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ORIGINAL INVESTIGATION

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Alterations in diurnal and nocturnal locomotor activity in rats treated with a monoamine-depleting regimen of methamphetamine or 3,4-methylenedioxymethamphetamine

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Abstract *Rationale:* The long-term neurochemical effects produced by the repeated administration of methamphetamine (MA) and 3,4-methylenedioxymethamphetamine (MDMA) are well documented; however, the functional consequences have not been clearly defined. *Objective:* The present study was designed to investigate whether rats treated with a monoamine-depleting regimen of MA or MDMA exhibit disturbances in locomotor activity during the diurnal and nocturnal cycles. *Methods:* Rats were treated with the vehicle or a monoamine-depleting regimen of MA or MDMA (10 mg/kg, IP, every 2 h for four injections on a single day). One week after drug treatment, the rats were placed in residential activity chambers and their locomotor activity was monitored for the next 7-day/night cycles. *Results:* MA-treated rats exhibited depletions of striatal dopamine and serotonin content of approximately 70%, whereas MDMA-treated rats showed depletions of striatal serotonin content of approximately 50%. Rats treated with MA demonstrated a significant reduction in diurnal, but not nocturnal, locomotor activity, whereas MDMA-treated rats exhibited significant reductions in both diurnal and nocturnal locomotor activity. Analysis of the difference in activity between the nocturnal and diurnal cycles revealed that MA-treated animals exhibited a significantly greater change in activity as compared to that observed in vehicle- and MDMA-treated rats. *Conclusions:* Although it is unknown whether the adaptations in locomotor activity observed in MA- and MDMA-treated rats are due to the loss of dopamine and/or serotonin, these data suggest that the administration of a monoamine-depleting regimen of MA or MDMA results in alterations in light-cycle-dependent locomotor activity.

Keywords Methamphetamine · MDMA · Neurotoxicity · Locomotor activity · Diurnal cycle · Nocturnal cycle

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Introduction

Methamphetamine (MA) and its derivative 3,4-methylenedioxymethamphetamine (MDMA) are psychostimulant drugs of abuse. Although the chemical structures of MA and MDMA are similar, the neurochemical consequences of the drugs are different. The administration of MA produces long-term reductions of dopaminergic and serotonergic axonal markers (Seiden et al. 1975), whereas the administration of MDMA produces selective long-term reductions of serotonergic axonal markers (Wagner et al. 1979; Morgan and Gibb 1980; Ricaurte et al. 1980; Stone et al. 1986; Battaglia et al. 1987, 1991; Commins et al. 1987; O'Callaghan 1991; O'Dell et al. 1991). The depletion in serotonin content induced by MA and MDMA occurs within the striatum as well as several other forebrain regions; however, the MA-induced loss of dopamine occurs primarily within the striatum (Seiden et al. 1988; Ohmori et al. 1993). There is evidence of axonal damage in both MA- and MDMA-treated animals (Ricaurte et al. 1984), although MA has also been shown to induce astrogliosis (Pu and Vorhees 1993; Broening et al. 1997) and silver-staining indicative of nerve terminal degeneration (Ricaurte et al. 1982).

Although the neurochemical consequences of MA- and MDMA-induced monoamine depletions are well established, less is known about potential behavioral consequences that accompany these changes. Recently, Kita et al. (1998) have reported that animals treated with a neurotoxic regimen of MA are hyperactive during the nocturnal cycle. However, we have reported that

MA-treated rats exhibit a significant reduction in locomotor activity during a 1-h habituation period prior to the administration of a challenge injection of MA (Wallace et al. 1999). It was the intent of the present study to determine whether the short-term hypoactivity we observed in MA-treated animals persists during repeated diurnal and nocturnal cycles and to compare such effects to those of MDMA.

Material and methods

Animals

Male Sprague-Dawley CD rats (225–250 g) were obtained from Charles Rivers Laboratories (Portage, Mich., USA) and were housed two to three per cage with food and water ad libitum. Animals were maintained on a 12-h light/dark cycle for 1 week prior to experimental treatment. Rats were housed in a vivarium fully accredited by the Association for the Assessment and Accreditation for Laboratory Animal Care. The protocol for this research was approved by the Institutional Animal Care and Use Committee.

Treatment procedure

Animals were randomly assigned to receive IP injections of (+)-MA hydrochloride (Sigma, St Louis, Mo., USA) 10 mg/kg every 2 h for a total of four injections (expressed as the salt), (±)-MDMA hydrochloride (National Institute on Drug Abuse, Bethesda, Md., USA) 10 mg/kg IP every 2 h for a total of four injections (expressed as the salt), or 0.9% NaCl (vehicle) IP every 2 h for a total of four injections. Body temperatures were periodically recorded (Thermistor thermometer, Cole-Parmer Instruments, Vernon Hills, Ill., USA) throughout the dosing paradigm based on the known importance of hyperthermia in the development of long-term monoamine depletion (Bowyer et al. 1992, 1994). Animals that reached or exceeded a core body temperature of 41.5°C were wetted, hydrated and placed in a ventilated cage to prevent lethality associated with core temperatures exceeding 42°C.

Behavioral measurements

Residential activity chambers

Locomotor activity and the number of zone crossings were monitored in 30 residential activity chambers. The activity chambers consisted of a clear, acrylic enclosure measuring 40.6×40.6×38.1 cm containing a 40.6×40.6 cm photobeam array to measure activity (San Diego Instruments, San Diego, Calif., USA). Each activity chamber was housed inside ventilated, sound-attenuated cabinets (Cline Builders, Covington, Ken., USA) that contained a light to maintain the 12-h light/dark cycle (0600/1800 hours). Rats were provided with ad libitum food and water throughout the experiment.

Behavioral testing

One week after the initial treatment, rats were transported to the room containing the residential activity chambers at 0900 hours and allowed to acclimate for approximately 3 h before being placed individually into a residential activity chamber. The animals were allowed to habituate for an additional 2 h in the chambers before the activity monitoring began at 0200 hours. Light cycles were set for light onset at 0600 and offset at 1800 hours. Photocell interruptions were recorded every 15 s and compiled in 1-h intervals for 7 consecutive days for a total of 170 intervals. Two types of locomotion were recorded: total distance and zone crossings. The chamber was divided into four equal zones with four photobeam sets for each zone. Movements across zone boundaries were recorded as crossings and movements between successive photobeams were recorded as total distance. The activity counting algorithm was based on the movement of the average position of the animal by a minimum of 2.5 cm. Thus, if an animal occupied a space encompassing five photobeams at any given moment, its average position was represented by the third photobeam in this sequence. A movement was scored only if its net movement was such that its average position shifted to either the second or fourth photobeam in this sequence.

Biochemical measurements

Fifteen to 17 days after receiving the initial drug regimen (i.e., 1–3 days after rats were removed from the residential activity chambers), rats were killed by decapitation, and the brains rapidly removed. The neostriata were dissected from 1.0 mm coronal sections, frozen on dry ice, and stored at –70°C until assayed. Tissue samples were homogenized in 0.2 N perchloric acid. Following centrifugation (16,000 *g* for 7 min), the supernatant was injected onto a C18 reverse-phase column (Phenocenex, Torrance, Calif., USA) connected to a Coulochem II detector (ESA, Bedford, Mass., USA). The mobile phase used for the analysis of dopamine and serotonin consisted of 35 mM citric acid, 54 mM sodium acetate, 50 mg/l disodium ethylenediamine tetraacetate, 70 mg/l octanesulfonic acid sodium salt, 100 µl/l triethylamine, 6% acetonitrile, 3% methanol, pH 4.2, set at a flow rate of 0.4 ml/min. Peak heights were quantified using a Hewlett-Packard integrator.

Statistics

Locomotor activity was analyzed in two ways. The first analysis was a three-treatment by 168-interval (repeated measure) ANOVA. The second analysis was a three-treatment by two light-cycle by 7-day ANOVA with light-cycle and day being repeated measure factors. Interactions were further analyzed by simple-effect ANOVA, using Greenhouse-Geisser *F*-ratios wherever the sphericity assumption was not met. Post hoc group comparisons used the pairwise method of Duncan. For tissue monoamines, a one-way ANOVA was used followed by Duncan group comparisons.

Results

MA- and MDMA-induced monoamine depletions

Rats that received MA had a significant [$F(2,45)=95.5$; $P<0.001$] 69% depletion in neostriatal dopamine concentration as compared to vehicle- and MDMA-treated rats (Table 1). In addition, rats that received either MA or

Table 1 MA- and MDMA-induced striatal dopamine and serotonin depletions. Rats were treated with MA (10 mg/kg, IP, every 2 h for a total of four injections), MDMA (10 mg/kg, IP, every 2 h for a total of four injections) or vehicle, and were killed 15–17 days later. Striatal dopamine and serotonin concentrations are represented as the mean±SEM of each group

	Dopamine (ng/mg tissue)	Serotonin (ng/mg tissue)
Vehicle (*n*=13)	10.1±0.6	0.35±0.03
MA (*n*=20)	3.1±0.3*,#	0.11±0.01*,#
MDMA (*n*=15)	9.8±0.5	0.18±0.02*

*,# Significantly different from vehicle- or MDMA-treated rats, respectively ($P<0.05$) (Duncan's)

MDMA demonstrated a significant loss of neostriatal serotonin concentrations as compared to vehicle-treated rats [$F(2,45)=34.0$; $P<0.001$]. A posteriori group comparisons revealed that MA-treated rats exhibited a significantly greater loss of serotonin than rats treated with MDMA ($P<0.05$).

Effects of MA and MDMA on diurnal and nocturnal locomotor activity

Spontaneous locomotor activity (total distance) of vehicle-, MA- and MDMA-treated rats was recorded during the diurnal and nocturnal cycles for 7 consecutive days. Analyses of the data by light/dark cycles or by 1-h intervals showed the same pattern of effects; thus only the light/dark cycle analyses are presented. The main effect of treatment (i.e., MA, MDMA or vehicle) [$F(2,47)=238.0$; $P<0.0001$], and the treatment×cycle [$F(2,47)=6.69$; $P<0.01$] interaction were significant; however, the interaction of treatment×day was not significant. Further analyses of the treatment×cycle interaction indicated a significant effect for both diurnal [$F(2,47)=18.52$; $P<0.001$] and nocturnal [$F(2,47)=8.64$; $P<0.001$] activity. A posteriori group comparisons confirmed that animals treated with MA or MDMA were significantly hypoactive during the diurnal cycle as compared to control animals ($P<0.01$) (Fig. 1). Moreover, MDMA-treated animals were significantly less active during the nocturnal cycle as compared to vehicle-treated or MA-treated rats ($P<0.01$). The effects of MA and MDMA on the diurnal and nocturnal activity of rats were evident throughout the entire seven-light/dark cycles of the experiment (Fig. 2).

Change in locomotor activity during the nocturnal versus diurnal cycles

Activity for the seven light-dark cycles was combined for each treatment group, and the difference between the nocturnal and diurnal cycles for each group was calculated. The main effect of treatment [$F(2,47)=6.69$; $P<0.01$] was significant. Subsequent post hoc analyses revealed that the difference between the nocturnal and diurnal activity of MA-treated animals was significantly ($P<0.01$) greater than that for vehicle- or MDMA-treated animals (Fig. 3).

Zone crossings

The number of zone crossings each animal made within the four quadrants of the activity chamber also was measured. The main effects of treatment [$F(2,47)=3.74$; $P<0.05$] and the treatment×cycle interaction [$F(2,47)=7.40$; $P<0.01$] were significant. The general pattern of effects was similar to that observed for total distance; however, a posteriori group comparisons showed that no significant differences were observed between either MA- and MDMA-treated animals and vehicle-treated animals during either the nocturnal (mean crossovers±SEM: vehicle 72.1±10.8; MA 98.1±12.0; MDMA 48.6±7.6) or the diurnal (mean crossovers±SEM: vehicle 30.6±8.5; MA 31.8±4.1; MDMA 19.1±7.0) cycles. This was due to the fact that after day-1 zone crossings were low throughout the remaining 6-day test period, creating a floor effect in terms of detecting drug-induced decreases in crossovers.

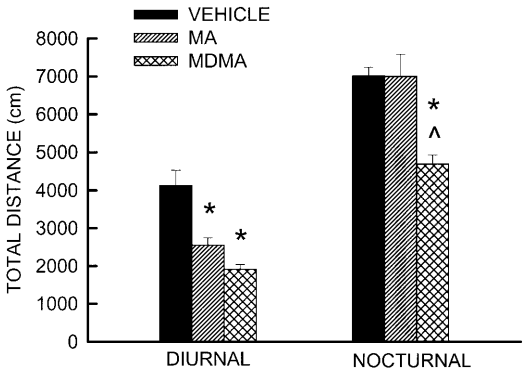

Fig. 1 Effects of a monoamine-depleting regimen of MA or MDMA on spontaneous locomotor activity. Rats were treated with MA (10 mg/kg, IP, every 2 h for a total of four injections), MDMA (10 mg/kg, IP, every 2 h for a total of four injections) or vehicle. Seven days later, rats were placed in residential activity chambers and locomotor activity (i.e., total distance) was monitored during both the diurnal and nocturnal cycles for 7 days. Values represent the mean±SEM of each group for either the diurnal or nocturnal cycles summed across 7 days. *,^Significantly different from vehicle- and/or MA-treated rats, respectively ($P<0.05$)

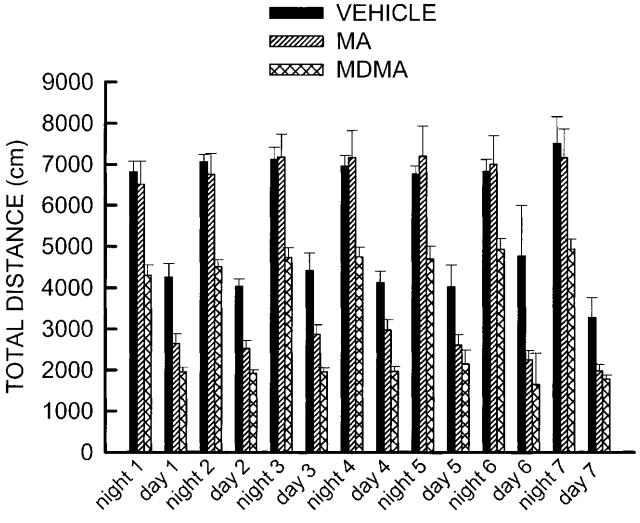

Fig. 2 Effects of a monoamine-depleting regimen of MA or MDMA on spontaneous locomotor activity across seven diurnal/nocturnal cycles. Rats were treated with MA, MDMA, or vehicle (as in Fig. 1). Seven days later, rats were placed in residential activity chambers and locomotor activity (i.e., total distance) was monitored during both the diurnal and nocturnal cycles for 7 days. Values represent the total distance traveled in each group per day and night cycle

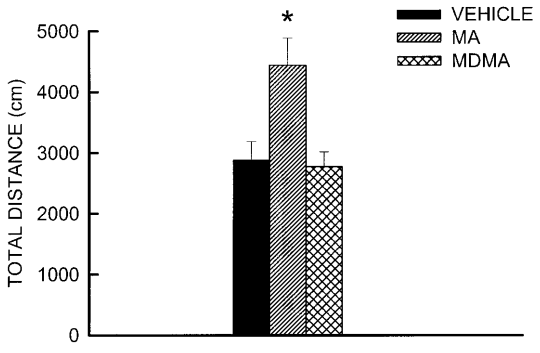

Fig. 3 Difference in spontaneous locomotor activity between nocturnal and diurnal cycles in MA- and MDMA-treated animals. Rats were treated with MA, MDMA, or vehicle (as in Fig. 1). Seven days later, rats were placed in residential activity chambers and locomotor activity (i.e., total distance) was monitored during both the diurnal and nocturnal cycles for 7 days. The difference in activity calculated across the seven nocturnal and diurnal cycles was calculated for each treatment group. *Significantly different from vehicle- and MDMA-treated animals. Values represent the mean±SEM for each group

Discussion

In the present study, the administration of a monoamine-depleting regimen of MA or MDMA to rats resulted in alterations in spontaneous locomotor activity. It has been reported previously that animals treated with this same regimen of MA exhibit a significant decrease in spontaneous locomotor activity during a 1-h habituation period begun 7 days post-treatment (Wallace et al. 1999). The hypoactivity observed in those animals occurred during the light cycle and was similar to the reduction in diurnal activity observed in the present study. The observed hypoactivity may be attributed, in part, to the MA-induced depletion of dopamine. It is generally believed that dopaminergic neurotransmission in the striatum is responsible for locomotor activity (Creese and Iversen 1974; Kelly et al. 1975; Kelly and Iversen 1976). Moreover, lesioning the mesolimbic tract with 6-hydroxydopamine has been reported to result in a significant decrease in the spontaneous activity of rats (Joyce et al. 1983).

The results observed in the present study are not in agreement with those obtained by Kita et al. (1998), who reported that animals treated with a neurotoxic regimen of MA are hyperactive during the nocturnal cycle. There are several possible explanations for the discrepancies in the results between the two studies. Kita et al. only report transient dopamine and serotonin depletions in MA-treated animals, i.e., dopamine and serotonin contents were reduced 3 days, but not 7 days following treatment. We report approximately 70% depletions in striatal dopamine and serotonin concentrations in MA-treated rats at 15–17 days post-treatment. In addition, Kita et al. began monitoring activity 2.5 h after the last injection of MA, whereas we did not begin to monitor the activity of the animals until 7 days post-treatment. Finally, the strain of rats in the two studies (Sprague-Dawley versus Wistar) was also different.

In the present study, the hypoactivity observed in animals treated with MA or MDMA may be due to the repeated exposure of animals to MA or MDMA (i.e., 10 mg/kg every 2 h for four injections). Robinson and Camp (1987) reported a decrease in basal locomotor activity in rats that have become sensitized to *d*-amphetamine. Although Robinson and Camp (1987) report a more pronounced deficit in activity during the nocturnal cycle in *d*-amphetamine sensitized animals, a significant reduction in spontaneous locomotor activity occurred during the diurnal cycle as well. Consistent with these results, it has been demonstrated recently that the repeated administration of MA or MDMA produces properties of behavioral sensitization in rats (Kalivas et al. 1998; Wallace et al. 1999, 2001; Horan et al. 2000).

In addition to the potential dopaminergic involvement in the hypoactivity of MA-treated rats, serotonin also has been implicated in modulating locomotor activity (Williams and Azmitia 1981; Jacobs and Azmitia 1992). However, it has been reported that 5,7-dihydroxytyptamine lesions of the fornix-fimbria, medial forebrain bundle or median raphe nucleus produce hyperactivity in rats (Srebro and Lorens 1975; Geyer et al. 1976; Bouhuys and Van Den Hoofdakker 1977; Mackenzie et al. 1978; Williams and Azmitia 1981). Therefore, the hypoactivity observed in animals treated with a serotonin-depleting regimen of MA or MDMA is not likely to be due to a decrease in the serotonergic modulation of locomotor activity alone.

Alternatively, the suppression of spontaneous locomotor activity in MA- and MDMA-treated rats may be due to the reported regulatory effects of serotonin on the sleep-wake cycle (Williams and Azmitia 1981; Portas et al. 2000). A positive relationship exists in the sleep-wake cycle between the discharge rate of serotonergic neurons in the dorsal raphe nucleus and spontaneous motor activity (Cespuglio et al. 1981; Lydic et al. 1983; Shima et al. 1986). Moreover, the firing patterns of dorsal raphe neurons are higher during the wake cycle than during non-REM sleep, and absent during REM sleep (McGinty and Harper 1976; Trulson and Jacobs 1979; Cespuglio et al. 1981; Lydic et al. 1983). Therefore, the MA- or MDMA-induced loss of serotonin content could result in the dysregulation of the sleep-wake cycle, and a subsequent alteration in locomotor activity. Consistent with this idea, Allen et al. (1993) have reported a decrease in both non-REM sleep and total sleep in human MDMA users. Although MA- and MDMA-treated rats exhibited alterations in spontaneous locomotor activity, there were no apparent changes in the onset or offset of the activity, i.e., activity in all animals was appropriately entrained for lights-off and lights-on phase transitions.

It is interesting to note the different patterns of activity exhibited by animals treated with either MA or MDMA. MA-treated animals were hypoactive during the diurnal but not nocturnal cycles, whereas MDMA-

treated animals were consistently hypoactive throughout the day/night cycles. Although MA and MDMA are structurally similar, the present data illustrate that the administration of a monoamine-depleting regimen of MA or MDMA not only results in differential neurochemical depletions, but also differential behavioral consequences.

Rats in all treatment groups showed an elevation in activity during the night cycle versus the day cycle. However, analysis of the difference in the total activity during the nocturnal and diurnal cycles revealed that MA-treated animals exhibited a significantly larger overall change in activity between the nocturnal and diurnal cycles as compared to that observed in vehicle- and MDMA-treated rats. This pattern of activity may be due to the activation of compensatory mechanisms as a result of the MA-induced loss of dopamine. It has been proposed that following damage to the nigrostriatal dopamine system, the remaining dopamine neurons compensate in order to maintain normal function (Stricker and Zigmond 1976). Consistent with this idea, an increase in dopamine synthesis and in the amount of dopamine released during each impulse has been observed in 6-hydroxydopamine- and MPTP-lesioned animals (Lloyd et al. 1975; Zigmond et al. 1984; Onn et al. 1986; Snyder et al. 1986; Stachowiak et al. 1987). Although basal extracellular dopamine concentrations have been reported to be equivalent between animals treated with a monoamine-depleting regimen of MA and control animals, these studies only measured extracellular dopamine during the diurnal cycle (Cass 1997; Cass et al. 1998; Wallace et al. 1999). Paulson and Robinson (1994) have reported that the extracellular concentrations of dopamine in the dorsolateral caudate nucleus are significantly increased during the nocturnal cycle as compared to the diurnal cycle. Therefore, it may be that during the nocturnal cycle MA-treated animals release an increased amount of dopamine thereby normalizing their nocturnal activity levels.

In summary, the administration of a monoamine-depleting regimen of MA or MDMA to rats results in persistent alterations in spontaneous locomotor activity. It is presently unclear whether the behavioral changes can be attributed to the monoamine-depleting effects of these psychostimulants; however, these results suggest that persistent modifications in behavior occur in rats exposed to MA and/or MDMA at monoamine-depleting doses. In addition, these results may serve as a useful behavioral model for investigating functional consequences of MA and MDMA administration.

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