Progress in Neuro-Psychopharmacology & Biological Psychiatry 58 (2015) 22–31

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

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

Effects of rimonabant on the development of single dose-induced behavioral sensitization to ethanol, morphine and cocaine in mice

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ARTICLE INFO

Article history:
Received 19 August 2014
Received in revised form 1 November 2014
Accepted 18 November 2014
Available online 10 December 2014

Keywords:
Behavioral sensitization
Cocaine
Ethanol
Morphine
Rimonabant

ABSTRACT

Rationale: The endocannabinoid system has been implicated in the neurobiological mechanism underlying drug addiction, especially the primary rewarding dopamine-dependent processes. Therefore, endocannabinoid receptor antagonists, such as the CB1 cannabinoid antagonist rimonabant, have been proposed as candidates for preventive addiction therapies.
Objectives: Investigate the possible involvement of CB1 receptors in the development of behavioral sensitization to ethanol, morphine and cocaine in mice.
Methods: We compared the effects of different doses of rimonabant (0.3, 1, 3 and 10 mg/kg) on spontaneous locomotor activity in the open-field, hyperlocomotion induced by acute administration of ethanol (1.8 g/kg), morphine (20 mg/kg) or cocaine (10 mg/kg) and on subsequent drug-induced locomotor sensitization using a two-injection protocol in mice. We also investigated a possible depressive-like effect of an acute rimonabant challenge at the highest dose and its potential anxiogenic property.
Results: At the highest dose, rimonabant abolished ethanol- and cocaine-induced hyperlocomotion and behavioral sensitization without modifying spontaneous and central locomotor activity or inducing depressive-like behavior on the forced swim test in mice. The other doses of rimonabant also selectively blocked acute ethanol-induced central hyperlocomotion. Although rimonabant at 0.3 and 1 mg/kg potentiated the central hyperlocomotion induced by acute morphine injection, it was effective in attenuating morphine-induced behavioral sensitization at all doses.
Conclusions: Because the neural basis of behavioral sensitization has been proposed to correspond to some components of addiction, our findings indicate that the endocannabinoid system might be involved in ethanol, cocaine and morphine abuse.

1. Introduction

Psychostimulants and other drugs of abuse, such as opiates and ethanol, induce behavioral sensitization in rodents (De Vries et al., 1998; Didone et al., 2008; Masur et al., 1986; Piazza et al., 1990; Robinson and Becker, 1986), an increased behavioral response to the drug after its repeated presentation (Kalivas and Stewart, 1991; Robinson and Becker, 1986). Studies in rats and mice show that even a single exposure to drugs of abuse can induce behavioral sensitization, a model that is less influenced by variables that complicate the interpretation of behavioral responses in multiple drug exposure protocols. Indeed, a single injection of cocaine (Valjent et al., 2010), amphetamine (Chinen et al., 2006; Frussa-Filho et al., 2004), morphine (Valjent et al., 2010; Vanderschuren et al., 2001) or ethanol (Fukushiro et al., 2010) enhances the locomotor stimulation produced by subsequent injection of the respective drug given hours, days or weeks later, which is potentiated when the locomotor-stimulating effect of the priming injection is paired with the test environment (Chinen et al., 2006).

As shown by Valjent et al. (2010), the two-injection protocol of behavioral sensitization provides an excellent model for investigating

Abbreviations: Sal, saline; Veh, vehicle; Rim, rimonabant; Eth, ethanol; Mor, morphine; Coc, cocaine; VTA, ventral tegmental area; NAc, nucleus accumbens; GABA, gamma-aminobutyric acid.

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[1] The first two authors equally contributed to this study.
[2] 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.pnpbp.2014.11.010
0278-5846/

the long-lasting effects of drugs of abuse. Although evidence indicates a dissociation between locomotor sensitization and drug consumption (Ahmed and Cador, 2006; Boyson et al., 2014), the neurocircuitry that underlies behavioral sensitization and relapse to drug seeking behavior is similar in both neurochemistry and neuropharmacology (for a review see Steketee and Kalivas, 2011). Regardless of its exact correlate with human behavior, behavioral sensitization is a reliable physiopathologic model for the study of the mechanisms underlying addiction because the neural changes responsible for this phenomenon may be an important component of drug abuse (Wise and Bozarth, 1987). Of note, in the two-injection protocol, the changes in responsiveness induced by the first psychostimulant administration are revealed by the second administration. As a primary effect, most drugs that are abused by humans increase dopamine release in the nucleus accumbens (Di Chiara and Imperato, 1988), which is innervated by neurons from the mesolimbic dopaminergic system, thereby leading to hyperlocomotion in rodents (Einhorn et al., 1988; Ellinwood et al., 2000). A large body of evidence suggests that this system mediates most neuroadaptations related to the behavioral sensitization induced by distinct drugs of abuse (Costa et al., 2007; de Araujo et al., 2009; Henry and White, 1991; Wolf et al., 1994), even in a two-injection protocol (Valjent et al., 2010). Furthermore, the repeated use of addictive drugs produces incremental neuroadaptations in the mesolimbic dopamine system, characterizing drug craving in addicted individuals, which have led to the hypothesis that drug-induced neuroadaptations underlying the phenomenon of behavioral sensitization may play an important role in the induction and maintenance of the compulsive patterns of drug-seeking behaviors that characterize addiction (Robinson and Berridge, 1993).

Several lines of evidence have implicated the endocannabinoid system in behavioral responses to drugs of abuse, especially conditioned drug seeking and relapse (De Vries and Schoffelmeer, 2005; Maldonado et al., 2006). Among the two types of cannabinoid receptors, CB1 and CB2 (Mackie, 2006), CB1 has been suggested as the most important one regarding the events related to drug abuse and dependence. CB1 receptors are densely expressed within the mesolimbic dopamine pathway (Tsou et al., 1998), and they are linked to the rewarding aspects of drugs of abuse (De Vries et al., 2001). In addition, CB1 receptors seem to mediate the expression of cocaine-induced locomotor sensitization (Kupferschmidt et al., 2012). The pharmacological blockade of cannabinoid CB1 receptors by rimonabant, a CB1 receptor antagonist, decreases psychostimulant-induced neurobiological effects, which is paralleled by the inhibition of their behavioral responses (Corbille et al., 2007; Filip et al., 2006; Mereu et al., 2013). However, little is known about the role of the endocannabinoid system and CB1 receptors on acute drug effects and on the development of addiction to other drugs of abuse, such as ethanol and opiates.

The present study aimed to investigate the dose-dependent effects of rimonabant on spontaneous locomotor activity of mice, on hyperlocomotion induced by acute drug administration and on the development of single injection-induced behavioral sensitization produced by three different drugs of abuse: ethanol, cocaine and morphine. Because clinical trials have revealed that rimonabant may induce symptoms of anxiety and depression (Moreira and Crippa, 2009), we also evaluated the possible depressive-like effect of an acute challenge with rimonabant at the highest dose as well as the central and peripheral locomotion frequencies of mice in the open-field under rimonabant effect as a measure of anxiety-like behavior in mice.

2. Materials and methods

2.1. Animals

Three-month-old Swiss EPM-M1 male mice (outbred, raised and maintained in the Center for Development of Experimental Models in Medicine and Biology of UNIFESP) were used. Animals weighing 30–35 g were housed under controlled temperature (22–23 °C) and light (12 h light, 12 h dark; lights on at 6 h 45 a.m.) conditions. Food and water were available *ad libitum* throughout the experiments. Animals were maintained according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 8023), revised in 2011, the EU Directive 2010/63/EU for animal experiments, and the Brazilian Law for Procedures for Animal Scientific Use (#11794/2008). The Institutional Ethical Committee of UNIFESP approved the experimental procedures under protocol #470/07. The four different experiments were done with separate cohorts of naive animals.

2.2. Drugs

Absolute ethanol (Merck®), cocaine-HCl (Sigma®) and morphine (Sigma®) were diluted in 0.9% saline solution. Rimonabant (Sanofi-Aventis®) was dissolved in Tween 80 and propylene glycol and diluted to the correct concentrations with saline. A solution of saline + 1% Tween 80 + 3% propylene glycol was used as vehicle solution (Veh) for rimonabant. Drugs and vehicle solutions were administered intraperitoneally at 10 ml/kg of body weight. The selected dose range of rimonabant was based on previous literature (Gerdeman et al., 2008; Singh et al., 2004), and the doses of ethanol, cocaine and morphine used in the present study were based on previous studies conducted by our group (Fukushiro et al., 2008; Fukushiro et al., 2012a, 2012b; Procopio-Souza et al., 2011).

2.3. Open-field evaluation

Locomotor activity was measured in an open-field apparatus as described previously (Chinen and Frussa-Filho, 1999). The apparatus consisted of a circular wooden arena (40 cm in diameter and 50 cm high) with an open top and a floor divided into 19 squares. Hand-operated counters were used by an observer who was blind to the treatment to score total (total number of any squares entered), peripheral (number of entries into any floor unit contiguous to the apparatus walls) and central (number of entries into any floor unit not contiguous to the apparatus walls) locomotion frequencies during the 10-min sessions. To ensure inter- and intra-observer reliability, all researchers observed animals from all groups and the same observers were present during all behavioral evaluations of each experiment, observing the same animals on each day. Because cocaine- and amphetamine-induced behavioral sensitization shows a diurnal pattern (Akhisaroglu et al., 2004; Gaytan et al., 2000) and following the protocols previously established in our laboratory (Marinho et al., 2014; Procopio-Souza et al., 2011), all behavioral tests were conducted in the same period of the day, during the light phase of the cycle (2 h 00 p.m. to 5 h 00 p.m.).

2.4. Forced swim test

For the evaluation of a possible depressive-like effect of rimonabant at a high dose, mice were placed individually in a cylindrical glass container (30 cm height, 16 cm diameter, 11 cm of water depth, 23 °C) for 6 min. The duration of immobility was manually scored during the last 4 min by observers who were blind to the manipulation applied. A mouse was considered immobile when it floated in an upright position and made only small movements to keep its head above water.

2.5. Experimental procedure

2.5.1. Experiments I to III: effects of acute rimonabant administration on spontaneous locomotor activity, hyperlocomotion and behavioral sensitization induced by ethanol, morphine and cocaine

The experimental design was performed according to the model developed by our group (Marinho et al., 2014). For the first experiment, 70 mice were exposed to the open-field apparatus for 2 consecutive days