



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.

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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 innumerable 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.

Sleep deprivation also seems to play an important role in the events related to the neurotransmission of the dopaminergic system. Increased density of both D₁ [12,13] and D₂ 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

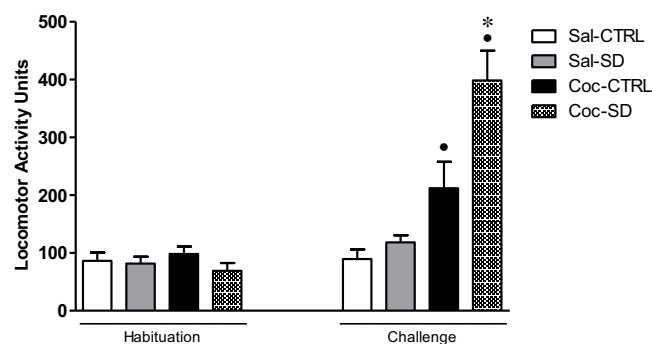


Fig. 1. Total locomotion of mice in the open field during the third habituation day or in the challenge session, when mice were sleep deprived (SD) or maintained in their home cages (CTRL) and subsequently treated with an acute cocaine (Coc, 15 mg/kg) or saline (Sal) i.p. injection. Total sleep deprivation for 6 h potentiated the hyperlocomotion induced by acute cocaine administration. Data are reported as mean \pm SEM ($n = 12$ per group). $\bullet p < 0.05$ 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).

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.

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

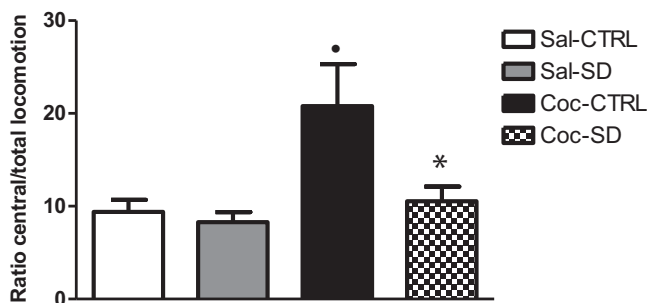


Fig. 2. Ratio central/total locomotion in mice submitted to sleep deprivation (SD) or maintained in their home cages (CTRL) and subsequently treated with an acute cocaine (Coc, 15 mg/kg) or saline (Sal) i.p. injection. Cocaine induced a decrease in central locomotion frequency of mice, which was reverted by total sleep deprivation for 6 h. Data are reported as mean \pm SEM ($n = 12$ per group). • $p < 0.05$ compared to the Sal-CTRL group; * $p < 0.05$ compared to the Coc-CTRL group. Two-way ANOVA followed by Tukey's test.

for the data of the challenge session, as shown in Fig. 2. Two-way ANOVA showed a significant interaction effect between sleep condition (SD vs control) and treatment (cocaine vs saline) factors [$F(1,46) = 3.21, p < 0.05$]. Tukey's *post hoc* test revealed a higher ratio central/total locomotion frequency in mice treated with cocaine and kept in their home cages (Coc-CTRL), as well as a decrease of this ratio in the group previously deprived of sleep in response to cocaine (Coc-SD) compared to the cocaine control group (Coc-CTRL).

4. Discussion

In the present study, our major findings were that acute total SD (6 h) potentiated the hyperlocomotor effects of cocaine in mice, and this effect was accompanied by a decrease in the cocaine-induced higher ratio central/total locomotion.

As far as we know, this is the first study reporting the effects of acute total SD on cocaine-induced locomotor stimulation. In this respect, it has been widely demonstrated that SD shares similar neurobiological effects with psychostimulants. Drugs such as cocaine and amphetamine dramatically elevates mesoaccumbens dopamine function [3], and the same effects occur after SD [12–14,22–25]. Thus, the hyperresponsiveness of sleep deprived mice to cocaine could reflect an exacerbated function of the mesolimbic dopaminergic system due to the combination of these two factors.

This potentiating effect was accompanied by decreased ratio central/total locomotion in the cocaine sleep deprived group compared to the cocaine control group. Relative to the total locomotion frequency during the whole challenge session, mice treated with cocaine showed a decreased central locomotion frequency compared to those treated with saline (Coc-CTRL > Sal-CTRL, Fig. 2). Notwithstanding, animals that were sleep deprived before the acute cocaine challenge showed a reduced ratio central/total locomotion compared to the cocaine control group (Coc-SD < Coc-CTRL, Fig. 2). This is an interesting finding, because changes in rodents' spatial distribution are usually explained as a result on emotionality [26]. Rodents spontaneously prefer the periphery of the open field to activity in the central parts of the apparatus, and an increase of the ratio central/total locomotion usually indicates anxiolysis [27]. In addition, activity in the central parts of the open field is also used as a marker of impulsivity because high impulsive rats show a markedly enhanced preference for the open-field central squares [28–31]. Thus, our data suggest that total SD may have reduced the anxiety effects of cocaine or enhanced mice's impulsivity despite of cocaine-induced anxiety. Because previous studies have reported that both acute cocaine administration and SD *per se* are capable

of inducing anxiogenic effects in rodents [32–35], the decreased ratio central/total locomotion in the cocaine sleep deprived group might be related to an increase in impulsiveness rather than to an anxiolytic effect.

High impulsive rats show greater escalation of cocaine self-administration [36] and an increased propensity to develop compulsive cocaine-seeking and relapse compared with low impulsive rats [37,38]. Thus, impulsivity is a behavioral construct that is highly associated with drug addiction [39], being a vulnerability marker for substance-use disorders [20]. Preclinical and clinical studies demonstrate that high impulsivity and its related psychopathological disorders involve a dysregulation of the brain dopaminergic systems [40–42]. Hence, the increased responsiveness of the dopaminergic system induced by both SD [43] and cocaine [44] could also be responsible for the impulsive-like behavioral profile observed in SD mice under cocaine effects.

Drug addiction has been conceptualized as a disorder that progresses from impulsivity to compulsivity [45]. Additionally, nowadays it is not unusual to skip one night's sleep due to a party, for example, where there is a greater availability of abusive drugs. Thus, although the above mentioned assumptions are speculative, the fact that SD potentiates the acute cocaine stimulant effect and the impulsivity of mice under cocaine influence indicate that acute periods of sleep loss should be considered risk factors for cocaine abuse.

5. Conclusions

Our data demonstrated that 6 h total SD potentiated acute cocaine-induced locomotor-stimulant effect and induced an impulsive-like behavior in cocaine-treated mice. Although one must always be wary of extrapolating clinical relevance from animal data, from a translational point of view our data indicate that acute periods of sleep loss should be considered risk factors for cocaine abuse. When present immediately before cocaine's first use, SD would elicit an impulsive behavior, thereby reversing cocaine-induced anxiety, and potentiate the acute cocaine stimulant effect. Thus, lack of sleep, a condition frequently observed during events in which drugs of abuse are socially available, might be a strong contributor to the continuation of cocaine use after its primary experience.

Conflicts of interest

The authors declare there are no conflicts of interest.

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