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Research article

Social interaction with rat exposed to constant light during lactation prevents depressive-like behavior induced by constant light in adulthood

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HIGHLIGHTS

- Constant light (LL) induces depressive-like behavior in rats.
- Neonatal constant light prevents LL-induced depressive-like behavior in adult rats.
- Social interaction with a rat exposed to neonatal constant light prevents LL-induced depressive-like behavior.

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ABSTRACT

Circadian rhythm disruptions are often observed in depressed patients, and changes in the light/dark cycle promote depressive-like behavior in animal models. Prolonged exposure to constant light (LL) is known to lead to arrhythmicity of circadian locomotor activity and depressive-like behavior in rats. Interestingly, neonatal exposure to LL prevents both arrhythmicity and depressive behavior in adulthood. Arrhythmic rats under LL conditions that cohabitate with a rhythmic rat exhibit improvement in circadian rhythms. We tested whether such cohabitation also protects against LL-induced depressive-like behavior. Wistar rats were assigned to conditions of either neonatal constant light (neonatal-LL) on postnatal days 10–22 or a regular light/dark cycle (neonatal-LD). On day 45, the animals were assigned to three possible pair combinations. After a baseline sucrose preference test, half of the pairs were placed under LL conditions. Weekly sucrose preference tests were conducted to evaluate depressive-like behavior. The animals were isolated by an aluminum wall on the test day. At week 2 of LL, sucrose preference was reduced in neonatal-LD/neonatal-LD pairs of animals. At week 5, neonatal-LD/neonatal-LD pairs exhibited anhedonic-like behavior, but the pairs with at least one neonatal-LL rat did not. The LL cycle was returned to an LD cycle, and the neonatal-LD/neonatal-LD pairs exhibited a restoration of sucrose preference 2 weeks later. We conclude that social interaction can prevent depressive-like behavior induced by circadian rhythm disruption as long as one of the animals is more prone to present a strong rhythm.

1. Introduction

The disruption of circadian rhythms has long been known to be related to mood disorders. Although the causality of this relationship is not well established, the manipulation of circadian rhythms via light schedules, meals, and social interaction might provide a valuable tool for improving treatments for mood disorders or even preventing their onset.

Constant light (i.e., conditions of a 12 h/12 h light/light [LL] cycle, in contrast to the usual light/dark [LD] cycle) has been shown to induce depressive-like behavior [9,19] and reduce hippocampal neurogenesis in animal models [12]. Prolonged exposure to LL also induces arrhythmicity in circadian locomotor activity [7]. Neonatal exposure to LL prevents this arrhythmicity in adulthood [4]. This protocol has been shown to prevent LL-induced depressive-like behavior [19]. Therefore, arrhythmicity appears to be essential for the effects of LL.

Rats under LL conditions that cohabitate with a rhythmic rat (i.e., a rat that was exposed to LL during weaning) exhibit improvements in circadian patterns of motor activity [3]. Therefore, we sought

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to determine whether this cohabitation can also protect against depressive-like behavior induced by LL. We hypothesized that pairs of rats that consist of at least one rat that was exposed to neonatal LL would be protected from LL-induced depressive-like behavior. We also hypothesized that pairs that consist of both animals that were not previously exposed to LL would be more resilient to the effects of LL than single-housed animals, given that social isolation has already been used as a model of depression [26].

2. Materials and methods

Adult male and female Wistar rats were obtained from the Federal University of Paraná and maintained under a controlled temperature (22 ± 3 °C) and 12 h/12 h light/dark (LD) cycle (lights on 7:00 AM – 7:00 PM). Food and water were available ad libitum. All of the animal procedures were approved by the Ethical Committee of Animal Experimentation of the Federal University of Paraná (protocol no. 600) and were in accordance with the Guide for the Care and Use of Laboratory Animals adopted by the Department of Pharmacology, Federal University of Paraná. The mating procedure involved placing each male in a cage with three female rats for 1 week as described previously [19]. For this experiment, 18 females were used, and 13 of them had litters.

2.1. Experimental design

On postnatal day 10–22, a total of 13 litters were assigned to two groups: neonatal-LD (control) group and neonatal-LL group (~200 lx) [19]. This developmental period has been reported to be the most sensitive for preventing arrhythmicity in adulthood [6]. The litters were randomized into neonatal-LD and neonatal-LL groups according to the total number of pups within each litter to minimize possible litter size effects. Seven litters were exposed to the regular LD cycle (36 males), and six litters (30 males) were exposed to LL. The behavior and weight of the dams were not evaluated during or after LL exposure. The LL-exposed rats were maintained in a separate room that was used specifically for this experiment. The neonatal-LD group was maintained in a common room. After weaning, we randomly distributed the male rats into pairs. To evenly distribute the influence of eventual fighting across groups, we avoided placing siblings together. During distribution of the pairs at weaning, the rats were weighed, and no differences were found between LD and LL animals. The animals were not further weighed throughout the experiment. As depicted in Fig. 1, the final experimental pairings were the following: neonatal-LD housed with neonatal-LD (LD-LD), neonatal-LD housed with neonatal-LL (LD-LL), and neonatal-LL housed with neonatal LL (LL-LL). We then randomly distributed the cages into the LD room ([LD-LD-LD], [LD-LL]-LD, and [LL-LL]-LD) and a room that would later be placed under LL conditions ([LD-LD]-LL, [LD-LL]-LL, and [LL-LL]-LL). Finally, for the rats in adulthood, we had five cages for each pair combination. Six neonatal-LD rats were assigned to an additional group that was housed two per cage but separated by an aluminum wall throughout the entire experiment. These no-pair animals were later placed under LL conditions (LD[no-pair]-LL). This group was included as an internal control, given that it was similar to our previous experiment with LL [19].

In a previous experiment, imipramine treatment rescued LL-induced anhedonic-like behavior while the rats were still maintained under LL conditions [19]. For this experiment, after detecting a reduction of sucrose preference in week 5, the rats that were under the LL cycle were returned to a regular LD cycle to evaluate possible spontaneous improvements in depressive-like behavior (Fig. 1).

2.2. Sucrose preference test

To evaluate anhedonic-like behavior, sucrose preference tests were conducted [27]. The tests consisted of a modified two-bottle choice procedure. When the rats were 45 days old, they were habituated to the sucrose solution (0.5%, w/v) for 2 days, during which they were allowed to choose freely between the sucrose solution and water. After 2 days, a baseline test was performed. To measure individual intake for each animal in the pair, the rats were separated by an aluminum wall for the duration of the test. The bottles were weighed before they were offered to the animals and weighed again 24 h later. Sucrose preference was calculated as the percentage of the volume of sucrose intake over the total volume of fluid intake. Subsequently, sucrose preference tests were performed weekly in the same manner.

In a previous experiment, the no-pair group exhibited a reduction of sucrose preference at week 3 [19]. Given that no reduction was observed in the current experiment at week 4, we sought to increase the sensitivity of the test by devaluating the reward. At week 5 of exposure to LL, we reduced the sucrose concentration by half (0.25%). The animals were first habituated to this concentration to minimize possible negative contrast effects [15]. For habituation, the animals were offered two bottles, one with water and the other with the new sucrose concentration, for 24 h. The test was then performed 1 day after the end of habituation. The tests at weeks 6 and 7 were also performed using this concentration.

2.3. Statistical analysis

The data are expressed as mean ± SEM and were analyzed using two-factor (group × week) repeated-measures analysis of variance

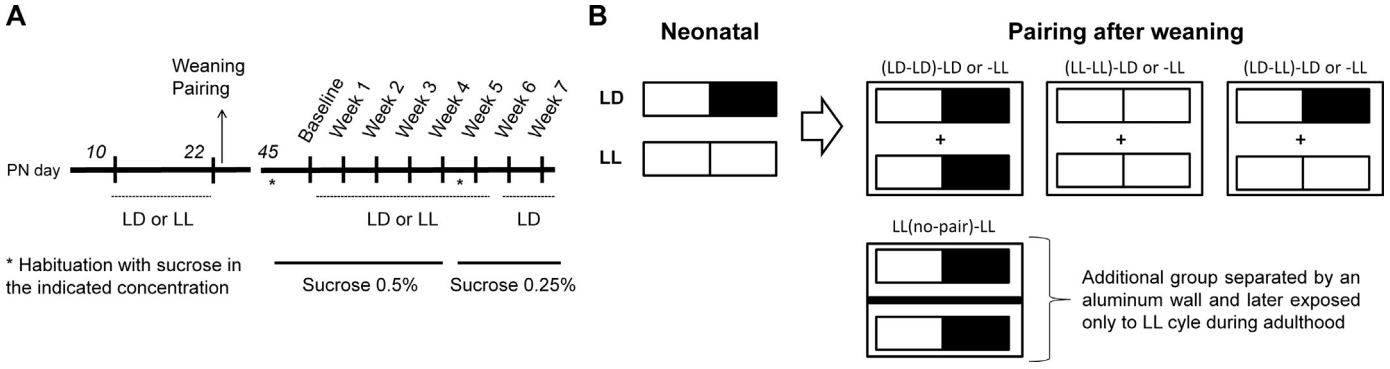

Fig. 1. (A) Experimental timeline and (B) group distribution. All pair combinations were set according to the neonatal light schedule and later divided into LD and LL groups in adulthood. *One additional group consisted of pairs of two rats that were housed in the same cage separated by an aluminum wall. These animals were all exposed to LL during adulthood, as in a previous study [5].

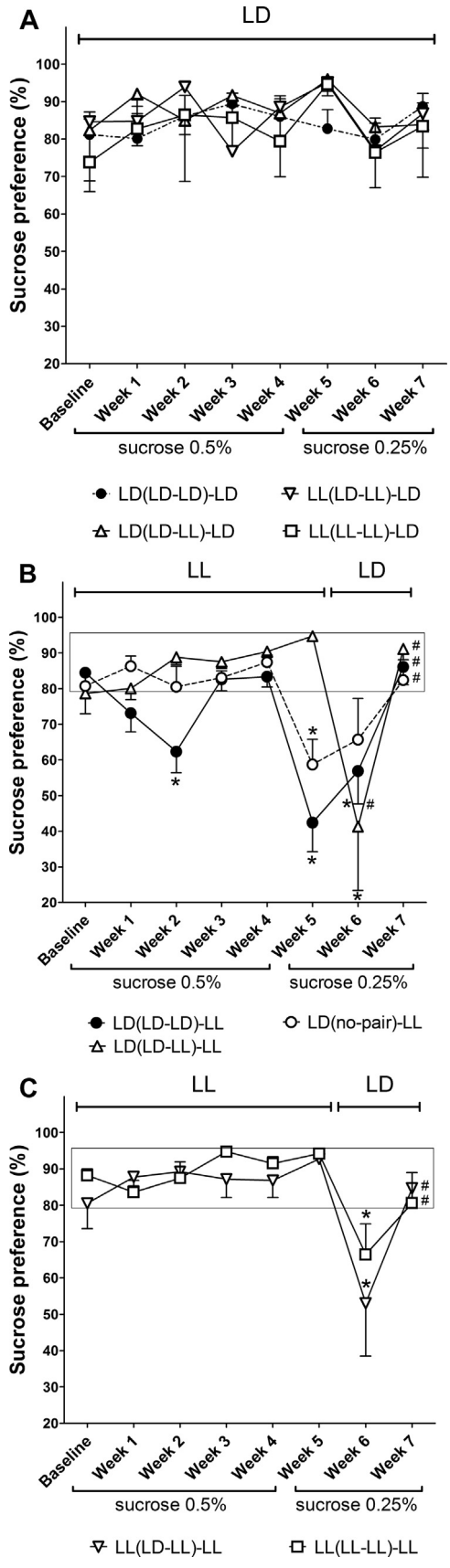

Fig. 2. Sucrose preference in rats subjected to constant light (LL) during the neonatal period and adulthood. (A) Control groups exposed to LD during all of adulthood. (B,C) Groups exposed to LL during weeks 1–5 and LD during weeks 6 and 7. The data are expressed as mean ± SEM (n = 5–10 rats/group). The box in B represents the maximum and minimum 95% confidence intervals (calculated from each week) for the control group (i.e., LD[LD-LD]-LD). *p < 0.05, compared with baseline in the same group; #p < 0.05, compared with previous week in the same group.LD, standard light/dark cycle; LL, light/light cycle (lights on for entire 24 h).†p < 0.05 compared with LD(LD-LD)-LD in the same week. The group abbreviations are the following: LD cycle during the neonatal phase (the pair in the cage during adulthood refers to the neonatal cycle)-LD cycle in adulthood. For example, LD(LD-LL)-LL indicates an animal that was under LD conditions during the neonatal phase and shared a cage with an animal that was under LL conditions during the neonatal phase, and both animals were exposed to LL during adulthood.

(ANOVA) followed by Duncan's post hoc test. Differences were considered statistically significant at $p < 0.05$.

3. Results

The ANOVA revealed significant main effects of group ($F_{8,57} = 5.80$, $p < 0.001$) and week ($F_{7,399} = 15.79$, $p < 0.001$) and a significant group × week interaction ($F_{56,399} = 3.73$, $p < 0.001$). In week 2, neonatal-LD animals that were housed in pairs with one another (other neonatal-LD rat) and exposed to LL in adulthood (LD[LD-LD]-LL) exhibited a reduction of sucrose preference compared with baseline ($p < 0.05$) and the equivalent LD group (LD[LD-LD]-LD; $p < 0.05$), but this difference did not persist in weeks 3 or 4, during which preference returned to control levels (Fig. 2B).

After reward devaluation (weeks 5–7), neonatal-LD animals that were exposed to LL in adulthood, both animals that were housed in pairs with similar animals (i.e., LD[LD-LD]-LL; $p < 0.001$) and animals that were separated by the aluminum wall (i.e., LD[no-pair]-LL; $p < 0.01$), exhibited a reduction of sucrose preference in week 5 compared with baseline (Fig. 2B). LD(LD-LD)-LL and LD(no-pair)-LL rats also exhibited a reduction of sucrose preference compared with the control group (LD[LD-LD]-LD) and the other groups that were exposed to LL (LD[LD-LL]-LL and LL[LL-LL]-LL; $p < 0.05$ for all comparisons).

One week after changing the light schedule from LL back to LD in week 6, all of the groups that were previously protected from LL-induced anhedonia-like behavior (i.e., all of the groups with at least one neonatal-LL rat in the cage) exhibited a reduction of sucrose preference ($p < 0.01$; Fig. 2B and C). In week 6, the LD(LD-LL)-LL and LL(LD-LL)-LL groups exhibited a reduction of sucrose preference compared with the LD-(LD-LD)-LD group ($p < 0.001$), but the LL(LL-LL)-LL group did not. The LD(LD-LD)-LL group also exhibited an increase in sucrose preference compared with the previous week ($p < 0.005$), although sucrose preference in this group was significantly lower compared with baseline ($p < 0.05$). In the second week under LD conditions (week 7), sucrose preference was at baseline levels in all of the groups that were previously exposed to the LL cycle, with no differences compared with the LD(LD-LD)-LD group.

4. Discussion

The main finding of the present study was that LL-induced anhedonia-like behavior could be prevented by social interaction with an animal that was presumed to be rhythmic. These results reinforce the influence of circadian rhythms on mood and extend our previous data that showed that LL induces anhedonia, which can be reversed by imipramine treatment [19]. In this study, rats with a stronger rhythm under LL conditions were protected from depressive-like behavior, consistent with a previous study [19], but the presence of rats with stronger rhythms also protected the other rat in the cage from exhibiting anhedonia-like behavior.

However, LL with standard constant light (200 lx) is not the only manipulation that promotes depressive-like behavior. Another type of LL that employs a dim light (~5 lx) rather than a normal light at night also decreases sucrose preference and increases the latency to float in the Nile grass rat, which is a diurnal rodent

[10]. Moreover, citalopram reversed depressive-like behavior in the forced swim test in ovariectomized female hamsters that were exposed to dim light at night [1].

Cohabitation with a rhythmic rat was shown to improve locomotor activity and temperature rhythms in a previous study [3] and prevent anhedonia in arrhythmic rats in the present study. In the previous study, social interaction commenced after long-term exposure to LL, and the animals that were born under the LD condition exhibited gradual increases in the stability of their temperature rhythms. In the present study, the animals were already in the same cage at the time LL was imposed to prevent the weakening of circadian rhythm stability rather than rescue such stability later. Another difference between these studies was that we examined all possible combinations of neonatal-LL and neonatal-LD pairings, whereas the previous study [3] examined only one group, which involved social interactions between animals with strong and weak rhythms under LL conditions. Notably, interactions with neonatal-LD rats increased rhythm stability in neonatal-LL rats during cohabitation [3]. However, as addressed in another study, social interaction itself does not delay the time at which the animals become arrhythmic under LL conditions [2]. Accordingly, we observed that social interactions between two animals that were expected to show weak or absent rhythms were insufficient to prevent LL-induced anhedonia-like behavior. Therefore, to prevent or rescue the depressive phenotype, social interaction must strengthen circadian rhythmicity. To further support this conclusion, after long exposure to LL, the pairs of protected animals could be switched (i.e., by replacing a neonatal-LL rat with a neonatal-LD rat). Thus, according to our hypothesis and the present results, we expect that the new pair would become more susceptible to depressive-like behavior. Instead, we opted to test whether the anhedonic-like behavior induced by LL would be restored by switching the light/dark cycle back to LD.

Unexpectedly, sucrose preference in anhedonia-protected animals was reduced after their light/dark cycles were changed from LL to the regular LD schedule. Because this reduction occurred in LL animals that were supposed to be rhythmic and exhibited high sucrose preference, this shift may have been too abrupt and caused temporary mood changes. For example, after a delay of 10 h in the light/dark schedule, male Wistar rats exhibited desynchronization of the dorsomedial and ventrolateral portions of the suprachiasmatic nucleus that lasted for approximately 6 days [21]. Additionally, chronic light/dark shifts have been shown to be stressful and reduce immune responses in rats [16].

In the present study, the reduction of the sucrose concentration effectively increased the sensitivity of the sucrose preference test. Importantly, all of the control groups that were always under the LD cycle during adulthood were unaffected by this reduction (Fig. 1A). In our previous study [19], we observed reductions of sucrose preference in the third week of LL while sucrose concentrations remained constant. Therefore, the difference between the present and previous results may be attributable to a borderline effect of LL exposure (i.e., when a 0.5% sucrose solution is used, the results are more variable). Another possibility is that the high hedonic value of the sucrose solution could have masked differences between groups. Depressive-like effects of LL after 4 and 8 weeks have been reported using a 5% sucrose concentration [23]. However, this previous study used a different procedure for the sucrose preference test that included food and water deprivation, which we chose to avoid. Moreover, other unknown factors might have influenced the sensitivity to LL and responses to the sucrose concentration. Interestingly and consistent with our hypothesis, a recent study confirmed that these animals were arrhythmic under LL conditions [23].

The present results may be related to the loss of circadian rhythms or changes in these rhythms. Other light/dark cycle manipulations, such as shortening the photoperiods for both diurnal and nocturnal animals [8,22], exposure to constant darkness [14], and changing the 24 h period to a 7 h period with 3.5 h of light and 3.5 h of dark [17], have also been shown to cause depressive-like behaviors. A common feature of these studies is that these manipulations did not lead to the loss of circadian locomotor activity rhythms. Thus, although the loss of circadian rhythms can induce depressive-like behaviors, such loss is not necessary to induce depression. Moreover, the mechanism of the induction of depressive-like behavior does not appear to involve reductions of neurogenesis. One study did not detect a reduction of neurogenesis after arrhythmicity induced by prolonged LL exposure [20].

Changes in the light/dark cycle can influence mood by modulating circadian rhythms, and light can also influence mood through a direct pathway [18]. For example, light has an acute arousal effect in humans. Interestingly, this effect is also observed in a small portion of blind patients, suggesting a role for melanopsin-expressing retinal ganglion cells [25]. Mice that did not express photosensitive retinal ganglion cells also did not exhibit depressive-like behavior or memory impairments after exposure to a 7 h light/dark period [17]. Interestingly, depressive-like behavior induced by constant light in mice was partially reversed by providing an opaque tube for escape from the light [9]. Therefore, constant light might also lead to anhedonia through a direct effect of light. Although animals that are exposed to LL during lactation have normal synchronization to the light/dark cycle [4], one cannot exclude the possibility that a reduction of sensitivity to light protects against LL-induced anhedonia. In fact, the response to light pulse-induced phase shifts in animals under constant darkness was reduced, depending on the number of days of LL exposure during lactation, although this effect was only observed in a specific phase of the subjective day during which the light pulse was administered [5]. In the present study, both rats that were exposed to LL during lactation and cage conspecifics that were exposed to LD during lactation were protected from the reduction of sucrose preference under LL conditions in adulthood, thus reinforcing the putative role of improvements in circadian rhythmicity in protection against anhedonia.

Unexpectedly, pairs of rats under a regular LD cycle during lactation that were exposed to a LL cycle in adulthood exhibited a reduction of sucrose preference in the second week of LL (i.e., before reward devaluation), whereas the single-housed animals did not. Perhaps social interactions between two arrhythmic animals have more deleterious effects compared with rats that are arrhythmic and single-housed. However, the reduction of sucrose preference was transient. The level of preference was restored to normal levels by the third week, and both groups exhibited a reduction of sucrose preference after devaluation of the sucrose solution. Additionally, the aluminum wall did not provide complete separation, and the animals might have still been influenced by each other through movement and noise.

The sucrose preference test protocol that was used in the present study spanned over 24 h for behavioral evaluation during the entire circadian period. Animals that are exposed to LL during lactation are expected to have a lengthened circadian period under LL conditions in adulthood [4]. Control animals that are exposed to LL conditions initially show a lengthened period and gradually become arrhythmic. Not necessarily all animals that are exposed to LL become arrhythmic; they might be free-running with a lengthened circadian period as well. Therefore, the sucrose preference test did not span the entire cycle of all of the animals in this study, which might have influenced the results of the sucrose preference test. However, the groups that were more prone to show a lengthened circadian period in LL conditions were the pairs that contained at least one rat that was exposed to LL during lactation (i.e., the same pairs that were protected from depressive-like behavior). Rats ingest more liquid during their active phase and exhibit an increase in

sucrose preference in the dark phase, although this effect faded after repeated testing [24]. Thus, not covering part of the inactive phase may not have significantly impacted the results of the sucrose preference test, whereas not covering part of the active phase could result in lower sucrose preference. However, the groups of animals that were expected to have a lengthened circadian period were also the groups that did not exhibit a reduction of sucrose preference.

In conclusion, the present results are consistent with previous studies that showed that disrupting circadian rhythms can trigger depressive-like behavior [23]. Considering the effects of constant light and cohabitation [3], our results also suggest that the maintenance of circadian rhythms caused by social interaction can restore depressive-like behavior. This result should be relevant for non-pharmacological treatments that seek to recover circadian rhythms for mood disorders, such as Interpersonal Social Rhythm Therapy [11] and bright light therapy [13].

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