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Mirtazapine prevents induction and expression of cocaine-induced behavioral sensitization in rats

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ABSTRACT

Cocaine abuse is a major health problem worldwide. Treatment based on both 5-$HT_{2A/C}$ and 5-HT_3 receptor antagonists attenuate not only the effects of cocaine abuse but also the incentive/motivational effect related to cocaine-paired cues.

Mirtazapine, an antagonist of postsynaptic α_2-adrenergic, 5-$HT_{2A/C}$ and $5HT_3$ receptors and inverse agonist of the 5-HT_{2C} receptor, has been shown to effectively modify, at the preclinical and clinical levels, various behavioral alterations induced by drugs abuse. Therefore, it is important to assess whether chronic dosing of mirtazapine alters locomotor effects of cocaine as well as induction and expression of cocaine sensitization.

Our results reveal that a daily mirtazapine regimen administered for 30 days effectively induces a significant attenuation of cocaine-dependent locomotor activity and as well as the induction and expression of behavioral sensitization. These results suggest that mirtazapine may be used as a potentially effective therapy to attenuate induction and expression of cocaine-induced locomotor sensitization.

1. Introduction

Cocaine abuse is a major health problem worldwide. Relapse is a major clinical problem in disorders related to cocaine use (Shalev et al., 2002).

It is noteworthy that despite the many efforts aimed to design an effective drug therapy against cocaine relapse, none of the current pharmacological treatments has succeeded in preventing it (Vocci and Elkashef, 2005). Given the lack of success of these therapies and the powerful reinforcing effects of cocaine—by acting directly on mesolimbic dopamine system—, alternative therapeutic strategies have been proposed. These have been based, mainly, on alterations in the functions of other neurotransmission systems, which interact directly with dopaminergic neurons and have the ability to alter the function of dopaminergic pathways, indirectly modulating the effects of cocaine (Fletcher et al., 2008).

Previous research has demonstrated that the 5-HT system plays an important role in cocaine abuse-related alterations (Howell and Cunningham, 2015; Filip et al., 2005, 2010). These studies show that 5-$HT_{2A/C}$ and 5-HT_3 receptors may be potential targets to treat some aspects of cocaine abuse (Fletcher et al., 2008; Bubar and Cunningham, 2008).

Administration of 5-HT or 5-$HT_{2A/C}$ and 5-HT_3 receptor agonists increases locomotor sensitization. In contrast, a treatment with 5-HT_{2A} (Ketanserin) and 5-HT_3 (Ondansetron) receptor antagonists attenuates the locomotor-stimulant effects of cocaine as well as incentive/motivational responses (i.e., conditioned place preference in rodents) associated with cocaine-paired cues (King et al., 2000, 2002; Filip et al., 2010; Bubar and Cunningham, 2008; Rothman et al., 2006, 2008).

Mirtazapine (REMERON, Schering-Plough-Organon 3770 USA) is an atypical antidepressant approved for the treatment of moderate to severe depression with comorbid anxiety disorders. Initially, mirtazapine was thought to antagonize pre- and post-synaptic α_2-adrenergic receptors and block postsynaptic $5HT_{2A}$ and $5HT_3$ and histamine 1 (H1R) receptors in the central nervous system (CNS) of mammals, including humans (de Boer, 1996). Nonetheless, recent evidence suggests that mirtazapine can also act as an inverse agonist of the 5-HT_{2C} receptor

Abbreviations: AM, morning; ANOVA, analysis of variance; cm, centimeter; CNS-, central nervous system; COFEPRIS, Federal Commission for Protection against Health Risks; D, dopamine; D1, D1-like receptor; D2-, D2-like receptor; e.g., for example; g, grams; i.p., intraperitoneal; kg, kilogram; min, minute(s); mg, milligrams; n, number of animals; NAcc, nucleus accumbens; NaCl, sodium chloride; NE, noradrenergic system; NOM, Official Mexican Standard; NS, non-significant; PC, personal computer; PFC, prefrontal cortex; PGR, Office of the Attorney General of Mexico; PM, afternoon; SSA, Ministry of Health; S.E.M., standard error; VTA, ventral tegmental area; %, percentage; 5-HT, serotonergic system; 5-HT_{2A}, serotonergic 2A receptor; 5-HT_{2C}, serotonergic 2C receptor; 5-HT_3, serotonergic 3 receptor; °C, degrees celsius; COC, cocaine group; COC + MIR, cocaine plus mirtazapine group; MIR, mirtazapine group; MIR_{INI} + COC, mirtazapine initial plus cocaine group; MIR + COC, mirtazapine plus cocaine group; SAL, saline group.

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and indirectly as an agonist of the 5-HT_{1A} receptor (Chanrion et al., 2008; Nakayama et al., 2004).

Several studies have found that mirtazapine mitigates various behavioral alterations induced by drugs of abuse. At the preclinical level, mirtazapine attenuates morphine and methamphetamine withdrawal, reduces morphine-induced rewarding effects in rats, inhibits the acquisition of morphine dependence, and attenuates the establishment of conditioned place preference to morphine and methamphetamine in rats (Voigt and Napier, 2012; Voigt et al., 2011; Herrold et al., 2009). In humans, mirtazapine ceases street benzodiazepine abuse and reduces cocaine and methamphetamine abuse (Zueco-Pérez, 2002; Colfax et al., 2011). In addition, mirtazapine significantly improves symptoms of depression, anxiety, insomnia, minimizing physical and subjective discomfort and dysphoric symptoms that appear during benzodiazepine, alcohol and cocaine withdrawal (Liappas et al., 2004; Chandrasekaran, 2008; Afshar et al., 2012).

These data collectively indicate that 5-$HT_{2A/C}$ and 5-HT_3 receptors significantly modulate the behavioral effects of cocaine and that drugs that alter the activity of 5-$HT_{2A/C}$ and 5-HT_3 receptors may be potential targets of cocaine therapies (Fletcher et al., 2008; Bubar and Cunningham, 2008). The ability of mirtazapine to simultaneously alter the functioning of 5-$HT_{2A/C}$ and 5-HT_3 receptors (de Boer, 1996) and its proven effectiveness in reducing the stimulating and reinforcing effects of drug abuse (Voigt and Napier, 2012; Kang et al., 2008; Chandrasekaran, 2008; Liappas et al., 2004) warrant research to determine whether chronic dosing of mirtazapine alters the locomotor effects of cocaine and the induction and expression of cocaine sensitization.

As the enhancement of locomotor activity induced by cocaine exhibits drug-induced neuronal plasticity—a prerequisite for the development of locomotor sensitization—, our study used the locomotor stimulant effects of cocaine as a behavioral tool to determine the effect of mirtazapine on the induction and expression of locomotor sensitization. Our results showed that a daily mirtazapine regimen administered for 30 days effectively induces a significant attenuation of cocaine-dependent locomotor activity, a finding that makes it possible to warrant its clinical use as a novel pharmacological agent to meaningfully reduce sensitized behaviors caused by psychostimulants.

2. Materials and methods

2.1. Animals

The study used male Wistar rats weighing 250–280 g at the onset of the experiments. They were housed four per cage in standard plastic rodent cages (57 cm × 35 cm × 20 cm) in a colony room maintained at 21 ± 2 °C and at 40–50% humidity under a 12-h light/dark cycle (lights on at 7:00 AM). The animals had free access to water and rodent chow pellets, except during experimental sessions. All the experiments were conducted during the light phase (between 9:00 AM and 3:00 PM) of the light/dark cycle. The study procedures were approved by Institutional Care and Use of Laboratory Animals and Bioethics Committees, in strict compliance with the Guide for the Care and Use of Laboratory Animals issued by the National Institutes of Health.

2.2. Drugs

Cocaine hydrochloride was kindly donated by the Mexican government under strict regulatory controls. All the drugs used in experimental animals were kept under official surveillance (COFEPRIS-LC-0004-2003). Cocaine hydrochloride and Mirtazapine (REMERON, Schering-Plough-Organon) were dissolved in sterile saline solution (0.9% NaCl, Sigma Aldrich); both solutions were freshly prepared before their intraperitoneal (i.p.) administration to the animals. During the experiment, the solutions were maintained at −20 °C. Saline (0.9% NaCl) was used as control in all experiments. Mirtazapine was given 30 min before cocaine or saline administration, in order to that mirtazapine reaches their sites of action (α_2-adrenergic and 5-HT receptors) in the brain. The volume injected into each animal depended on its Body Weight (BW): BW (g)/100. Previous studies allowed determining the optimal mirtazapine dose (30 mg/kg) used in our experiments. The studies showed that lower mirtazapine doses (<15 mg/kg) produce hyperphagia, weight gain, and sedation, whereas higher doses (>60 mg/kg) lead to hypoactivity, somnolence, and reduced exploratory activity, as well as altered behavioral responses (Timmer et al., 1997). Dosage time was established based on clinical studies (Timmer et al., 2000) that indicate that the minimum time of treatment necessary to reduce the symptoms of severe depression is 2–6 weeks and that the appropriate duration is 1 to 4 months.

2.3. Behavioral sensitization procedure

2.3.1. Apparatus and devices

For each animal, locomotor activity was assessed in transparent Plexiglass activity chambers (50 × 50 × 30 cm) linked to a PC. Each activity chamber was surrounded by a 16 × 16 photocell beam array located 3 cm from the floor surface to scan locomotor activity (OMNIALVA, Instruments, Mexico). Photobeam interruptions were automatically quantified with OABiomed software (1.1) and analyzed afterward. Locomotor activity was defined as the interruption of consecutive photobeams (OMNIALVA, Mexico).

2.3.2. Methodology

Spontaneous locomotor activity was estimated with a standard protocol (Vanderschuren and Pierce, 2010). Animals were habituated to the activity chambers in three 30-minute sessions and were randomly assigned to different pharmacological treatment groups. Locomotor activity was recorded for 30 min. The rats were returned to their home cages after each experimental session had been completed.

2.4. Experimental procedures

The study used 144 male Wistar rats in four groups, and each group underwent a different experiment. For experiments 1 to 3, we used 32 animals further divided into four experimental groups (n = 8); for experiment 4, we used 48 animals in six groups (n = 8). Each experimental group received a different pharmacological treatment.

2.4.1. Experiment 1—mirtazapine alters the induction of cocaine-induced locomotor sensitization

Chronic dosing with Mirtazapine (30 mg/kg) prior to daily exposure to cocaine attenuated induction of cocaine-induced locomotor sensitization.

This experiment included three pharmacological phases. Phase I, or the pre-induction phase, which lasted 30 consecutive days. Phase II of cocaine-induction locomotor sensitization, lasted 25 days. Finally, Phase III, or the post-induction phase, lasted 15 consecutive days (Fig. 1A).

After three-day habituation, the saline (SAL) and the mirtazapine (MIR) groups received saline solution (NaCl 9%, i.p.) and mirtazapine (30 mg/kg, i.p.), respectively, during the three aforementioned phases. The rats in the cocaine group (COC) received saline in the pre-induction phase and cocaine (10 mg/kg, i.p.) in both the cocaine-induction and the post-induction phases, 30 min before saline administration. In contrast, the rats in the MIRini + COC group were exposed to mirtazapine (30 mg/kg, i.p.) during both the pre-induction and the induction phases, 30 min before receiving either saline or cocaine. In the post-induction phase, mirtazapine was withdrawn and the group received cocaine only. After administration of