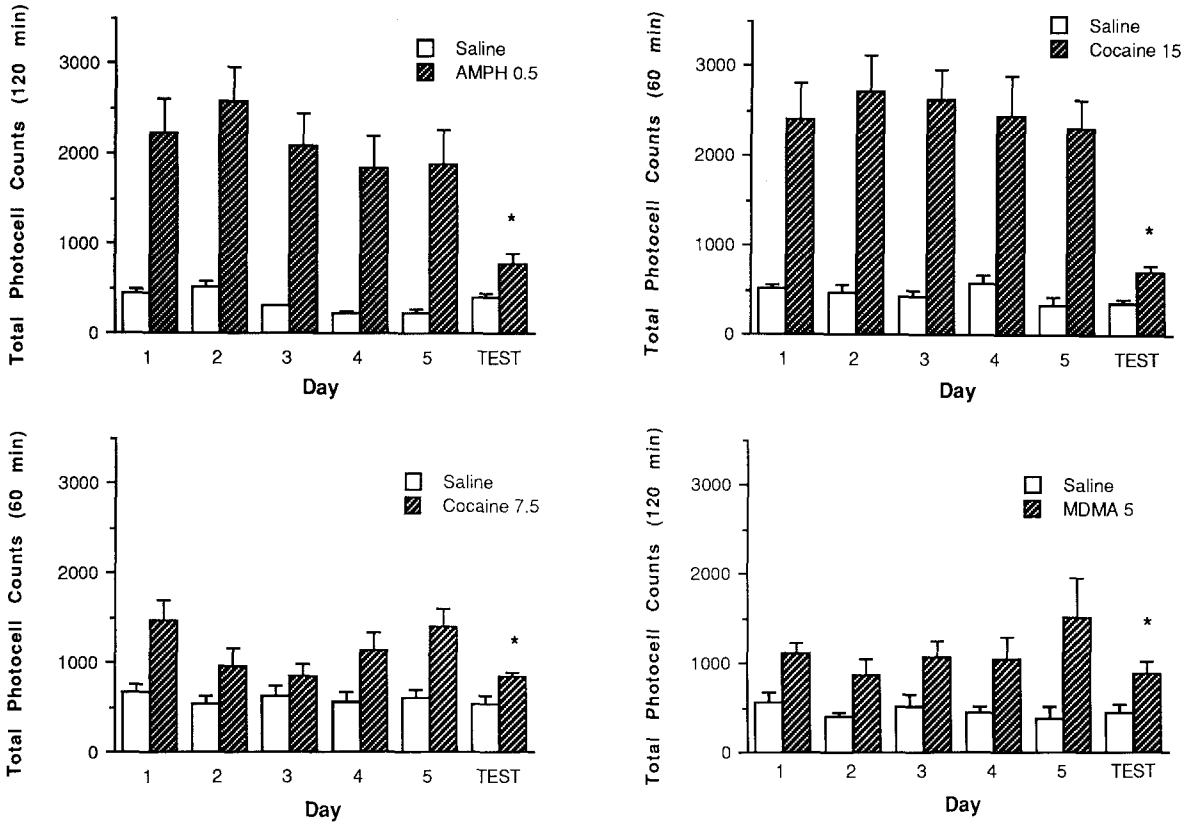

Fig. 1. The ability of AMPH (0.5 mg/kg), cocaine (7.5 mg/kg, 15 mg/kg) and MDMA (5 mg/kg) to produce conditioned locomotor responses. The unconditioned locomotor activity for saline and drug injected rats is portrayed for 5 days. On the test day (day 6) all rats were injected with saline and locomotor activity measured for 60 or 120 min. *Bars* represent total number of photobeam interruptions (mean ± SEM) during 60 or 120 min session for each group. $N=8$ rats/group, except day 3, $N=7$ for MDMA group due to equipment problem. $^*P<0.05$

day 1 or day 6 (refer to Figs. 1 and 2). An examination of the individual animals across days suggested subpopulations of rats with differing responses to MDMA which were maximal by day 5. A divergence in response tendencies following 5 mg/kg MDMA has also been observed in an analysis of the behavioral complexity induced by acute injections of MDMA (Paulus et al. 1988). For all experiments the effects on crossovers were not qualitatively different from beam interruptions and therefore are not reported.

Discussion

Conditioned responses have been demonstrated for a variety of drug effects (see Stewart and Eikelboom 1987 for an extensive review). Classic stimulant drugs have been shown to produce conditioned locomotion when tested in a way that environmental cues are repeatedly associated with the drug experience (Tilson and Rech 1973; Hinson and Poulos 1981; Post et al. 1981), and the present study extends these observations to MDMA. The abilities of AMPH and cocaine to produce conditioned locomotion were replicated in this report and MDMA tested in a conditioned locomotion protocol also engendered a conditioned effect. In addition, a gradual loss of the conditioned response produced by cocaine was demonstrated. This effect would be expected due to extinction and has been described in other classical conditioning situations (Kling 1971). Particularly notable in the present study with MDMA is the similarity in amount of locomotor activity generated by the unconditioned state (MDMA injection) and the conditioned state (saline injection following 5 days of exposure to MDMA in a distinctive environment). In contrast, amphetamine appears to produce much larger increases in locomotor activity in the unconditioned state than the conditioned state (this paper and see also Gold et al. 1988b). A comparison of two doses of cocaine included in this report suggests that this difference may be related to dose.

It has been suggested that conditioning of the activity effects of drugs may only reflect a return to prehabituation baseline of the animals such that the conditioned locomotion observed on the test day represents some kind of interference with apparatus habituation (Pickens and Dougherty 1971). However, it can be argued that this is not the case for several reasons. First, in an attempt to control for such habituation effects the rats are left in the photocell cages overnight prior to the beginning of drug testing, which allows them extensive exploration during their active phase. Also the locomotor path that a rat takes on the test day is more highly correlated with the path taken on the previous drug day than on the initial exposure to the experimental chamber (Gold et al. 1988c). Closer examination of the time course of the conditioned locomotion in this study, suggests that multiple responses may be occurring on the test day. Within the first 20 min, the rats look very much like the saline group on day 1 (compare MDMA rats in Fig. 2C with saline rats in Fig. 2A). However, the saline rats (day 1) show a time-related decrement in locomotion (within session habituation) while the MDMA rats (day 6)

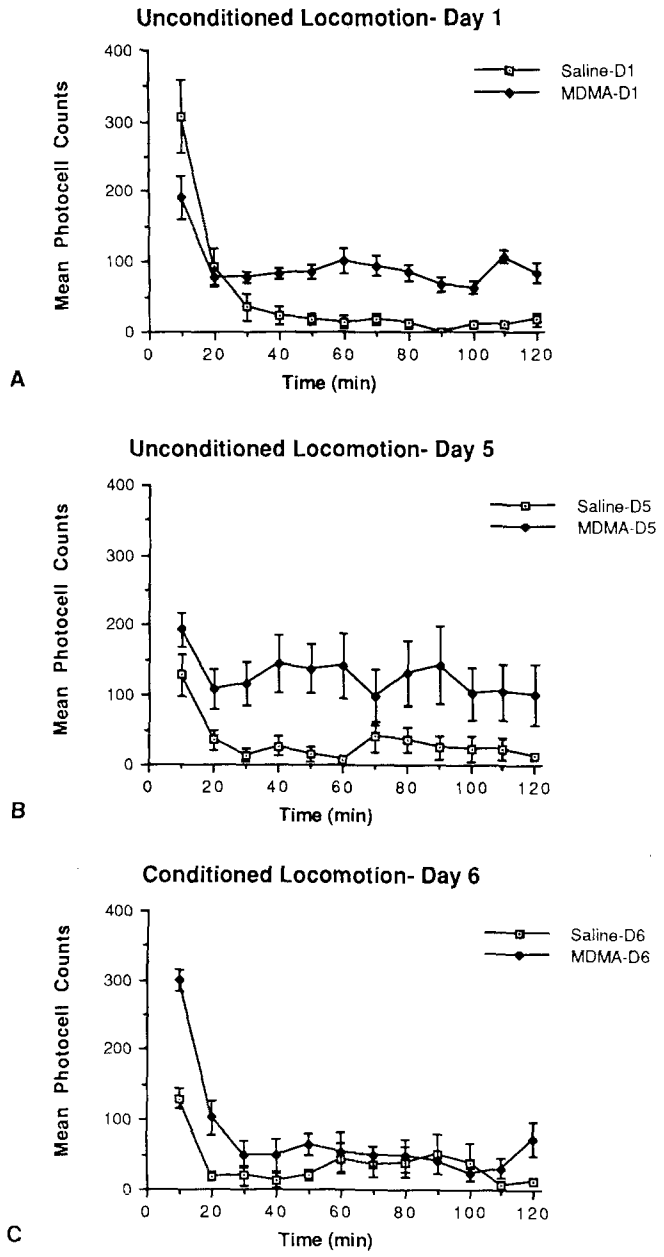

Fig. 2A–C. Time course of locomotor activity during 120 min test sessions. The time course of the unconditioned locomotion produced by MDMA is shown for days 1 (**A**) and 5 (**B**) of the drug conditioning trials. Conditioned locomotion is measured on day 6 following saline injection (**C**). Ten minute means ± SEM are plotted. $^*P<0.05$

exhibit a more elevated and stable level of locomotion for much of the session.

An additional criticism directed against studies that report classical conditioning of activity effects of drugs is that the results obtained may be an operant phenomenon rather than classical conditioning because the drugs used to condition activity increases also serve as reinforcers of operant activity (Pickens and Dougherty 1971). This criticism would also apply to the results obtained with MDMA in this study, as MDMA has produced positive results in investigations utilizing animal models which assess the reinforcing properties of drugs such as self-administration (Lamb and Griffiths 1987; see also Beardsley et al. 1986) and self-stimulation (Hubner et al. 1988). Indeed, there have been several reports documenting that MDMA is a recreationally used drug with significant potential for abuse (Beck and Morgan 1986; Peroutka 1987; Peroutka et al. 1988).

To separate the operant and classical conditioning effects, it would be necessary to demonstrate conditioned activity to drugs that do not also serve as reinforcers (Pickens and Dougherty 1971). However, the reinforcing effects of drugs may be inextricably linked with their ability to support classical conditioning. The relationship between the reinforcing properties and other properties of drugs may be especially difficult to separate when one considers drugs which stimulate locomotion since the locomotor activating properties of psychomotor stimulants have been hypothesized to be one aspect of their reinforcing properties (Mucha et al. 1982; Spyraki et al. 1982; Swerdlow and Koob 1984). In fact one theory, the psychomotor stimulant theory of addiction, suggests that the common denominator of a wide range of addictive substances is their ability to cause psychomotor activation (Wise and Bozarth 1987).

The importance of the environment in influencing drug craving and relapse has become an important area of research in the field of drug abuse. The environment and internal stimuli that have been repeatedly associated with heroin or alcohol consumption (O'Brien et al. 1976; Meyer 1988) or cocaine use (Gawin and Kleber 1986; Childress et al. 1988) become positive reinforcers that continue to shape individual behavior. In human addicts reports of craving are associated with both drug seeking behavior and the gratification achieved through suppression of mild abstinence signs. The ability of the environment or drug-related cues to stimulate craving is of particular concern, and animal models of environmentally conditioned drug responses may provide a useful experimental approach to study this problem. Studies of conditioned locomotor responses may be measuring an aspect of appetitive drug seeking behavior, which results from repeated drug state/environmental pairings. The conditioned increase in activity may reflect a conditioned appetitive response to the incentive properties of the drug similar to the locomotor activation associated with feeding in a given environment. In fact, Poncelet et al. (1987) demonstrated that AMPH conditioned locomotion showed a similar pharmacologic sensitivity with the behavioral excitation induced by the daily anticipation of food delivery. Alternatively, the conditioned increase in activity may reflect an absence of the primary drug effect in the environment previously paired with the drug state. In conditioned subjects, context-dependent abstinence may promote drug seeking behavior. More importantly, the ability of MDMA to produce a conditioned locomotor response may correlate with its abuse liability and reflect a potential behavioral toxicity.

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