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# Diurnal differences in amphetamine sensitization

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**Abstract**

A computerized motor activity monitoring system was used to investigate the development and time dependence of sensitization to repeated exposure of amphetamine. Male Sprague–Dawley rats were acclimated for 7 days to light/dark cycle (0700 h:1900 h) in the testing room, and were then housed in the test cages for 16 days of continuous recording. The locomotor responses to s.c. administration of amphetamine (0.3, 0.6, or 1.2 mg/kg) were compared before and after five daily injections of 0.6 mg/kg of amphetamine. Different groups of rats were administered drug at either 0800 h, 1400 h, 2000 h, or 0200 h. The locomotor indices studied were total distance and vertical activity. Sensitization was more pronounced for total distance (i.e., forward ambulation) than for vertical activity (i.e., rearing), and its expression was dependent on the challenge dose. Sensitization was also time-dependent, with the strongest sensitized response occurring during the middle of the dark cycle (0200 h). Repeated administration of amphetamine (0.6 mg/kg) did not cause post-stimulant depression as has been seen at higher doses. 

*Keywords:* Amphetamine; Behavioral sensitization; Psychomotor stimulant; Motor activity; Circadian

## 1. Introduction

Intermittent administration of psychomotor stimulants, such as amphetamine or cocaine, can produce either behavioral sensitization (Post and Rose, 1976; Robinson and Becker, 1986; Kalivas et al., 1993), or tolerance (Ellison and Eison, 1983; Fischman, 1987), to their locomotor and stereotypic effects in animals. Most studies on behavioral sensitization to stimulants were performed in the rat and were conducted during the light cycle (i.e., the sleep time of the rat), with little attention given to other times of the day, even though motor behavior varies considerably throughout the light/dark cycle (Honma et al., 1986; Paulson and Robinson, 1994; Gaytan et al., 1996a). Many drugs, including stimulants, have also been shown to vary in their pharmacokinetics and their efficacy throughout the day (Scheving et al., 1968, 1994; Smolensky and D'Alonzo, 1993). Additionally, the neurotransmitters reported to be involved in the regulation of motor activity, as well as in the response to stimulants, have been shown to exhibit circadian rhythms that peak during the middle of the dark cycle, with fluctuations in both neurotransmitter levels and receptor densities of dopamine, α- and β-adrenergic systems (Lemmer and Berger, 1978; Lemmer et al., 1985; Kafka et al., 1981, 1985; Bruinink et al., 1983). Circadian fluctuations in these neurotransmitters may result in differences throughout the day in the motor response of animals to single and repeated stimulant administration.

Only a few reports have tested the hypothesis that sensitization to stimulants may vary throughout the day, reporting tolerance to the stimulatory effects of continuously infused amphetamine during the light phase, but not during the dark phase (Martin-Iverson and Iversen, 1989). Moreover, daytime tolerance and nocturnal sensitization were reported to continuous administration of (+)-4-propyl-9-hydroxynaphthoxazine (PHNO), a direct dopamine receptor agonist selective for dopamine $D_2$ receptor subtype, while intermittent administration of PHNO produced sensitization during the light phase (Martin-Iverson et al., 1987, 1988). Consequently, this investigation focused on determining whether there are diurnal differences in the dose-related effects of amphetamine between naive and sensitized rats, and whether sensitization to the locomotor effects of amphetamine will differ if a low dose is intermittently administered at different times throughout the light/dark cycle.

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To control for the circadian differences in baseline activity prior to drug administration, this study followed a protocol similar to that used in previous investigations of diurnal differences in the dose-related effects of amphetamine and methylphenidate (Gaytan et al., 1997, 1998). Continuous computerized recording system (24 h for 16 days) was used to circumvent limitations of direct human observation (Ellinwood and Balster, 1974; Robbins, 1977; Fray et al., 1980; Rebec and Bashore, 1984; Donat, 1991). Two different motor indices were utilized (Gaytan et al., 1997, 1998), since the effects of stimulants on motor behavior are complex, and the use of one dimensional recordings, such as latch-counts, or horizontal activity, might conceal the presence of distinct drug effects (Dougherty et al., 1990; Donat, 1991; Paulus and Geyer, 1993). The doses of amphetamine used in this study were chosen from previous dose-response experiments (Gaytan et al., 1998) ranging from a low locomotor effect at 0.3 mg/kg of amphetamine to a maximal effect on locomotion following 1.2 mg/kg of amphetamine. Finally, animals were housed in the test cages throughout the experiment to minimize the influence of novel environment or context-dependency on the development of sensitization (Segal and Mandell, 1974; Post et al., 1981; Badiani et al., 1995).

In summary, the present study used three different amphetamine challenge, and re-challenge, dosages to investigate whether the expression of sensitization to the locomotor effects of amphetamine was dose-dependent. Moreover, the experimental protocol was also run at the beginning and middle of both the light and dark phase (i.e., four different times of administration) to test the influence of circadian timing of administration on the development of sensitization to amphetamine.

## 2. Material and methods

Male Sprague–Dawley rats ($n = 108$) weighing from 180 to 225 g were housed in the experiment room in groups of four at an ambient temperature of $21 \pm 2$°C and relative humidity of 37–42%. Animals were maintained on a 12:12 light/dark schedule (light on at 0700 h) for a minimum of 7 days before experimentation in order to internally synchronize their neuroendocrine systems; food pellets and water were supplied ad libitum throughout the experiment. On the last day of acclimatization, rats were weighed and individually housed in the test cages (i.e., these test cages became their home cages), and allowed a minimum of 12 h of accommodation before 16 days of continuous recording of locomotor activity began.

### 2.1. Apparatus

The computerized animal activity monitoring (CAAM) system has been described in detail (Dougherty et al., 1990; Gaytan et al., 1996b). In short, the activity chambers consist of clear acrylic open field boxes ($40.5 \times 40.5 \times 31.5$ cm) with two levels of infrared motion sensors. The first and second levels of sensors were 6 and 12.5 cm, respectively, from the cage floor. The activity monitoring system checked each of the beams at a frequency of 100 Hz to determine whether beams were interrupted. The interruption of any beam was recorded as an activity score. Interruptions of two or more consecutive beams separated by at least one second apart was recorded as a movement score. Cumulative counts were compiled and downloaded every 10 min into OASIS data collection program (Accuscan, Columbus, OH), and organized into several motor indices.

Due to the similarity of data between the different motor indices such as horizontal activity, only the following two motor indices were presented—total distance, and vertical activity, which measure the specific motor behaviors of forward ambulation and rearing, respectively, and were used to assess these two locomotor effects of amphetamine.

### 2.2. Time control and treatment groups

After 7 days of acclimation, and 12 h of accommodation to test cages, motor activity was recorded continuously and summed into 10 min bins throughout the 24 h cycle for 16 days. One group ($n = 12$) was not handled throughout the 16 experimental days and served as time control. The rest of the animals were divided into 12 separate groups ($n = 8$ each) which received the following injection regimen at either 0800 h, 1400 h, 2000 h, or 0200 h (i.e., three different challenge dose groups at each time of administration for a total of 12 experimental groups).

Two days of baseline recording (days 1–2) were averaged together, since they exhibited similar activity, and served as baseline activity for comparison with treatment data. On day 3, all experimental rats received a s.c. saline injection and served as their own handling controls. Rats were then randomly assigned on day 4 (challenge day) to receive s.c. injections of either 0.3, 0.6, or 1.2 mg/kg of amphetamine sulfate (Sigma) at their assigned time of day. The three challenge doses were used as a measure of the dose-related effects of amphetamine on the drug-naive animal. On days 5 to 9, all groups received s.c. injections of 0.6 mg/kg amphetamine once a day to induce a sensitized response (i.e., repetitive treatment phase). Recording was continued for 5 days without treatment (days 10–14) to allow for washing out of any metabolites during this time, and to test for any persistent effects on baseline activity caused by the repeated administration of amphetamine. On day 15, each dose group was re-challenged with the same dose as on day 4 to test for the expression of a sensitized response to amphetamine by comparing the dose-related response of the treated animal (day 15) to that of the drug-naive response (day 4). An additional day of post treatment monitoring (day 16) was also collected. All injections were of equal volume (0.8 ml).

### 2.3. Data analysis

The effect of amphetamine was considered as the difference between activity during the initial 2 h after injection and the same rat's average baseline (days 1 and 2) at the same time of day. The handling effect (i.e., saline injection on day 3), which increased activity from baseline for only the first 10 min, was also subtracted from the effect of drug administration. In a previous saline control study conducted in our laboratory (Bjork et al., 1998), it was found that the handling effect diminished by the end of the repetitive treatment phase (day 9) and there was also no handling effect on re-challenge (day 15). However, since the increase caused by saline injection occurs only in the initial 10 min, we subtracted the initial 10 min of handling effect from both the drug-naive response on day 4, and the response to re-challenge on day 15.

To test for a sensitized response for each dose group and motor index, data for the first 2 h after injection on day 4 (i.e., twelve sequential 10 min samples) were compared to the response on day 15, using a repeated measures analysis of variance (ANOVA) with two between group factors and two within group factors [i.e., 4 (time of administration) × 3 (dose) × 2 (day) × 12 (10-min interval)]. This was followed with either Fischer's least square's difference (LSD) test or another repeated measure ANOVA.

In addition, to identify any persistent effects caused by repeated exposure to amphetamine, the 12 h total counts for each index during the light and dark phase of baseline (days 1 and 2 averaged) and the period following repeated treatment (days 12 to 14 averaged) were compared using repeated measures ANOVA. All three dose groups ($n = 24$) were combined at each time of administration for this analysis since all three dose groups received the same treatment from days 5 to 9 (i.e., 0.6 mg/kg). Significance for comparison was set at $P < 0.05$.

## 3. Results

### 3.1. Time control

The total distance traveled in cm during the dark phase (12 h) and light phase (12 h) of days 1 through 16, and the hourly pattern of this activity (24 h) on representative days are shown in Fig. 1. Baseline activity was stable from day to day during both the dark and light phase (Fig. 1A and B). The hourly histogram (Fig. 1C) shows a clear difference in activity levels between the rats' inactive (light phase) and active periods (dark phase), with a fivefold increase occurring between the photoperiods. Moreover, there was a consistent circadian rhythm of activity throughout the day. Similar observations were obtained for vertical activity. In summary, the time control group displayed stable daily baseline levels of activity, as well as a consistent circadian pattern of activity, in all the indices recorded over the length of the study.

### 3.2. Effect of different timing of amphetamine administration

The dose-related effects of amphetamine on total distance in the first 2 h after injection on day 4 (naive) and day 15 (treated) are presented in Fig. 2 for all four times of drug administration studied (either 0800 h, 1400 h, 2000 h, or 0200 h). There was a dose-dependent increase in the effect of amphetamine at all times of administration which resulted in a significant main effect of dose ($F(2,84) = 30.8$; $P < 0.0001$) as well as a significant interaction between dose and interval sample [i.e., a change in the time course between doses ($F(22,924) = 4.96$; $P < 0.0001$). The middle amphetamine dose of 0.6 mg/kg significantly increased total distance ($P < 0.01$) more than the lowest dose (0.30 mg/kg), while the largest dose (1.2 mg/kg) elicited a significantly higher response ($P < 0.001$) than the other two doses studied (Fig. 2). There was no significant main effect for the time of administration, as well as no significant interaction between dose and the time it was studied, indicating that the dose-related effects of amphetamine were similar at all four times of administration.

There was, however, a significant main effect of day ($F(1,84) = 26.56$; $P < 0.0001$), as well as a positive interaction between the injection day and the time of amphetamine administration ($F(3,84) = 3.12$; $P < 0.05$), indicating that, although sensitization occurred, it differed between the times of drug administration. Post-hoc analysis revealed that the dose-related effects of amphetamine injection were significantly increased between challenge day 4 and re-challenge day 15 only at 0200 h and at 0800 h ($P < 0.001$; $P < 0.01$, respectively). At both times of administration (0200 h and 0800 h), the sensitized response on day 15 was characterized by an increase in the magnitude of the dose-related effects of amphetamine and not a change in the dose-response.

In the middle of the dark cycle (0200 h), the response to both 0.3 mg/kg and 1.2 mg/kg in the initial 2 h following drug administration on day 15 were significantly increased ($P < 0.05$; $P < 0.001$, respectively) when compared to the response of the drug-naive animal on day 4 (Fig. 2A). At the beginning of the light phase (0800 h), there was an augmented response on day 15 compared to day 4 ($P < 0.05$) for the two lower doses of amphetamine (0.3 and 0.6 mg/kg), but not for the highest dose (Fig. 2A).

Administration of amphetamine at 1400 h showed no significant difference in the effects of amphetamine on total distance between day 4 and day 15 for any of the dose groups studied (Fig. 2A). However, post-hoc comparisons of data from the groups injected at 2000 h revealed that there was a significant increase in the effect of the lowest dose of amphetamine (0.3 mg/kg) on day 15 when compared to day 4 ($P < 0.05$; Fig. 2A).

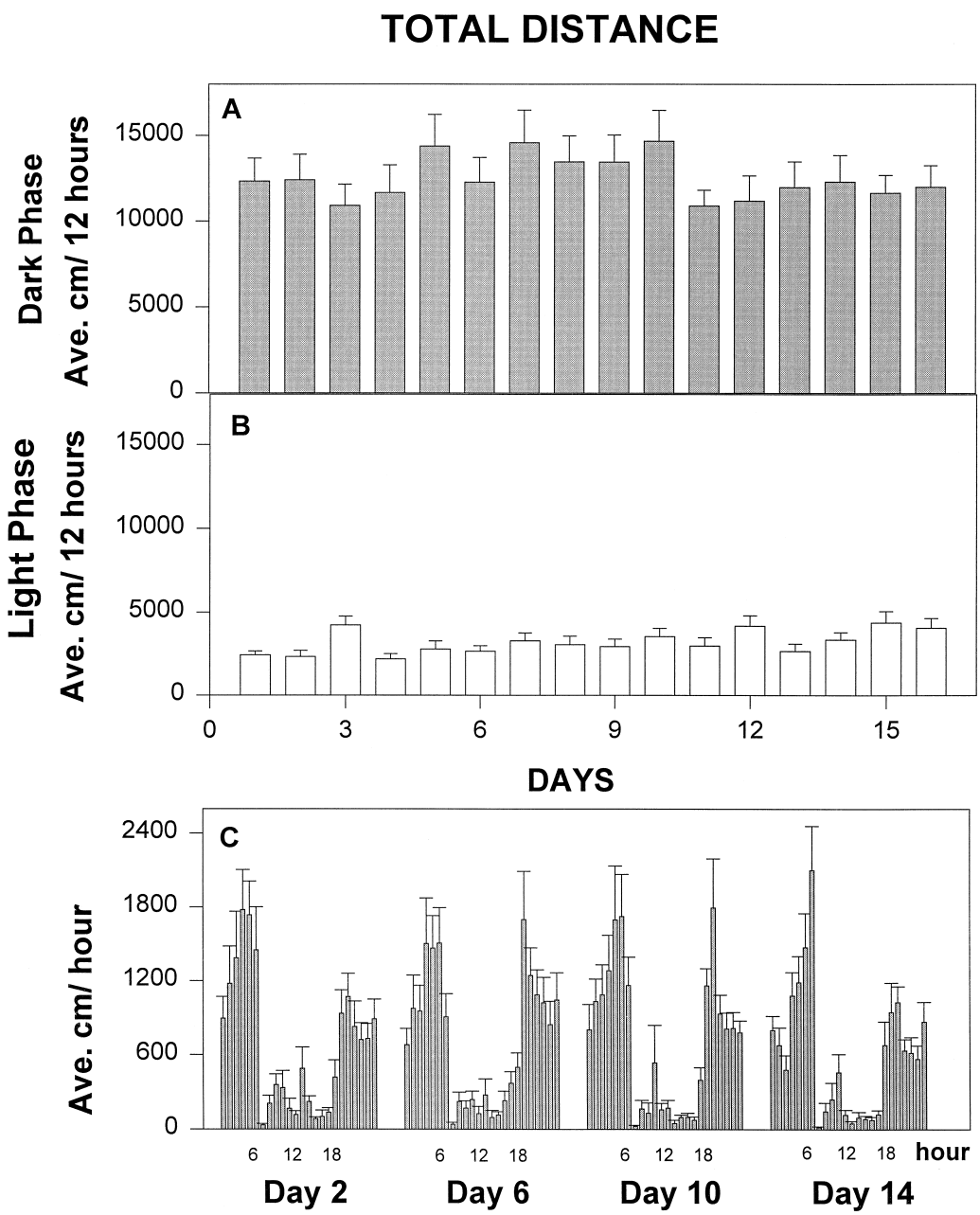


Fig. 1. Total distance for the untreated time control group ($n = 12$) are displayed as mean ± S.E.M for the following: (A) The average total activity counts (12 h) during the dark phase of Days 1–16. (B) The average total activity counts (12 h) during the light phase of days 1–16. (C) The average hourly activity counts for representative days organized as 6 dark cycle hours, 12 light cycle hours, and the first 6 h of the next dark cycle; thereby creating a circadian pattern of activity. One way repeated ANOVA revealed no significant difference between days.

For the motor index of vertical activity, there were no significant differences between the three amphetamine doses at any of the times studied (i.e., all doses caused the same amount of increase from baseline; Fig. 2B). There was also no significant effect by day. Only when the times of administration were tested separately was there a significant difference between days 4 and 15 on vertical activity, which occurred when amphetamine was administered at 0800 h ($F(1,20) = 10.59$; $P < 0.01$). This difference was due to a significant increase in the effect of 0.6 mg/kg of amphetamine on day 15 ($P < 0.05$) and a slight, but non-significant, increase in the effect of 0.3 mg/kg of amphetamine (Fig. 2B). Therefore, there appears to be a time-dependent difference in the development of sensitization to amphetamine that is also more specific for forward ambulation (i.e., total distance) than for rearing (i.e., vertical activity).

### *3.3. Dose-response comparison of amphetamine's effects on naive and treated animals injected at 0200 h*

The temporal response to all three amphetamine doses (0.3, 0.6, and 1.2 mg/kg) on day 4 (i.e., drug naive) and

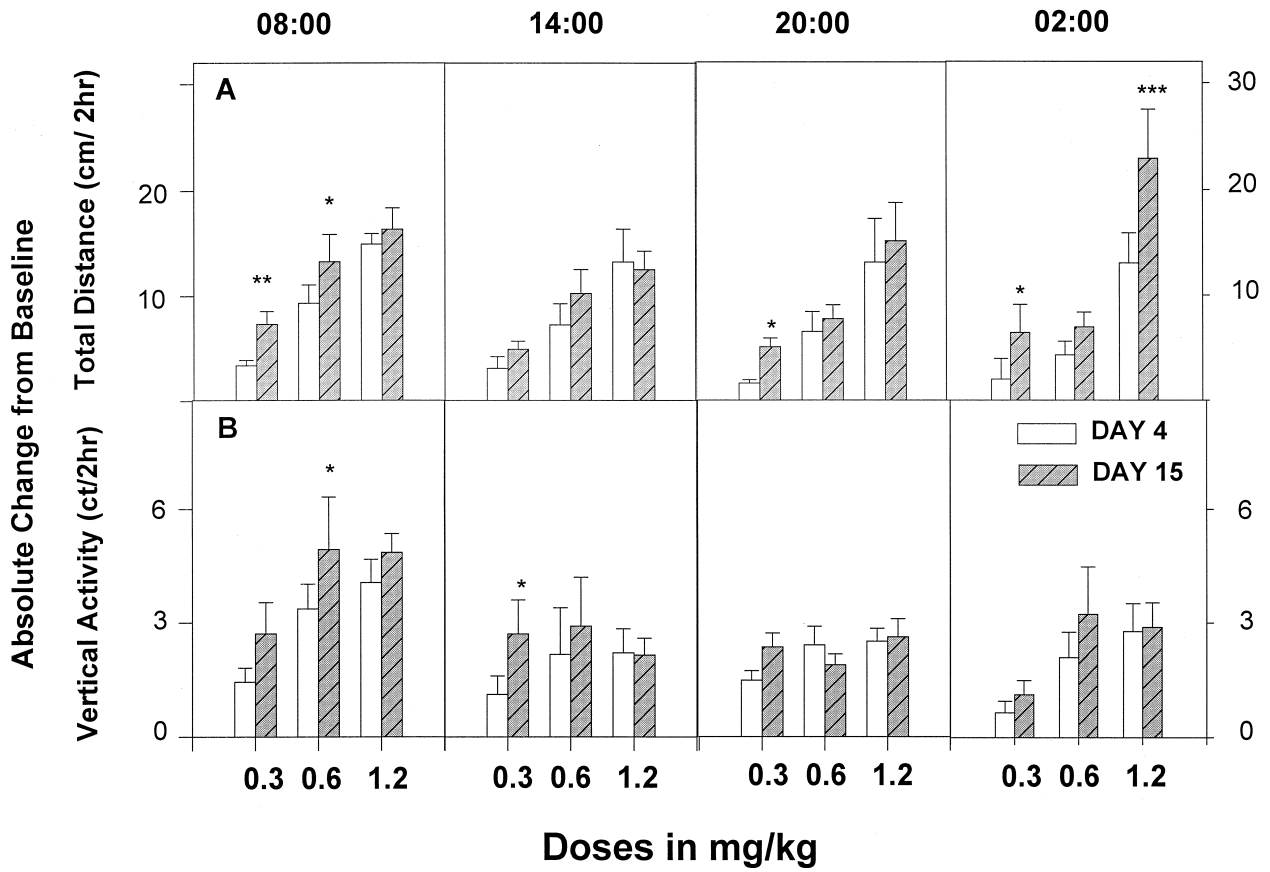


Fig. 2. The dose-response histograms for the total change from baseline (days 1 and 2) in the initial 2 h after s.c. administration of the three different amphetamine doses (0.3, 0.6, 1.2 mg/kg; each $n = 8$) at 0800, 1400, 2000 and 0200 are shown for (A) total distance and (B) vertical activity. Data are presented as the mean ± S.E.M. in counts/2 h. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$;—all comparisons are day 15 vs. day 4.

day 15 (i.e., after 5 daily injections of 0.6 mg/kg of amphetamine) are presented in Fig. 3 for total distance. There was a significant and dose-dependent increase in amphetamine's effect on total distance ($F(2,20) = 8.46$; $P < 0.01$), as well as a significant main effect of injection day between day 4 and day 15 ($F(1,20) = 37.3$; $P < 0.0001$). Moreover, there was a significant interaction between injection day and sample time ($F(11,220) = 9.64$; $P < 0.001$), indicating a change in the temporal response patterns between days 4 and 15.

The lowest dose of amphetamine (0.3 mg/kg) caused the lowest increase of activity on day 4. Post-hoc analysis revealed that the response to the re-challenge of 0.3 mg/kg of amphetamine on day 15 was significantly ($P < 0.01$) elevated (i.e., sensitized) for the initial 50 min of drug effect when compared to response on day 4 (Fig. 3A). The response to 0.6 mg/kg of amphetamine was also sensitized on day 15 for the initial 30 min after drug re-challenge ($P < 0.01$; Fig. 3B) when compared to day 4. Finally, the effect of the highest dose of amphetamine (1.2 mg/kg), which on day 4 caused the largest increase over baseline, showed a significantly increased ($P < 0.001$) effect on day 15 of amphetamine re-challenge when compared to day 4 for the initial 90 min of drug effect (Fig. 3C).

Therefore, repeated administration of amphetamine at 0200 h (i.e., challenge dose on day 4 and five daily injections of 0.6 mg/kg of amphetamine) caused a sensitized response to the locomotor effects of all three doses that was specific for the motor index of total distance.

### 3.4. Post-amphetamine activity levels

The average activity during the 12 h periods of the light and dark phase for the baseline period (days 1 and 2 averaged) and during the last three days of the post-treatment phase (days 12 to 14 averaged) were analyzed for all dose groups and motor indices. There was no change in the light and dark phase activity levels between days 12–14 and their baseline values on days 1–2 regardless of the motor index studied or which time of day amphetamine was administered. These observations were similar to those shown in Fig. 1. There was also no significant differences between the post-treatment period and baseline if the dose groups were analyzed separately. Therefore, the repeated administration of amphetamine (0.6 mg/kg), which was

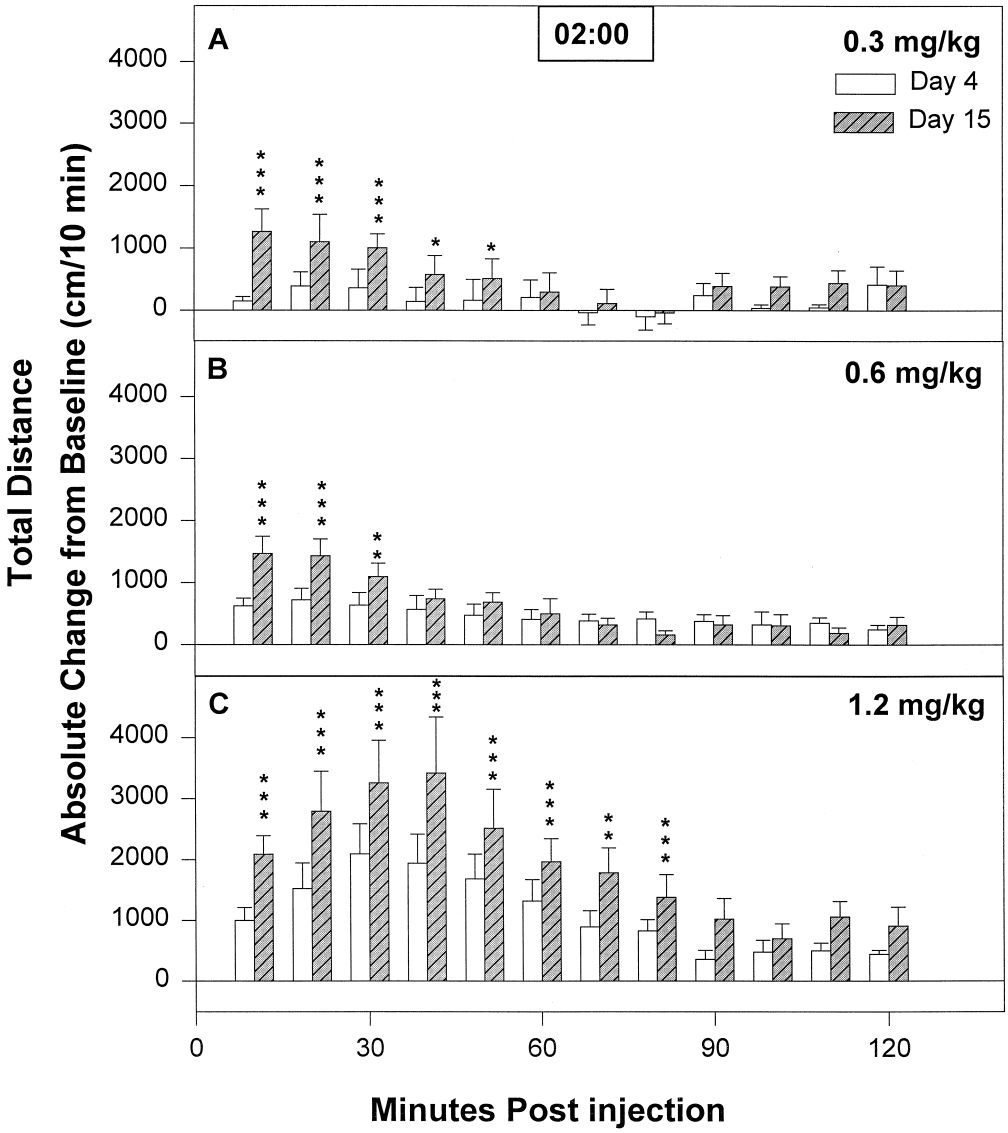


Fig. 3. The temporal response pattern of total distance following (A) 0.3 mg/kg; (B) 0.6 mg/kg; and (C) 1.2 mg/kg amphetamine are presented for the initial 2 h of drug effect on day 4 (naive) and day 15 (treated with five daily injections of 0.6 mg/kg) for the groups ($n = 8$ each) which received drug administration at 0200. Data are presented as mean ± S.E.M. in cm/10 min of the change from baseline (days 1 and 2) with baseline values arbitrarily set at 0. Repeated measure ANOVA was used for pairwise comparison. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$;—all comparisons are day 15 vs. day 4.

the dose that all three dose groups were administered on days 5 to 9, did not produce any persistent effects on rat's activity levels (i.e., post-stimulant depression) for any of the motor indices studied.

## 4. Discussion

The major findings reported in this paper are: (i) the sensitization produced by repeated administration of a low dose of amphetamine is not uniform among the motor indices studied, but is specific to forward ambulation and is dependent on the challenge dose; (ii) sensitization to the locomotor effects of amphetamine is also dependent on the time of drug administration; and (iii) five repeated administrations of a low dose of amphetamine has no persistent effects on locomotor activity.

Both motor indices of activity studied displayed consistent baseline levels and circadian patterns of activity over the course of the study (Fig. 1). Each animal could then serve as its own control and the treatment effect on day 4 could be compared to a time-matched average baseline for the same animal, allowing for correction of circadian differences in activity prior to drug administration, as well as individual differences in activity levels between rats. Thus, the results presented in the present study show that five consecutive daily injections of amphetamine in the rat's home cage resulted in the expression of a sensitized response that was dependent on both the dose used to test

for the augmented response, as well as the time of drug administration.

The sensitized response produced in the present study at the beginning of the light phase (0800 h) was consistent with what has been reported for repeated administration of similar doses (0.5–1.0 mg/kg) in previous studies which have all been conducted during the light phase (Robinson and Becker, 1986; Kuczenski and Segal, 1988). The use of three separate challenge dose groups in the present experiment showed that the nature of the sensitized response at 0800 h may be due to an increase in its potency (i.e., a leftward shift of dose-response), but not in its efficacy (i.e., a maximum effect elicited by the largest dose), while the sensitized response during the middle of the dark phase (0200 h) also displayed an increase in the efficacy (i.e., the maximal effect of the largest dose) of amphetamine dose-related locomotor effect. One recent study which looked at the dose-related effects of quinpirole, a dopamine $D_2/D_3$ receptor agonist which predominantly affects locomotor behavior, found that the sensitized response to quinpirole is a result of both changes in efficacy (i.e., maximal response) and potency, which were differentially affected by context and environmental factors (Szumlinski et al., 1997). Contrary to our findings at 0800 h, they reported that rats which received their injections in their home cage only show an augmentation in efficacy but not potency, however, this may be a function of the different specificity for dopamine receptors between these two dopamine agonists (i.e., quinpirole is a direct agonist and amphetamine is an indirect agonist).

The sensitized responses of dose groups on day 15 (treated rats) compared to day 4 (drug-naive rats) were not as strong as has been seen in previous studies. However, the housing of rats in their home cage, removing any context-dependent response, has been reported to produce a drop in the magnitude of the sensitized response, which may partially account for the lack of robust sensitization in this study (Post et al., 1981; Badiani et al., 1995). It is also important to note that the different challenge doses used on day 4 could have contributed to the development of a sensitized response on day 15, since single injections have been shown to produce sensitized responses to subsequent administration (Robinson and Becker, 1986; Robinson et al., 1982). However, it is more likely that the sensitized responses seen on day 15 received a greater contribution from the repeated treatment phase (days 5 to 9) than from the challenge doses on day 4. The sensitization produced was also specific to forward ambulation, since vertical activity (i.e., rearing) did not show the same amount of sensitization as total distance (Fig. 2). This observation could reflect a true difference in the susceptibly to timing of administration in sensitization to rearing. However, the large variation in vertical activity at 0800 h and 1400 h could mask a sensitized response at that time.

More importantly, sensitization to amphetamine was dependent on the time of drug administration, with the strongest expression of a sensitized response in the present study occurring with repeated administration during the middle of the dark cycle (0200 h; i.e., the active period of the rats) where an augmented response was found for all three amphetamine doses studied (Fig. 3). Yet, with amphetamine administration at 0800 h, only the two lowest doses (0.3 and 0.6 mg/kg) were found to produce a sensitized response (Fig. 2), and there was no sensitized response to any dose studied when the drug was given at 1400 h (Fig. 2). Only a few studies (Martin-Iverson et al., 1987, 1988) have compared sensitization to stimulants throughout the day, but they concentrated on effects of continuous administration, and it is, therefore, difficult to correlate our results with these studies.

However, the sensitization produced to amphetamine's locomotor effects during the middle of the dark phase (0200 h), is consistent with reports that daytime tolerance and nocturnal sensitization occurred following continuous administration of (+)-4-propyl-9-hydroxynaphthoxazine (PHNO), a direct dopamine receptor agonist selective for the dopamine $D_2$ receptor subtype, while intermittent administration of PHNO produced sensitization during the light phase (Martin-Iverson et al., 1987, 1988). Although continuously infused, amphetamine did not produce nocturnal sensitization, but tolerance to the stimulant effects of amphetamine was only reported during the light phase and not during the dark phase (Martin-Iverson and Iversen, 1989). These findings, along with the reports of higher concentrations of dopamine and dopamine receptors during the dark phase (Lemmer and Berger, 1978), suggest that sensitization to stimulants should be greater during the dark phase than during the light phase as was found in this study. However, the time dependence of sensitization to stereotypic effects elicited by higher doses of amphetamine should not be automatically assumed from the present results, since the dose-related stereotypic and locomotor effects of a single injection of amphetamine were found to differ in their response throughout the day (Gaytan et al., 1998).

The circadian variation in sensitization to amphetamine probably reflects a difference in the ability to induce a sensitized response, since in previous studies it has been reported that the expression of the acute locomotor response to amphetamine throughout the day was not time-dependent (Gaytan et al., 1998). Although speculative, the circadian variation in inducing sensitization to amphetamine could reflect a relationship between amphetamine's effects and the circadian patterns of endogenous dopamine release and/or dopamine $D_1/D_2$ receptor interactions throughout the day, as has been suggested previously to account for the circadian differences in continuous administration of amphetamine (Martin-Iverson and Yamada, 1992). The present protocol would allow for the investigation of sensitization and its interaction with what time of day a stimulant is administered, which dose is administered repeatedly, for how long, and which doses

are used to elicit the expression of sensitization. These are all issues that deserve further study before the phenomena of sensitization can be fully understood.

Moreover, many hypotheses exist about how behavioral sensitization may relate to the pathophysiology of psychiatric disorders such as psychosis (Robinson and Becker, 1986). Since psychiatric disorders are often associated clinically with disturbances in normal circadian rhythms, a clearer understanding of how circadian rhythms of motor activity or dopaminergic function interact with the process of sensitization to stimulants is essential before we can fully grasp what role, if any, the phenomena of sensitization plays in psychiatric disorders (Martin-Iverson and Yamada, 1992). Identifying the underlying mechanisms involved in the relationship between the time of injection and the development of sensitization to amphetamine and other stimulants, can also aid in better understanding the role of dopamine receptor interaction in sensitization, as well as specifying what physiologic conditions are optimal for inducing sensitization (e.g., arousal state, tyrosine hydroxylase function, dopamine receptor interaction). Finally, since drug abusers do not restrict their use of stimulants to any particular time of day, it appears appropriate to study sensitization during both the active and inactive cycles, if the results from such studies are to be correlated to drug addiction in humans, as has been suggested in the past (Robinson and Berridge, 1993).

Previous studies have reported a decrease in nocturnal activity levels following repeated administration of low to moderate doses, of amphetamine, or the acute administration of large doses ($>$ 2.5 mg/kg) (Segal and Kuczenski, 1987; Segal and Mandell, 1974; Gaytan et al., 1996a). This post-stimulant depression was not found following repeated administration of 0.6 mg/kg amphetamine in this study regardless of the time of drug administration. In the present study, the lack of post-stimulant depression is most likely due to the use of such a low dose of amphetamine (0.6 mg/kg) during the repetitive drug treatment phase, since the studies which reported depressed nocturnal activity all utilized intermediate or large doses of amphetamine (Segal and Mandell, 1974; Kuczenski and Segal, 1988).

In summary, this investigation showed that repeated exposure to amphetamine in their home cage produces sensitization to its locomotor effects that was more specific for forward ambulation than for rearing. This sensitized response was both dose- and time-dependent. Moreover, amphetamine (0.6 mg/kg) exhibited no persistent effects on locomotor activity levels following the cessation of repeated injections.

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