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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

Bruno Jacson Martynhak*, Luiz Kae Sales Kanazawa, Guilherme Messias do Nascimento, Roberto Andreatini

Departamento de Farmacologia, Universidade Federal do Paraná Cel. Francisco H. dos Santos, Centro Politécnico, Curitiba, Paraná 81530-900, Brazil

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

* Corresponding author. Tel.: +55 4133611693.
E-mail address: brunojm@ymail.com (B.J. Martynhak).

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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

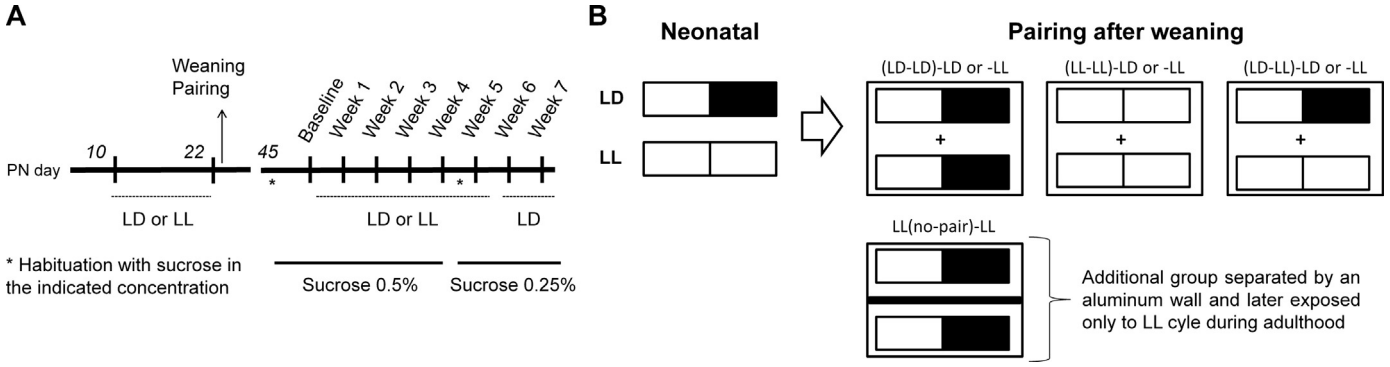

Fig. 1. (A) Experimental timeline and (B) group distribution. All pair combinations were set according to the neonatal light schedule and later divided into LD and LL groups in adulthood. *One additional group consisted of pairs of two rats that were housed in the same cage separated by an aluminum wall.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