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Acute total sleep deprivation potentiates cocaine-induced hyperlocomotion in mice

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HIGHLIGHTS

- Total sleep deprivation potentiated cocaine-induced hyperlocomotion in mice.
- Total sleep deprivation potentiated the impulsivity of mice under cocaine effect.
- Data suggest the contribution of the sleep condition to cocaine primary effects.

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ABSTRACT

Sleep deprivation is common place in modern society. Nowadays, people tend to self-impose less sleep in order to achieve professional or social goals. In the social context, late-night parties are frequently associated with higher availability of recreational drugs with abuse potential. Physiologically, all of these drugs induce an increase in dopamine release in the mesolimbic dopaminergic system, which leads to hyperlocomotion in rodents. Sleep deprivation also seems to play an important role in the events related to the neurotransmission of the dopaminergic system by potentiating its behavioral effects. In this scenario, the aim of the present study was to investigate the effects of total sleep deprivation (6 h) on the acute cocaine-induced locomotor stimulation in male mice. Animals were sleep deprived or maintained in their home cages and subsequently treated with an acute i.p. injection of 15 mg/kg cocaine or saline and observed in the open field. Total sleep deprivation for 6 h potentiated the hyperlocomotion induced by acute cocaine administration. In addition, the cocaine sleep deprived group showed a decreased ratio central/total locomotion compared to the cocaine control group, which might be related to an increase in the impulsiveness of mice. Our data indicate that acute periods of sleep loss should be considered risk factors for cocaine abuse.

1. Introduction

Sleep deprivation is becoming a feature of the human's current lifestyle. Nowadays, it is not unusual to skip one night's sleep due to job or parties [1]. The homeostatic changes caused by the sleep patterns of a 24/7 life-schedule lead to several deleterious consequences, including innumerous psychiatric disorders. Of note, late-night parties are usually associated with the use of recreational drugs of abuse, which continues to expand without limitations [2].

Regardless of their specific mechanisms, all drugs with abuse potential induce an increase in dopamine release in the mesolimbic dopaminergic system, particularly in the nucleus accumbens [3], which modulates both their rewarding and psychomotor arousal effects [4,5]. In fact, locomotor stimulation in rodents has been extensively related to increased dopaminergic neurotransmission in the mesoaccumbens system [6,7], and acute administration of most common drugs of abuse stimulate locomotor activity in rodents [8–11].

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[1] This paper is in memory of Dr. Roberto Frussa-Filho, who dedicated his entire life to Science, because a man is alive while his name is still spoken.

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Sleep deprivation also seems to play an important role in the events related to the neurotransmission of the dopaminergic system. Increased density of both D_1 [12,13] and D_2 dopaminergic receptors [14] in the mesoaccumbens dopamine system has been reported following sleep deprivation periods. In addition, animal studies describe increased dopamine release and increased firing of dopaminergic neurons associated with functional hyperactivity of the dopaminergic system after sleep deprivation [15,16].

Thus, both sleep loss and psychostimulants administration seem to be related to increased responsiveness of the mesoaccumbens dopaminergic system. Bearing this in mind, and because sleep loss is a condition frequently associated with drug availability during nighttime parties, the aim of the present study was to investigate the effects of acute total sleep deprivation (6 h) on the acute locomotor stimulation produced by cocaine.

2. Materials and methods

2.1. Subjects

Three-month-old Swiss male mice (45–50 g, outbred, raised at CEDEME, UNIFESP) were used in the experiments. Animals were housed 7 per cage under controlled temperature (22–23 °C) and lighting (12 h light, 12 h dark; lights on at 6:45 a.m.) conditions with free access to food and water throughout the entire study. The protocol used in the present study was in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals and with the Brazilian Law for Procedures for Animal Scientific Use (#11794/2008), and was approved by the Institutional Ethical Committee of UNIFESP (#1608/11).

2.2. Drug

Cocaine (Sigma®) was dissolved in 0.9% saline solution, which was used as control solution. Both cocaine and control solutions were given intraperitoneally at a volume of 10 ml/kg body weight. Cocaine was administered at the dose of 15 mg/kg.

2.3. Sleep deprivation (SD)

Mice were subjected to total SD through the gentle handling method, which consists of keeping the animals awake in their home cage by gentle manipulations whenever behavioral signs of sleep were observed, as previously validated in our laboratory [9,17]. Mice were sleep-deprived for 6 h (starting at 8 a.m.) immediately before behavioral evaluations. It has been previously demonstrated that this protocol of SD leads to almost total suppression of both paradoxical (REM) and slow wave sleep (97.8%) in mice [18].

Besides the gentle handling method, which deprives mice from total sleep (both paradoxical/REM and slow-wave sleeps), the paradoxical (REM) sleep deprivation (PSD) by the multiple platform method is another widely used model to evaluate the effects of sleep loss in mice. This method selectively suppresses paradoxical (REM) sleep because mice are placed into a platform surrounded by water and when they experience muscle atonia, which is characteristic of paradoxical (REM) sleep, animals contact the water and wake up [9]. However, situations of total SD are more common than a specific PSD in humans. In this scenario, we chose to conduct a total SD protocol in order to achieve a more circumspect translational applicability.

2.4. Assessment of locomotor activity

Animals were individually placed in the center of the open-field arena for direct quantification of locomotor activity during 10 min as previously described by Chinen et al. [19]. During the 10-min session, the total locomotion (total number of entries into any floor unit with the four paws) and the central locomotion (number of entries into any floor unit not contiguous to the apparatus walls) were measured using hand operated counters by an observer who was blind to treatment allocation.

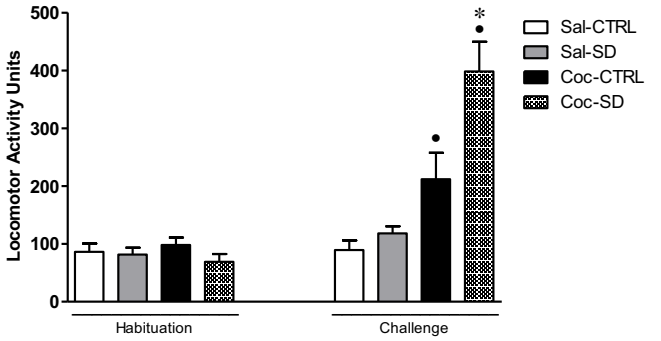

Fig. 1. Total locomotion of mice in the open field during the third habituation day or in the challenge session, when mice were sleep deprived (SD) or maintained in their home cages (CTRL) and subsequently treated with an acute cocaine (Coc, 15 mg/kg) or saline (Sal) i.p. injection. Total sleep deprivation for 6 h potentiated the hyperlocomotion induced by acute cocaine administration. Data are reported as mean ± SEM ($n = 12$ per group). •$p < 0.05$ compared to its respective saline control group (within day); *$p < 0.05$ compared to the Coc-CTRL group. One-way ANOVA (habituation) or two-way ANOVA followed by Tukey's test (challenge).

2.5. Experimental procedure

Forty-eight mice were given a 10-min habituation period in the open-field on 3 consecutive days and basal locomotor activity was measured on day 3. Four groups of animals were formed ($n = 12$ per group), which were statistically equivalent with respect to the basal levels of locomotor activity. Twenty-four hours after the third day of habituation, mice were kept in their home cages (Sal-CTRL and Coc-CTRL groups) or were sleep deprived for 6 h (Sal-SD and Coc-SD groups). After the end of the 6 h period, animals received an i.p. injection of saline (Sal) or 15 mg/kg cocaine (Coc) 5 min prior to being placed in the open-field apparatus for 10 min for the quantification of their locomotion frequency.

2.6. Statistical analysis

For the analysis of the habituation data, 1-way ANOVA was performed. The SD/cocaine challenge data were evaluated by 2-way ANOVA with treatment (cocaine *vs* saline) and sleep condition (SD *vs* CTRL) as between subject factors. Tukey's test was used as *post hoc* test. A p value less than 0.05 was considered to be a statistically significant difference.

3. Results

Data from the habituation and challenge sessions are shown in Fig. 1. In the habituation session, 1-way ANOVA did not show significant differences between groups [$F(3,44) = 0.85$, $p > 0.05$]. On the challenge day, 2-way ANOVA showed a significant interaction effect between sleep condition (SD *vs* control) and treatment (cocaine *vs* saline) factors [$F(1,46) = 4.81$, $p < 0.05$], thereby revealing the potentiation of the acute cocaine stimulant effect in animals under total SD. In fact, Tukey's *post hoc* test showed that an acute cocaine injection increased the locomotion frequency of mice (Coc-CTRL > Sal-CTRL), which was potentiated by a previous SD period (Coc-SD > Coc-CTRL).

Because impulsivity has clear relevance to substance-use disorders [20] and a decrease of the ratio central/total locomotion may be an indication of impulsivity [21], this parameter was analyzed