Pharmacology, Biochemistry and Behavior 117 (2014) 7–16

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

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

Acute total sleep deprivation potentiates amphetamine-induced locomotor-stimulant effects and behavioral sensitization in mice ☆

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ARTICLE INFO

Article history:
Received 1 May 2013
Received in revised form 13 November 2013
Accepted 23 November 2013
Available online 4 December 2013

Keywords:
Amphetamine
Behavioral sensitization
Hyperlocomotion
Mice
Paradoxical sleep deprivation
Total sleep deprivation

ABSTRACT

It has been demonstrated that a prolonged period (48 h) of paradoxical sleep deprivation (PSD) potentiates amphetamine (AMP)-induced behavioral sensitization, an animal model of addiction-related neuroadaptations. In the present study, we examined the effects of an acute short-term deprivation of total sleep (TSD) (6 h) on AMP-induced behavioral sensitization in mice and compared them to the effects of short-term PSD (6 h). Three-month-old male C57BL/6J mice underwent TSD (experiment 1—gentle handling method) or PSD (experiment 2—multiple platforms method) for 6 h. Immediately after the sleep deprivation period, mice were tested in the open field for 10 min under the effects of saline or 2.0 mg/kg AMP. Seven days later, to assess behavioral sensitization, all of the mice received a challenge injection of 2.0 mg/kg AMP and were tested in the open field for 10 min. Total, peripheral, and central locomotion, and grooming duration were measured. TSD, but not PSD, potentiated the hyperlocomotion induced by an acute injection of AMP and this effect was due to an increased locomotion in the central squares of the apparatus. Similarly, TSD facilitated the development of AMP-induced sensitization, but only in the central locomotion parameter. The data indicate that an acute period of TSD may exacerbate the behavioral effects of AMP in mice. Because sleep architecture is composed of paradoxical and slow wave sleep, and 6-h PSD had no effects on AMP-induced hyperlocomotion or sensitization, our data suggest that the deprivation of slow wave sleep plays a critical role in the mechanisms that underlie the potentiating effects of TSD on both the acute and sensitized addiction-related responses to AMP.

1. Introduction

When administered acutely, psychostimulants increase locomotion in rodents (Fukushiro et al., 2007a,b; Phillips et al., 1997), and this effect is due to the ability of these drugs to increase dopamine levels in the mesolimbic dopaminergic system (Di Chiara and Imperato, 1988). When administered repeatedly, psychostimulants induce behavioral sensitization (Araujo et al., 2006; De Vries et al., 1998; Didone et al., 2008; Fukushiro and Frussa-Filho, 2011; Fukushiro et al., 2008, 2012a, b; Kameda et al., 2011; Robinson and Becker, 1986; Wuo-Silva et al., 2011), which is defined by a progressive increase in drug-induced behavioral responses following repeated administration of the same dose of the drug in rodents (Robinson and Becker, 1986). Usually, this phenomenon is demonstrated by an increase in locomotion after a challenge injection of the drug in pretreated animals compared with naïve animals (Fukushiro and Frussa-Filho, 2011; Fukushiro et al., 2008, 2010; Kameda et al., 2011; Tzchentke and Schmidt, 1998), but there are other behavioral parameters that can also detect it (Alvarez et al., 2006; Araujo et al., 2005; Fukushiro et al., 2010). Interestingly, it has been demonstrated that it is not necessary to repeatedly administer the psychostimulant amphetamine (AMP) for long periods to promote behavioral sensitization. Indeed, even a single pretreatment with AMP is able to increase locomotor stimulation produced by an injection of AMP given hours, days or weeks later (Alvarez et al., 2006; Calzavara et al., 2008; Chinen et al., 2006; Vanderschuren et al., 1999).

Behavioral sensitization is considered a useful pharmacological tool to examine the plasticity in the mesolimbic dopaminergic circuitry that may underlie drug craving and drug-seeking behavior in humans (Robinson and Becker, 1986; Robinson and Berridge, 1993, 2000, 2001, 2008). Within this context, alterations within the mesoaccumbens dopaminergic system, including autoreceptor subsensitivity in the ventral tegmental area as well as increased dopamine release and increased

☆ This paper is in memory of Dr. Roberto Frussa-Filho, who dedicated his entire life to Science, and taught us all that its main ingredient is love.

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http://dx.doi.org/10.1016/j.pbb.2013.11.032

dopamine D_1 sensitivity in the nucleus accumbens, have been described in rats sensitized to psychostimulants (Henry and White, 1991; Wolf et al., 1993, 1994).

It has been demonstrated that, similar to the behavioral sensitization phenomenon, prolonged periods of paradoxical sleep deprivation (PSD) also produce neuroplastic changes in the dopaminergic system. Indeed, enhanced density of both dopamine D_1 (Demontis et al., 1990) and D_2 (Nunes et al., 1994) receptors in the mesolimbic system has been described in rats deprived of paradoxical sleep for a prolonged period of time. This dopaminergic supersensitivity may enhance the behavioral effects of psychostimulants and other dopaminergic agonists (Andersen et al., 2005b; Andersen and Tufik, 2005; Tufik, 1981a, 1981b; Tufik et al., 1978), as seen previously for other factors that also induce this phenomenon (Kosten et al., 1996). Consistent with the increased plasticity in the mesolimbic dopaminergic system following both prolonged PSD and behavioral sensitization, we previously demonstrated that PSD for 48 h potentiated the development of locomotor sensitization induced by a single injection of AMP in mice (Frussa-Filho et al., 2004).

Although the consequences of prolonged PSD for the response to dopaminergic agonists have been studied for many decades, total sleep is comprised of both slow wave (or NREM) sleep (SWS) and paradoxical (or REM) sleep (PS). Most of the sleeping period typically consists of SWS, which is characterized by behavioral and anatomic nervous system quiescence, and by high-amplitude slow waves, as measured by the electroencephalogram (EEG). On the other hand, PS is characterized by brief movements of the extremities, facial muscles and, especially, the eyes, and by shorter periods of low-amplitude waves on EEG recordings. A typical mammalian sleep pattern consists of SWS interspersed with PS episodes (see Elgar et al., 1988;Sunagawa et al., 2013). In this regard, the effects of total sleep deprivation (TSD) on the responses elicited by dopaminergic agonists (such as psychostimulants), as well as the neurobiological changes associated with it, have been overlooked. TSD is a simple method to deprive rodents from sleep that is achieved by removing or introducing objects within the cages (Toppila et al., 1997) or by gently handling them (Franken et al., 1993), usually for a brief period (6 h), thus keeping the animals awake and depriving them from both SWS and PS (Fenzl et al., 2007).

In humans, situations of TSD are more common than a specific PSD (Bonnet and Arand, 2003). For example, it is not unusual to skip one night's sleep due to a party or a job (shift workers) (National Sleep Foundation, 2005). In addition, abundant evidence reveals that TSD is becoming a feature of our current lifestyle (National Sleep Foundation, 2005). Thus, the aim of the present study was to investigate the effects of acute TSD (6 h) on the acute locomotor stimulation produced by AMP as well as on the development of behavioral sensitization induced by a single injection of this psychostimulant in mice. The specific participation of SWS and PS in the TSD effects was also investigated in another experiment by subjecting the animals for an equally short-term period of PSD (6 h) before the behavioral tasks.

2. Material and methods

2.1. Subjects

Subjects were 3-month-old male C57BL/6J mice (25–30 g) from the UNIFESP breeding colony (CEDEME), originated from Jackson laboratories (USA). This strain was purchased by CEDEME in 2006 and has been maintained in foundation stock, expansion and multiplication colonies since then. The animals were housed 5 per cage, under controlled temperature (22–23 °C) and lighting (12 h/12-h light/dark, lights on at 6:45 h) in polypropylene cages (32 cm × 42 cm × 18 cm). Food and water were available ad libitum throughout the experiments. Each cage contained animals from the same experimental group.

The experimental protocols were approved by the committee for the use of animal subjects from our institution (Universidade Federal de São Paulo, UNIFESP—1202/09). The experiments were performed in accordance with the guidelines established by the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23, revised 1996) and the Ethical and Practical Principles for the Use of Laboratory Animals (Andersen et al., 2004b). All measures were taken to minimize the pain and discomfort of the animals.

2.2. Drug

D-Amphetamine (Sigma®) was diluted in saline solution (NaCl 0.9%). The drug was administered intraperitoneally (i.p.) at a volume of 10 ml/kg body weight. Control groups received an equivalent volume of saline solution.

AMP was administered at a dose of 2.0 mg/kg. We used the same dose of AMP which has been reported to interact with prolonged PSD (48 h) and produce enhanced behavioral sensitization in C57BL/6 mice (Frussa-Filho et al., 2004).

2.3. Total sleep deprivation (TSD)

TSD was accomplished through the gentle handling method, as described previously by Fenzl et al. (2007) and Franken et al. (1993). This method consists of keeping the animals awake by tapping on the cage and, if necessary, by gently touching them with a soft brush if behavioral signs (e.g. closed eyes and immobility) of sleep were observed. The animals were sleep-deprived for 6 h in their home cages and immediately submitted to behavioral tasks. Food and water were provided ad libitum throughout the TSD period. Control animals were maintained in their home cages undisturbed and in the same room.

2.4. Paradoxical sleep deprivation (PSD)

PSD was accomplished using the multiple platform method (Silva et al., 2004a; Zager et al., 2007). Groups of 5 mice were placed on platforms in PSD tanks (32 cm × 42 cm × 18 cm). Each tank contained 10 platforms (3 cm in diameter) surrounded by water up to 1 cm beneath the surface of the platforms. The animals may move inside the tank by jumping from one platform to another. This method selectively suppresses PS because when the characteristic muscle atonia occurs, the animal contacts the water surrounding the platform and wakes up. Animals were sleep deprived using this method for 6 h (to allow direct comparison with the TSD procedure), and immediately after this period they were tested in the behavioral tasks. Food and water were made available through a grid placed on top of the water tank. Control animals were maintained in their home cages in the same room.

2.5. Open-field test

The open-field apparatus used 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). The apparatus was made impervious to water to avoid any possible bias due to smells from the wood or other animals. During the 10-min session, using hand-operated counters and stopwatches, the following behavioral parameters were measured by an observer who was blinded to treatment allocation:

- total locomotion = total number of entries into any floor unit with the four paws;
- peripheral locomotion = number of entries into any floor unit contiguous to the apparatus walls;
- central locomotion = number of entries into any floor unit not contiguous to the apparatus walls; and
- grooming duration = total seconds of mouth or paws on the body and on the head.

Behavior in the open field was observed for 10 min because even shorter periods have shown to be optimal for reliable and accurate