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Context-dependent efficacy of a counter-conditioning strategy with atypical neuroleptic drugs in mice previously sensitized to cocaine

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ABSTRACT

Rationale: We have previously demonstrated that treatment with ziprasidone and aripiprazole selectively inhibit the development of behavioral sensitization to cocaine in mice. We now investigate their effects on a counter-conditioning strategy in mice and the importance of the treatment environment for this phenomenon.
Objective: Evaluate the context-specificity of ziprasidone and aripiprazole on conditioned locomotion to cocaine and cocaine-induced hyperlocomotion and behavioral sensitization in a counter-conditioning strategy in mice.
Methods: Animals were sensitized with saline or cocaine injections in the open-field apparatus in a 15-day intermittent treatment and subsequently treated with vehicle, 5 mg/kg ziprasidone or 0.1 mg/kg aripiprazole paired to the open-field or the home-cage for 4 alternate days. Mice were then challenged with saline and cocaine in the open-field apparatus on subsequent days.
Results: While treatment with ziprasidone decreased spontaneous locomotion and conditioned locomotion alike, treatment with aripiprazole specifically attenuated the expression of conditioned hyperlocomotion to cocaine. Ziprasidone and aripiprazole had no effects on cocaine-induced conditioned hyperlocomotion observed during saline challenge after drug withdrawal. Treatment with either ziprasidone or aripiprazole when previously given in the cocaine-paired environment attenuated the subsequent expression of behavioral sensitization to cocaine. Animals treated with aripiprazole in the open-field, but not in the home-cage, showed a blunted response to cocaine when receiving a cocaine challenge for the first time.
Conclusions: Both neuroleptic drugs showed a context-dependent effectiveness in attenuating long-term expression of cocaine-induced behavioral sensitization when administered in the cocaine-associated environment, with aripiprazole also showing effectiveness in blocking the expression of acute cocaine effects.

1. Introduction

Cocaine addiction is a chronic, progressive and potentially fatal disease accompanied by criminality, loss of productivity and social problems for the individual and the society (American Psychiatric Association, 2013). Despite decades of research, there is no treatment for cocaine abuse to date. The demand for treatment is high, and the growing impact of cocaine dependence requires new approaches, including the investigation of factors influencing the different stages of drug abuse. It is well known that drug-environment conditioning is one of the biggest challenges in addiction treatment.

The reinforcing effects of cocaine are accompanied by an increase in mesocorticolimbic dopaminergic activity (Di Chiara and Imperato, 1988). Physiologically, enhanced dopamine signaling in the mesolimbic system is responsible for the creation of adaptive associations between relevant stimuli and environmental cues (Berridge and Robinson, 1998; Volkow et al., 2011). Therefore, the enhanced dopaminergic signaling induced by cocaine and drugs of abuse also leads to the development of strong associations between the drug effect and contextual cues (Kalivas, 2002). A key feature of conditioned behavior is that it can undergo extinction if the conditioned cue is repeatedly presented in the absence of the drug (Carey and Gui, 1997). More recently, reconsolidation and counter-conditioning strategies have been studied during extinction and permit the therapeutic-drug to become linked

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[†] 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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to the conditioned contextual cues and in effect form a new and different drug association with the contextual cues, modulating drug-induced behavior (Carrera et al., 2012).

Repeated treatment with cocaine induces behavioral sensitization to the acute psychomotor stimulating effects of this drug (Vanderschuren and Kalivas, 2000; Wolf et al., 2004), a phenomenon thought to share neuroadaptations with drug craving in humans (Robinson and Berridge, 1993) and to be mainly modulated by the dopaminergic neurotransmission (Steketee, 2005). Because dopamine seems to be involved in both the reinforcing and conditioned responses to cocaine, drugs acting at the dopaminergic system play an important role in the efforts to develop pharmacotherapies for the treatment of cocaine abuse. We have previously demonstrated that treatment with ziprasidone and aripiprazole, but not haloperidol, selectively inhibited the development of behavioral sensitization to cocaine in mice (Marinho et al., 2014). Ziprasidone is a second-generation antipsychotic drug acting as an antagonist at dopamine D2 receptors and serotonin 5-HT2A, as well as agonist at the 5HT1A receptor (Seeger et al., 1995). Aripiprazole is a third-generation neuroleptic drug that has been suggested to act as a partial agonist at dopamine D2 and serotonin 5-HT1A receptors, as well as an antagonist at the 5-HT2A receptor (Burris et al., 2002; Mamo et al., 2007). At a specific dose range, both ziprasidone and aripiprazole selectively abolished acute cocaine-induced hyperlocomotion and behavioral sensitization without modifying spontaneous locomotion (Marinho et al., 2014).

Of note, in the behavioral sensitization paradigm, the environment associated with cocaine treatments is capable of evoking conditioned locomotion in the absence of the drug (Cervo and Samanin, 1996; Di Ciano et al., 1998; Marin et al., 2009). This phenomenon is analogous to subjective and physiological conditioned responses elicited by cocaine-associated stimuli in humans (Pert, 1994). We have previously established a counter-conditioning protocol aiming to investigate the effectiveness of potential therapeutic agents to modify sensitized responses induced by a repeated treatment with drugs of abuse in mice (Oliveira-Lima et al., 2015). In light of the promising effects observed with ziprasidone and aripiprazole on the development of behavioral sensitization to cocaine, we now expanded this investigation by evaluating their effects on a counter-conditioning strategy in mice and the importance of the treatment environment for this phenomenon.

The present study reports two experiments designed to evaluate the context-specificity of ziprasidone and aripiprazole in reversing cocaine-related behaviors. By giving the therapeutic treatment in the home-cage and in the drug-associated environment, we aimed to investigate the influence of the treatment environment on ziprasidone- and aripiprazole-mediated changes in cocaine-induced conditioned locomotion and the expression of acute and sensitized responses to cocaine.

2. Materials and methods

2.1. Subjects

Two hundred and twenty male 3-month-old Swiss EPM-M1 mice (30–35 g) from our own colony (outbred, raised, and maintained in the Centre for Development of Experimental Models in Medicine and Biology of Universidade Federal de São Paulo) were used. This strain has been extensively used in behavioral pharmacology studies conducted by our group, with animals reliably expressing behavioral sensitization to several different drugs of abuse (Borçoi et al., 2015; Marinho et al., 2015; Oliveira-Lima et al., 2015), including cocaine (Berro et al., 2014). Animals were housed in polypropylene cages (32 cm × 42 cm × 18 cm) under conditions of controlled temperature (22–23 °C) and lighting (12/12 h light/dark, lights on at 06 h45). Food and water were available ad libitum. Experiments were performed in accordance with the National Institute of Health Guide for Care and Use of Laboratory Animals (NIH Publications No. 80-23, revised 1996) and animals were maintained in accordance with the Brazilian Law for Procedures for Animal Scientific Use (#11794/2008). The experimental procedures were approved by the Institutional Ethical Committee of UNIFESP under the protocol #0345/07.

2.2. Drugs

Cocaine (10 mg/kg, Sigma®) was diluted in 0.9% NaCl (saline) solution, which was used as control solution. Ziprasidone (5 mg/kg, Pfizer®) and aripiprazole (0.1 mg/kg, Bristol-Myers Squibb®) were dissolved in Tween 80 (1% final volume) and then diluted in distilled water to the correct concentration. Solution of Tween 80 + distilled water was used as ziprasidone and aripiprazole vehicle. All solutions were administered intraperitoneally (ip) at a volume of 10 ml/kg body weight.

The doses of ziprasidone and aripiprazole were based on previous studies from our group. The doses were chosen based on their ability to reduce both acute and sensitized responses to cocaine in a single dose-induced behavioral sensitization protocol (Marinho et al., 2014).

2.3. Open-field evaluation

Locomotor activity was measured in the open-field apparatus. The open-field apparatus consisted of cylindrical plastic walls (50 cm high) and a wooden base, both with the same diameter (40 cm). The base is divided into 19 approximately similar regions delimited by three concentric circles of different radii (8, 14 and 20 cm) intersected by radial line segments. During the behavioral tests, animals were exposed to normal light (200 lx — NL), mimicking lighting conditions in the vivarium. Animals were placed in the behavioral testing room at least 1 h prior to the beginning of the behavioral tasks in order to minimize possible handling stress from moving animals between rooms. Using hand-operated counters and stopwatches, locomotion frequency (i.e., total number of entrances into any square with the 4 paws) was measured by an observer (blind to treatment allocation) during a 10-min session. Quantification of locomotion frequency in the open-field apparatus has been demonstrated to be a very effective method in evaluating behavioral sensitization induced by cocaine under our experimental conditions (Fukushiro et al., 2008; Berro et al., 2014).

2.4. Experimental procedure

2.4.1. Experiment 1: effects of a treatment with ziprasidone in the sensitization environment or in the home-cage in animals previously sensitized to cocaine

One hundred and eight mice were given a 10-min habituation period in the open-field for 3 consecutive days after a saline injection, and their locomotor activities were measured on day 3. After the habituation phase, animals were allocated into 8 groups of similar basal locomotor activity (N = 13–14 per group). All groups were run in parallel within an experiment.

During the behavioral sensitization protocol ("cocaine treatment" phase), animals received an ip injection of either saline (Sal, 4 groups, 54 mice) or 10 mg/kg cocaine (Coc, 4 groups, 54 mice) every other day for 15 days (8 sessions, on days 1, 3, 5, 7, 9, 11, 13 and 15). Five minutes after treatments, animals were individually placed in the open-field for 10-min sessions. Locomotor activity was measured on the 1st and last days of this phase. During the alternate non-treatment days, mice were left undisturbed in their home-cages.

Forty-eight hours after the last cocaine treatment, the Ziprasidone Treatment phase began. During this phase, mice received an ip injection of vehicle or 5 mg/kg Ziprasidone every other day for 7 days (4 sessions, on days 1, 3, 5 and 7). Mice were then individually placed either in the open-field for 10-min sessions 30 min after treatments (Sal-Veh-OF, Coc-Veh-OF, Sal-Zip-OF, and Coc-Zip-OF groups, N = 13 per group) or in the home-cage immediately after treatments (Sal-Veh-HC, Coc-Veh-HC, Sal-Zip-HC, and Coc-Zip-HC groups, N = 14 per group). For animals exposed to the open-field, locomotor activity was measured on