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Time of day influences the voluntary intake and behavioral response to methamphetamine and food reward

Diana R. Keith [a], Carl L. Hart [a,b,c,*], Margaret Robotham [d], Maliha Tariq [d], Joseph Le Sauter [d], Rae Silver [a,d]

[a] Department of Psychology, Columbia University, New York, NY, USA
[b] Department of Psychiatry, College of Physicians and Surgeons of Columbia University, New York, NY, USA
[c] Division on Substance Abuse, New York State Psychiatric Institute, New York, NY, USA
[d] Psychology Department, Barnard College, New York, NY, USA

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ABSTRACT

The circadian timing system influences a vast array of behavioral responses. Substantial evidence indicates a role for the circadian system in regulating reward processing. Here we explore time of day effects on drug anticipation, locomotor activity, and voluntary methamphetamine (MA) and food intake in animals with ad libitum food access. We compared responses to drug versus a palatable treat during their normal sleep times in early day (zeitgeber time (ZT) 0400) or late day (ZT 1000). In the first study, using a between-subjects design, mice were given daily 1-h access to either peanut butter (PB-Alone) or to a low or high concentration of MA mixed in PB (MA + PB). In study 2, we repeated the experiment using a within-subjects design in which mice could choose between PB-Alone and MA + PB at either ZT 0400 or 1000. In study 3, the effects of MA-alone were investigated by evaluating anticipatory activity preceding exposure to nebulized MA at ZT 0400 vs. ZT 1000. Time of day effects were observed for both drug and palatable treat, such that in the between groups design, animals showed greater intake, anticipatory activity, and post-ingestional activity in the early day. Furthermore, there were differences among mice in the amount of MA ingested but individuals were self-consistent in their daily intake. The results for the within-subjects experiment also revealed robust individual differences in preference for MA + PB or PB-Alone. Interestingly, time of day effects on intake were observed only for the preferred substance. Anticipatory activity preceding administration of MA by nebulization was also greater at ZT 0400 than ZT 1000. Finally, pharmacokinetic response to MA administered intraperitoneally did not vary as a function of time of administration. The results indicate that time of day is an important variable mediating the voluntary intake and behavioral effects of reinforcers.

1. Introduction

The circadian timing system has a pervasive influence in that it modulates numerous behavioral and physiological responses, including the response to natural and drug reinforcers (Hasler et al., 2012). Indeed, for several types of reinforcers the pharmacological, physiological, and behavioral effects vary as a function of time of administration or availability over a 24-h cycle (Falcon and McClung, 2009; Webb et al., 2009a). These rhythms persist under constant conditions (Terman and Terman, 1975; Kosobud et al., 1998), suggesting that they are under endogenous circadian control by the brain clock located in the suprachiasmatic nucleus of the hypothalamus. Although there have been studies investigating the influence of time of day on the behavioral responses to drugs of abuse, surprisingly methamphetamine (MA) has received limited experimental attention. In humans, time-of-day effects may influence acute subjective, cognitive, and adverse effects of MA.

Data from participants in a prior experiment in our laboratory suggest that time of day influences of the euphoric effects of MA. When participants received MA at 0115 h, ratings of "good drug effects" were similar across low and moderate doses (5 versus 10 mg) (Hart et al., 2003). In contrast, unpublished data from this experiment reveal that when the same participants received 5 mg MA at 0915, their ratings of "good drug effects" were indistinguishable from ratings for placebo [Fig. S1.a (data) and b (study design)], (Supplementary material; Hart et al., 2003). While this experiment was not designed to examine the influence of time of day, the results do raise a question about how such an effect might influence drug self-administration: a question optimally addressed in studies of laboratory animals.

Although there have been few studies of time-of day effects of MA in humans (Shappell et al., 1996), diurnal variations in response to amphetamines have been reported in laboratory animals using a

* Corresponding author at: New York State Psychiatric Institute, 1051 Riverside Dr., Unit 120, New York, NY 10032, USA. Tel.: +1 212 543 5884; fax: +1 212 543 5991.
E-mail address: clh42@columbia.edu (C.L. Hart).

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variety of procedures including operant avoidance, sensitization, tolerance, general activity, conditioned place preference (CPP), and stereotypic behavior (Arvanitogiannis et al., 2000; Evans et al., 1973; Gaytan et al., 1998a,b; Gaytan et al., 1999; Kuribara and Tadokoro, 1982, 1984; Martin-Iverson and Iversen, 1989; Uchihashi et al., 1994; Urba-Holmgren et al., 1977; Webb et al., 2009b). Overall, these data show greater drug effects around dawn compared to dusk. However, to our knowledge, there has been no prior attempt to explore the impact of diurnal variations on self-administration of amphetamines.

The goal of the present experiment was to examine time of day effects on reinforcer intake, associated behaviors, and pharmacokinetics. A second goal was to compare time of day effects of two different reinforcers, specifically a palatable treat, peanut butter (PB-Alone), versus drug, methamphetamine (MA) mixed in peanut butter (MA + PB). We also investigated dose–response relationships and individual differences in these behaviors. Finally, we sought to explore changes in these behaviors over time. To investigate these questions, we used a paradigm involving voluntary intake, thereby allowing for simultaneous measurement of anticipatory behaviors, self-administered voluntary intake of drug and/or palatable treat, and locomotor activity. This paradigm is analogous to voluntary human drug use, and does not require surgical implantation of an indwelling catheter for acquisition of self-administration data. Further, because the mice are provided with food ad libitum they have very low activity levels during the day, allowing assessment of responses to reinforcers against low baselines (Mistlberger, 1994; Escobar et al., 2011). In Protocol 1, we used a between-subjects design to compare the behavioral responses to drug and/or palatable treat in the early versus late day. In that work, we noted that marked individual differences in MA intake with self-consistent responses over the course of the experiment. Protocol 2 used a within-subjects design, thereby permitting more detailed measurement of individual differences in intake and time of day effects. To isolate the effects of MA from PB, in Protocol 3 we investigated time of day effects on anticipatory activity associated with nebulized MA. Finally, to assess time of day effects on pharmacokinetic factors, in Protocol 4 MA was injected at several times of day and serum measurement of the drug were taken for the subsequent 4 h.

2. Methods and materials

2.1. Animals and housing

Adult male C57BL/6 N mice 6 weeks of age, weighing an average of 22 g (range 16°26 g) at the beginning of each experiment were subjects (Charles River, Wilmington, MA). Mice were housed individually in transparent polycarbonate cages (32 × 14 × 13 cm), equipped with a running wheel (diameter, 11 cm) placed in sound attenuating, ventilated chambers (Phenome Technologies Inc. Lincolnshire, IL). The room was maintained at 23 ± 2 °C and 72% humidity. Standard mouse chow (Purina, St. Louis, MO) and water were available ad libitum except as noted. The experimenter changed cages every two weeks, and the data from the 24 h following a cage change were not included in the analyses. For Protocols 1 and 2, body weight was taken on the first and last day of each experiment. For Protocol 3, to measure anticipation to nebulized MA, a skeleton photoperiod with lights on ZT 0000–0030 and ZT 1130–1200 was used to avoid the masking effects of light on activity. Nebulization was performed under dim red light (1 lx) illumination at ZT 0400–0415 or ZT 1000–1015. For all experiments, animals were adapted to a 12:12 light:dark cycle (200 lx), with lights off at zeitgeber time 1200 (ZT 1200) and on at ZT 0000 for 14–16 days before the start of the experiment. Animals were cared for in accordance with the Columbia University Institutional Animal Care and Use Committee and Animal Welfare regulations.

2.2. Preparation of drugs

For Protocols 1 and 2, stock solutions of MA hydrochloride (Sigma-Aldrich Inc., St. Louis, MO) were prepared at two concentrations as follows: MA (34 or 68 mg) was added to distilled water (30 ml) to create 1.13 mg/ml and 2.26 mg/ml. PB was commercially available (Jif® Brand, Creamy Peanut Butter). Each animal was assigned its own Petri dish (BD Falcon, 35 × 10 mm tissue culture dish) for the duration of the study. For use, 1.00 ± 0.01 g PB was placed in the center the dish. MA stock solution or water (40 μl of 0, 1.13, or 2.26 mg/ml MA) was mixed thoroughly in the PB to create 45 or 90 μg/g MA + PB or PB-Alone. Ingestion of the entire mixture yields a dose of 2 mg/kg and 4 mg/kg, based on the mean initial body weight of 22 g/mouse. For Protocol 3 the concentration of MA was 0.4 and 1.0 mg/ml. For Protocol 4, body weight was measured immediately prior to injection of 2 mg/kg MA.

2.3. Protocol 1: Study design

2.3.1. Experimental groups

Animals were placed in one of four groups (N = 10/grp) differentiated by the time, either early (ZT 0400) or late day (ZT 1000) at which they were given access to either PB-Alone or MA + PB. The training and testing intervals are shown schematically for the ZT 0400 group in Fig. 1A. During an initial 4 day training period, animals were acclimated to food restriction conditions by giving them access to standard chow for 8-h/day from either ZT 0400–1200 or ZT 1000–1800. On days 5–8, animals were provided MA + PB (3 g PB mixed with 45 μg MA) or PB-Alone (3 g PB) for the same 8-h intervals. On days 9–12, they received 1-h access to 1 g of either 45 μg/g MA + PB or PB-Alone, followed by 7-h access to standard chow (ZT 0400–1200 or ZT 1000–1800). On days 13–23 (Block 1), mice had ad-libitum access to chow, and daily 1-h access to 1 g of 45 μg/g MA + PB or PB-Alone at ZT 0400–0500 or ZT 1000–1100 continued. On days 24–34 (Block 2), the concentration of MA was doubled to 90 μg/g MA + PB, and subsequently returned on days 35–45 (Block 3) to 45 μg/g MA + PB.

2.3.2. Measures

The behavioral measures assessed were amount eaten, MA intake, anticipatory activity, activity after ingestion, and total daily activity. For determination of amount eaten, the experimenter was in the room for 20 min for placement and removal of Petri dishes. MA intake is reported in mg/kg body weight, adjusted for interpolated daily individual weight gain. Body weight on the last day of the study (day 45) averaged 28 g (range 24–31 g). Wheel running was monitored continuously using a computer-based data acquisition system, VitalView (Minimitter, Bend, OR, USA) and was quantified in 10 min bins across the 24 h day using Actiview (MiniMitter) and Excel (Microsoft). Activity was normalized within each animal to control for wheel resistance and was calculated by dividing the sum of activity counts in each activity measure by the number of wheel revolutions per bin averaged over 24 h. Anticipatory activity was defined as the average number of wheel revolutions in the 2-h prior to reinforcer access (ZT 0200–0400 or ZT 0800–1000). Activity after ingestion was the average wheel revolutions in the 2 h after the start of food access (ZT 0400–0600 or ZT 1000–1200).

2.3.3. Data analysis

Data was analyzed using a linear mixed model with both fixed and random effects in SAS (SAS Institute Inc., Cary, N.C., USA). One animal died during the first four days of training and data for this animal was not used. After removing outliers (or 2 s.d. from mean), observations from the last 10 days of each 11-day block were averaged for each animal (Total observations = 117). Independent variables included time of day (ZT 0400, ZT 1000), treatment group (PB-Alone, MA + PB), concentration (45, 90 μg/g MA + PB), and block (1, 2, and 3). Animal identity was analyzed as a random effect. Analyses were conducted in two