Pharmacology, Biochemistry and Behavior xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Sleep deprivation impairs the extinction of cocaine-induced environmental conditioning in mice

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ARTICLE INFO

Article history:
Received 24 February 2014
Received in revised form 22 April 2014
Accepted 8 May 2014
Available online xxxx

Keywords:
Sleep
Cocaine
Behavioral sensitization
Conditioning
Extinction
Mice

ABSTRACT

Persistence of a drug–environment conditioning induced by repeated psychostimulant treatment is thought to play a key role in the addictive cycle. In addition, sleep disorders are a common feature in patients with addictive disorders. Sleep deprivation shares similar neurobiological effects with psychostimulants. Therefore, we investigated whether sleep deprivation would impair the extinction of previously established conditioning between the drug effect and the environmental cues. Four cohorts of male adult mice underwent a behavioral sensitization procedure pairing drug (cocaine at 15 mg/kg, i.p.) or saline with environment (open-field apparatus). The extinction of conditioned locomotion was evaluated after control (home-cage maintained) or sleep deprivation (gentle handling method for 6 h) conditions. Sleep deprivation both postponed the initiation and impaired the completeness of extinction of the conditioned locomotion promoted by previous drug–environment conditioning in cocaine-sensitized animals. While the cocaine control group required 5 free-drug sessions of exposure to the open-field apparatus to complete extinction of conditioned locomotion, the cocaine pre-treated group that experienced sleep deprivation before each extinction session still significantly differed from its respective control group on Day 5 of extinction. The possibility that the sleep condition can influence the extinction of a long-lasting association between drug effects and environmental cues can represent new outcomes for clinically relevant phenomena.

1. Introduction

It has been widely demonstrated that repeated administration of psychostimulants in rodents produces a progressive and enduring increase in their psychomotor and positive reinforcing effects, which is usually measured in terms of locomotion (Bellot et al., 1997; Collins et al., 2011; Robinson and Berridge, 1993). This phenomenon, called behavioral sensitization, can be useful for studying the mechanisms underlying drug craving in humans, because sensitization-related neuroplasticity in brain reward system, especially in the mesoaccumbens dopamine system, may contribute to addiction (De Vries et al., 1998; Kalivas and Stewart, 1991; Robinson and Berridge, 1993). From a neurochemical point of view, drugs with abuse potential induce an increase in dopamine release in the mesolimbic dopamine system — specifically in the nucleus accumbens (for review see Koob and LeMoal, 2006). In addition, sensitization to the locomotor-stimulating effect of psychostimulants appears to require alterations within the mesoaccumbens dopamine system including autoreceptor subsensitivity in the ventral tegmental area, as well as increased dopamine release and increased D1 dopamine receptor sensitivity in the nucleus accumbens (Henry and White, 1991; Wolf et al., 1993, 1994).

Sleep deprivation seems to play an important role in the events related to the plasticity of the dopaminergic system. After sleep deprivation, animals present several symptoms that appear to mimic or potentiate those elicited by psychostimulants: hyperactivity, aggressiveness, hypersexuality, and stereotypy (Ferguson and Dement, 1969; Troncone et al., 1988; Tufik et al., 1978; Tufik, 1981a,b). These sleep deprivation-related behavioral changes have been explained by supersensitivity of dopaminergic postsynaptic receptors (Tufik, 1981a,b). Concerning the specific effects of sleep deprivation on the mesoaccumbens dopamine system, increased density of both D1 (Demontis et al., 1990; Fadda et al., 1993) and D2 dopamine receptors (Nunes et al., 1994) has been reported. Additionally, animal studies describe increased dopamine release and increased firing of dopaminergic neurons associated with functional hyperactivity of the dopaminergic system after sleep

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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.

http://dx.doi.org/10.1016/j.pbb.2014.05.001
0091-3057/

deprivation and behavioral sensitization to dopaminergic agonists (Ebert and Berger, 1998; Gessa et al., 1995).

Thus, both sleep deprivation and behavioral sensitization to psychostimulants seem to be related to increased responsiveness of the mesoaccumbens dopaminergic system. Physiologically, enhanced dopamine release in the nucleus accumbens signals the appearance of an important event that requires the creation and engagement of an adaptive behavioral strategy (Berridge and Robinson, 1998; Kalivas, 2002; Schultz, 1998). Within this context, it is reasonable to assume that the magnitude of dopamine release elicited by most drugs of abuse would result in the development of potent learned associations between the drug experience and the environmental stimuli (Kalivas, 2002). Indeed, an important aspect concerning both drug craving in humans and behavioral sensitization in rodents is the potentiating effect of environmental cues previously paired with drug effects on the development of both behavioral sensitization (Battisti et al., 2000; Chinen et al., 2006; Crombag et al., 2001) and drug craving (Carter and Tiffany, 1999; Childress et al., 1986; Niaura et al., 1988). Concerning animal studies, this drug–environment classical conditioning can be verified by an enhanced locomotor activity (conditioned locomotion) presented in a free-drug session performed in an experimental environment (such as an open-field) previously paired with the drug (Alvarez et al., 2006; Carey and Gui, 1997; Carey et al., 2008; Chinen et al., 2006). Importantly, a key dimension of conditioned behavior is that it undergoes extinction when tests are repeatedly given in the presence of the environment conditioned stimulus but in the absence of the drug (Carey and Gui, 1997).

Taking into account the common neuroadaptations underlying sleep deprivation, behavioral sensitization, and drug-induced environmental conditioning, we have previously demonstrated that sleep deprivation potentiated behavioral sensitization to amphetamine by increasing its conditioned component (Frussa-Filho et al., 2004). In that study, immediately after sleep deprivation, mice were given a priming injection of the psychostimulant and 7 days later were challenged with a second injection. Sleep deprivation potentiated the behavioral sensitization only when the priming psychostimulant injection was paired with the observation apparatus (open-field). In addition, we showed in a more recent study that when mice were allowed to sleep for 24 h after the sleep deprivation procedure and before the priming injection of amphetamine, the sleep rebound period attenuated the context-dependent behavioral sensitization induced by this psychostimulant (Calzavara et al., 2008).

The aim of the present study was to investigate the effects of sleep deprivation on the extinction of the conditioned locomotion of previously cocaine-sensitized mice. Because sleep deprivation potentiates the development of context-dependent psychostimulant-induced behavioral sensitization and sleep rebound attenuates it, our hypothesis was that sleep deprivation would impair the extinction of previously established drug–environment conditioning.

2. Experimental procedures

2.1. Animals

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, in polypropylene cages (30 × 20 × 12.5 cm), under controlled temperature (22–23 °C) and lighting (12 h light, 12 h dark; lights on at 6:45 a.m.) conditions. Mice were allowed at least 2 weeks of adaptation to the housing facilities before the start of the experiment. Food and water were available ad libitum throughout the entire study.

Animals used in this study were maintained in accordance with the National Institute of Health Guide for the care and use of laboratory animals (NIH Publications Nº 80-23, revised 1996), the EU Directive 2010/63/EU for animal experiments and the Brazilian Law for Procedures for Animal Scientific Use (#11794/2008). The experimental procedure 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.

2.3. Sleep deprivation

Mice were subjected to sleep deprivation through the gentle handling method, which consists of keeping the animals awake in their home cage by gently touching them with a soft brush and, if necessary, by tapping on or moving the cage, whenever behavioral signs of sleep, such as closed eyes or sleep posture, are observed (see Patti et al., 2010). Mice were sleep-deprived for 6 h (starting at 8 a.m.) immediately before behavioral evaluations. Food and water were available ad libitum throughout the entire period.

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. The open-field apparatus used in the present study was a circular wooden box (40 cm in diameter and 50 cm high) with an open top and a floor divided into 19 squares, as previously described by Chinen et al. (2006). Hand-operated counters were used to score total locomotion frequency (number of floor units entered). The observers were blind to treatment allocation.

The apparatus was cleaned with alcohol–water (5%) solution before each behavioral test to eliminate possible bias due to odors left by previous mice.

2.5. Experimental procedure

Thirty-nine mice were given a 10-min habituation period in the open-field on 3 consecutive days. Basal locomotor activity was measured on day 3. Four groups of animals were formed (N = 9–11), which were statistically equivalent with respect to the basal levels of locomotor activity. Twenty-four hours after the third day of habituation, the behavioral sensitization procedure began. 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, in 4 alternate days, in order to establish a drug–environment conditioning. Ten-minute sessions were performed because this period of time has been demonstrated to be effective in detecting psychostimulant-induced behavioral sensitization in mice (Bellot et al., 1997; Frussa-Filho et al., 2004). During the alternate non-conditioning days, mice were left undisturbed in their home-cages. On days 1 and 4 of the behavioral sensitization protocol animals were observed for the quantification of their locomotion frequency.

Forty-eight hours after the last day of the behavioral sensitization procedure, the extinction protocol began. Mice were kept in their home cages (control condition; Sal-CTRL, N = 11, and Coc-CTRL, N = 8) or were sleep deprived for 6 h (SD condition; Sal-SD, N = 11, and Coc-SD, N = 9). After the end of the 6 h period, mice received an i.p. injection of saline and were placed, 5 min later, in the open-field apparatus for 10 min. This protocol was repeated during alternate days until the complete extinction of the conditioned locomotion expressed by the cocaine control group (Coc-CTRL) (e.g., when the locomotor frequency exhibited by the Coc-CTRL group did not significantly differ anymore from that exhibited by the Sal-CTRL group). On the alternate non-extinction days, mice were left undisturbed in their home-cages. During all days of extinction, animals were individually observed in the open-field arena for

Please cite this article as: Berro LF, et al, Sleep deprivation impairs the extinction of cocaine-induced environmental conditioning in mice, Pharmacol Biochem Behav (2014), http://dx.doi.org/10.1016/j.pbb.2014.05.001