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Circadian Time Does Not Modify the Prepulse Inhibition Response or Its Attenuation by Apomorphine

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WEISS, I. C., J. FELDON AND A. M. DOMENEY. *Circadian time does not modify the prepulse inhibition response or its attenuation by apomorphine.* PHARMACOL BIOCHEM BEHAV **64**(3) 501–505, 1999.—The present study investigated the influence of circadian time (experimental testing during the light or dark phase of the light:dark cycle) on the acoustic startle response (ASR), prepulse inhibition (PPI), and apomorphine-induced PPI deficits in Wistar rats housed under a reversed light:dark cycle (lights off at 0700 h and on at 1900 h). There was no significant difference in the startle response amplitude or PPI response of animals tested during the light phase compared with those tested during the dark phase. Similarly, the response to apomorphine (0.01–0.05 mg/kg subcutaneously) was not modulated by circadian time. Thus, under the conditions adopted in the present study, ASR, PPI, and apomorphine-induced PPI deficits remained stable across the circadian cycle. Such findings may be of importance for other investigators using the PPI paradigm to study brain plasticity mechanisms and pharmacological manipulations of apomorphine-induced PPI deficits in rats housed under normal or reversed light:dark cycle conditions. © 1999 Elsevier Science Inc.

Prepulse inhibition Circadian time Apomorphine Wistar rat

THE acoustic startle response in mammals is represented by a short latency motor reaction that is elicited by intense acoustic stimulation. Because the acoustic startle response (ASR) shows different forms of reflex modification, including habituation (6), prepulse inhibition (19), and modification to prior associative learning (7,8), it has been extensively employed to study neural circuits involved in mechanisms of brain plasticity.

Notwithstanding that the ASR is shown to be a resilient and persistent reflex (6), there is evidence that the amplitude of the ASR is affected by different internal states, fear and anxiety being perhaps the most widely known examples (8,38). Additionally, there are several reports revealing that ASR amplitude in the rat is also modulated by the circadian cycle. Robust increases in ASR amplitude are shown to occur during the dark vs. the light phase in rats (4,5,10,12,20,21). Darkness facilitation of ASR is also shown in humans, but is in this case, significantly correlated with the intensity of the subjects' fear of the dark (15).

That the circadian cycle influences the ASR response may have implications for the investigation of mechanisms of brain plasticity based on modulation of the ASR, for example, prepulse inhibition. Prepulse inhibition (PPI) is the normal reduction of the startle response to an intense acoustic stimulus (pulse) when this stimulus is immediately preceded by a weaker intensity stimulus (prepulse) (1,14,19,31,32), and thus represents an operational measure of sensorimotor gating (16). There are, however, few reports providing direct evidence for the circadian modulation of PPI. In a study where rats were exposed to a series of prepulses of differing intensities, in a semi-random manner, auditory thresholds did not appear to be influenced by the time of day (4), suggesting that weaker prepulses may retain the ability to modify the normal startle response. The ability of a weaker prepulse to inhibit a subsequent startle response is reported to be reduced by the activity of the animal; thus, active rats do not respond as vigorously to a reflex-eliciting tone as do the same rats when

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quiet (39). Because locomotor activity itself is modulated by the circadian cycle in the rat, with greater activity during the dark phase of the cycle, this may contribute to level of PPI detected.

The present study was conceived from the observation that the Wistar rat strain used in our own laboratories show increased sensitivity to the dopamine agonist apomorphine compared to that reported in the literature for the induction of PPI deficits. For example, in our laboratories, the minimal effective dose to induce a PPI deficit with apomorphine is 0.02 mg/kg subcutaneously [(27,40), and other unpublished data] compared to 0.1–0.5 mg/kg subcutaneously used in other strains and laboratories (11,13,24,28,31,36). We considered that the increased sensitivity to apomorphine may be due to the fact that our rats were housed on a reversed light:dark cycle and, therefore, typically tested in the dark phase, while other studies report data from animals tested in the light phase (11,17,18,22,29,30,36,42).

Therefore, in this study, we investigated the influence of circadian time, light vs. dark phase of the light:dark cycle, on the startle and the PPI response in Wistar rats housed under a reversed light:dark cycle. In addition, because apomorphine is widely used to induce deficits in PPI as a model to screen antipsychotic drugs (3,11,13,18,31–35,37), and some of the effects of apomorphine are reported to be modulated by circadian time (25,26,41), we investigated apomorphine-induced PPI disruption as a function of test time.

METHOD

Animals

The study used 48 male Wistar rats [Zur:Wist(HanIbm)], bred at the Behavioural Biology Laboratory, Schwerzenbach (CH), weighing 336–426 g at the start of testing. The animals were housed in groups of four, in Macrolon cages containing sawdust (dimensions 59.0 × 38.5 × 30.0 cm). They were maintained under standard conditions, in a temperature (21 ± 1°C)- and humidity (55 ± 5%)-controlled room, on a 12–12-h reversed light:dark cycle (lights off at 0700 h and on at 1900 h). During the entire study, animals had free access to food (Nafag, 9431, Nafag Ecossan, Gossau, Switzerland) and water. All the experiments were carried out in agreement with the Swiss Federal Regulations for animal experimentation.

Prepulse Inhibition Apparatus

Prepulse inhibition was assessed in four identical sound-attenuated startle chambers (SR-LAB, San Diego Instruments, San Diego, CA), which were illuminated (45 Lux) and ventilated. Each startle chamber consisted of a transparent Plexiglas cylinder (diameter 8.2 cm, length 20 cm) mounted on a Plexiglas frame. A speaker mounted 24 cm above the cylinder provided the acoustic noise bursts. The startle responses of the rat were detected and transduced by a piezoelectric accelerometer mounted below the frame. Startle amplitudes were defined as the average of 100 1-ms stabilimeter readings collected from the stimulus onset.

The startle session started with a 5-min acclimatization period, with a 68 dB[A] background white noise level that continued throughout the test session. Four startle pulses of 120 dB[A], 30- ms duration were then presented to the animal to evaluate the basal startle response. Next, the animal received six blocks of 11 trials to measure PPI. Each block consisted of four different trial types presented pseudorandomly throughout the session, i.e.: pulse alone (two trials), prepulse alone (one trial for each prepulse intensity), prepulse followed by pulse (one trial for each prepulse intensity) or no stimulus (one trial). The four different prepulses had an intensity of either 72, 76, 80, or 84 dB[A] and a duration of 20 ms. The time interval between the prepulse offset and the pulse onset was 80 ms.

The percentage of PPI induced by each prepulse intensity was calculated as: [100 − (100 × Startle amplitude on prepulse trial)/(Startle amplitude on pulse-alone trial)].

Experimental Design

All of the 48 animals were experimentally naive when subjected to the first PPI test. This first study was conducted within a 24-h period. For half of the animals, the PPI test was performed during the dark phase of the light:dark cycle (D), i.e., between 0900 and 1300 h, and for the remaining animals, the PPI test was performed during the light phase of the light:dark cycle (L), i.e., between 2100 and 0100 h (the following day).

After 1 week without any experimental manipulation, a second PPI was conducted on the same animals following apomorphine (0.01, 0.025, or 0.05 mg/kg SC) or vehicle treatment. The injection took place immediately before the rats were placed in the startle chamber. In the same manner as in the first PPI test, the animals were divided into two identical groups comprising the same animals (D testing, $n = 24$ vs. L testing, $n = 24$) as used in the original PPI test. Each group of 24 animals was then divided into four separate treatment subgroups comprising of six animals each.

Drug

Apomorphine hydrochloride (Research Biochemicals Inc., Switzerland) was prepared immediately before use, as the base, in saline solution (NaCl 0.9%) containing 0.1% ascorbic acid (Sigma Chemical CO, Switzerland). Animals received doses of 0.01, 0.025, and 0.05 mg/kg, injected subcutaneously into the flank (1 ml/kg body weight).

Data Analysis

The data were analyzed using the Statview and SuperANOVA software system (Abacus Concepts Inc., Berkeley, CA). The analyses consisted of a two-way analysis of variance (ANOVA), with a between-subjects main factor of circadian time (D vs. L phase of the cycle) and a repeated-measurements main factor of either the 16 pulse-alone presentations (startle responses) or the four prepulse intensities (% PPI). The responses of the animals to the different doses of apomorphine treatment were analyzd using a three-way ANOVA, consisting of two between-subjects main factors of circadian time (D vs. L phase of the cycle) and APO treatment (0, 0.01, 0.025, or 0.05 mg/kg apomorphine) and repeated-measurements factors identical to those described for the first PPI test.

RESULTS

Effect of the Light:Dark Cycle on the PPI Response in Naive Animals

Acoustic startle response. There was no significant difference in the startle response amplitude of animals tested during the light phase in comparison with those tested during the dark phase (L 648.1 ± 58.1, and D 735.6 ± 64.9), although the trend (14% increase) was in the direction reported in the liter-

ature (see Fig. 1). An habituation of the startle response amplitudes over the 16 pulse-alone presentations was, however, apparent for the two groups, $F(15, 690) = 10.6$, $p < 0.001$.

Prepulse inhibition response. The mean percentage PPI was not significantly different between animals tested during the light phase (37.6 ± 4.1) and those tested during the dark phase (34.1 ± 3.0, see Fig. 2). There was, however, a significant effect of the prepulse intensity, $F(3, 138) = 58.5$, $p < 0.001$, reflecting the increased effectiveness of higher prepulse intensities of the prepulse stimulus to induce stronger PPI.

Effect of the Apomorphine Treatment on the PPI Response During the Light:Dark Cycle

Acoustic startle response. The circadian time of PPI testing did not affect the startle response amplitudes of the animals to the 16 pulse-alone presentations (L 737.1 ± 61.2, and D 785.8 ± 69.0). In addition, an habituation of the startle response amplitudes over the 16 pulse-alone presentations was apparent for all the groups, $F(15, 600) = 11.5$, $p < 0.001$. Although the main factor of apomorphine treatment condition was not significant, a treatment × pulse-alone interaction was apparent, $F(45, 600) = 1.61$, $p < 0.01$, reflecting a relative decrease in the startle responses at the end of the test session for the animals that had been treated with the two highest doses of apomorphine (0.025 and 0.05 mg/kg; see Fig. 3).

Prepulse inhibition response. Apomorphine treatment dose dependently decreased the mean percentage PPI, $F(3, 40) = 9.9$, $p < 0.001$ (see Fig. 4A). However, the main factor of circadian time and the circadian time × APO treatment interaction were not significant (see Fig. 4B). A significant effect of the prepulse intensity, $F(3, 120) = 39.5$, $p < 0.001$, reflected the increased effectiveness of higher prepulse intensities of the prepulse stimulus in inducing stronger PPI.

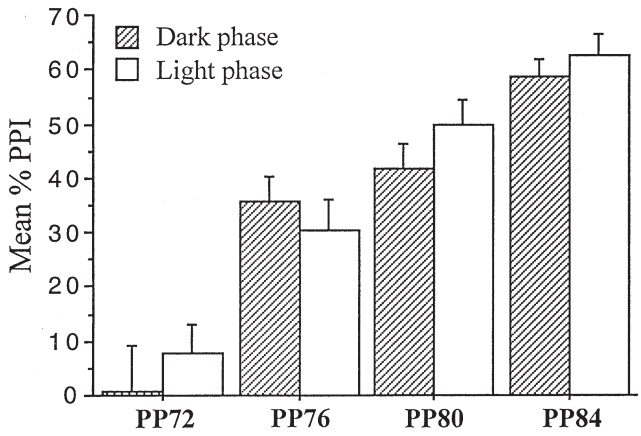

FIG. 2. Means ± SEM of percentage PPI in animals tested during the dark phase (between 0900 and 1300 h, $n = 24$) or during the light phase (between 2100 and 0100 h the following day, $n = 24$). Data are presented for each prepulse (PP) intensity tested (i.e., 72, 76, 80, and 84 dB[A]).

DISCUSSION

In the present studies, testing animals in the light or dark phase of the circadian cycle did not significantly influence the amplitude of the ASR. Furthermore, the PPI response in native animals was not modified by the test time during the circadian cycle. In apomorphine-treated rats there was no effect of light vs. dark phase testing on the amplitude of the ASR. However, a within-test session decrease in startle amplitude was apparent during the last six pulse-alone trials at doses of 0.025 and 0.05 mg/kg. Although apomorphine dose dependently decreased the PPI response, sensitivity to apomorphine was not modified by the circadian time at which the animals were tested.

The above findings, with respect to ASR, do not support those previously reported in the literature, namely that rats tested during the dark phase of the circadian cycle show significant increases (ranging from 25–100%) in ASR amplitude (4,5,10,12,20,21). In the limited number of studies conducted on the circadian modulation of the ASR a significant proportion used female rats (4,5,20,21). It could be envisaged that fe-

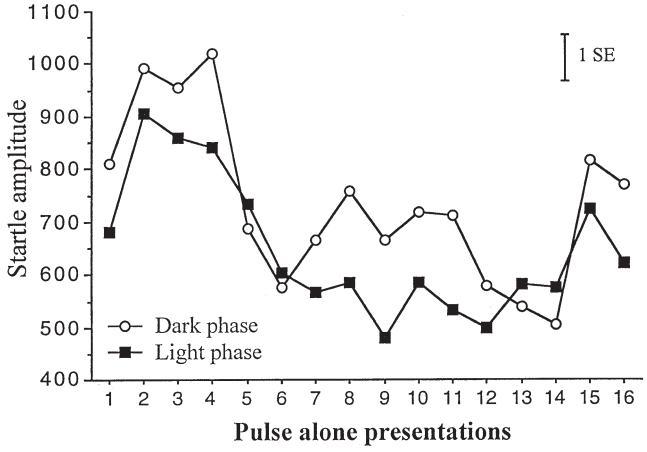

FIG. 1. Startle response amplitudes to the 16 pulse-alone presentations in animals tested during the dark phase (between 0900 and 1300 h, $n = 24$) or during the light phase (between 2100 and 0100 h the following day, $n = 24$). The bar on the upper right side indicates one standard error (SE) derived from the ANOVA.

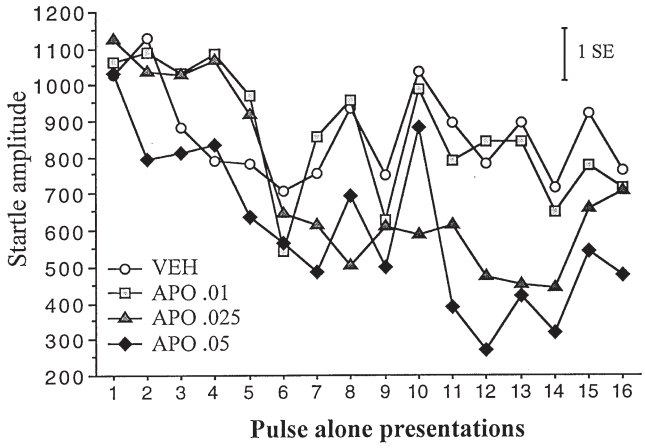

FIG. 3. Effect of apomorphine (0.01, 0.025, or 0.05 mg/kg, SC) or vehicle (VEH) on startle response amplitudes to the 16 pulse-alone presentations. Data are collapsed over the two testing times, i.e., light phase and dark phase ($n = 12$/treatment). The bar on the upper right side indicates one standard error (SE) derived from the ANOVA.

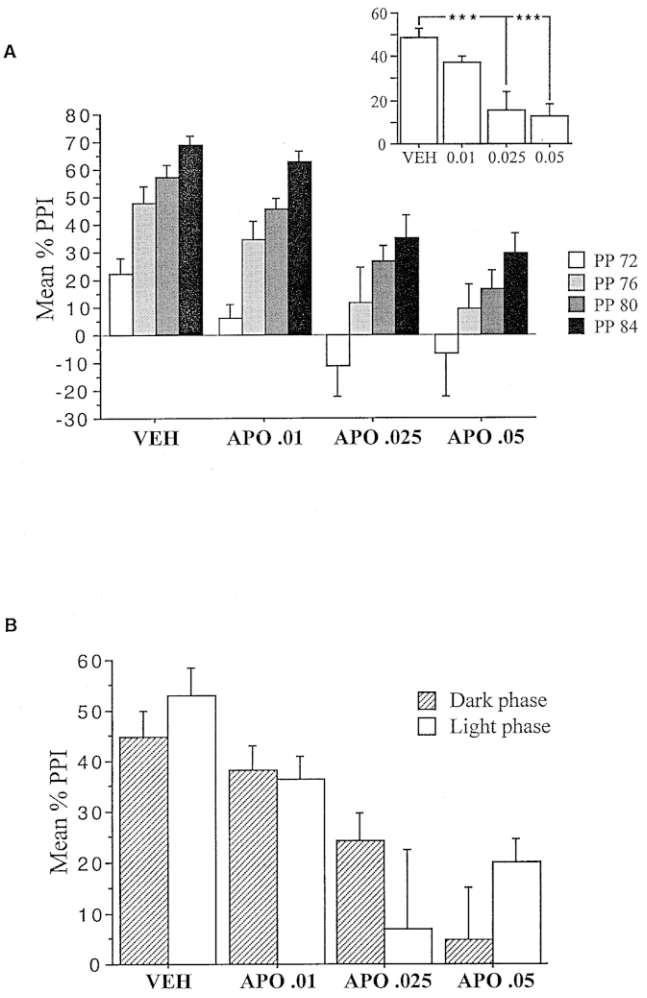

FIG. 4. (A) Effect of apomorphine (0.01, 0.025, or 0.05 mg/kg, SC) or vehicle (VEH) on the PPI response. Means ± SEM of percentage PPI are presented collapsed over the two testing times and for each prepulse (PP) intensity tested (i.e., 72 , 76, 80, and 84 dB[A]; $n = 12$/treatment; main graph) and as a total mean ± SEM over the four prepulse intensities (inset graph). $^{***}p < 0.001$. (B) Means ± SEM of percentage PPI in animals tested during the dark phase (between 0900 and 1300 h, $n = 6$/treatment) or during the light phase (between 2100 and 0100 h the following day, $n = 6$/treatment).

male rats, perhaps due to increased general levels of activity (2,23), may be differentially sensitive to acoustic startle during the dark phase than male rats.

In those studies where male rats were used, a higher level of ASR is reported to occur during the dark phase of the circadian cycle in Sprague–Dawley rats (10). However, in the latter study, the findings may be attributable to the lighting conditions during measurement of ASR as opposed to circadian time of testing, animals being tested in either illuminated or dark test chambers, depending on the phase of the light:dark cycle. In our own study, identical lighting conditions in the startle chambers were employed for all animals whether tested in the dark or the light phase of the circadian cycle. Thus, we were able to discriminate modifications occurring as a consequence of the test time during the circadian cycle and not to lighting conditions during the test. In the only published study employing male Wistar rats, animals were tested over 48 h at four hourly periods to obtain a time course of ASR modulation (12). Although the experimental method of the latter study contrasts with our own, in which rats were tested on one occasion only and at two hours after the change in light cycle, this does not adequately explain why marked increases in ASR during the dark phase could be detected as opposed to no difference in our own studies. It is possible that the basal startle level of the Wistar rats used in our own studies was already at a ceiling level, and thus prevented any further increase. This could only have been confirmed if the startle response of animals to weaker pulse intensities than 120 dB had been investigated. Despite this, different experimental methodologies for the measurement and presentation of the startle amplitudes do not allow for a direct comparison between our study and that of Frankland and Ralph (12).

In the present study, the PPI response was not influenced by the circadian time during which the test was conducted. Indeed, PPI response has been suggested to be independent of circadian variation in ASR (4). This, together with our own findings, leads to the conclusion that the PPI is a phenomenon that is stable and robust across the light:dark cycle.

Although the stereotypic and locomotor effects of apomorphine have previously been reported to be modulated by circadian time (25,26,41), our data suggest that this may not apply to apomorphine disruption of the PPI response. The decrease in the ASR at the end of the test session for animals that had been treated with the two highest doses of apomorphine (0.025 and 0.05 mg/kg) is likely to be as a direct consequence of drug action as opposed to changes in habituation per se. Modifications of the ASR following apomorphine have already been reported, occurring either concomitantly with changes in PPI (9,29,36), or nonrelated to PPI changes (28). Furthermore, Swerdlow et al. (32) emphasized that the effects of dopamine agonists, such as apomorphine, on PPI seem to be independent of modifications of the ASR amplitude. Startle amplitude has also been shown to be modified by the activity state of the animal (39); the indication being that startle amplitudes were substantially smaller when rats were active as opposed to quiet. It would, however, seem unlikely that apomorphine at the doses used in the present study may have exerted an action to increase activity levels of the animals.

In conclusion, the findings of the present study indicate that ASR and PPI are not modified by the circadian cycle in male Wistar rats under the conditions employed in this study. Further, the increased sensitivity to apomorphine previously detected in the Wistar rat strain used in our laboratories and housed on a reversed light:dark cycle does not seem to be explained by testing during the animals' dark phase. Such findings may be of importance for other investigators using the PPI paradigm to study brain plasticity mechanisms and pharmacological manipulations of apomorphine-induced PPI deficits in rats housed under normal or reversed light:dark cycle conditions.

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