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Dose- and time-dependent effects of mirtazapine on the expression of cocaine-induced behavioral sensitization in rats

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ABSTRACT

Relapse to cocaine use is a major problem in the clinical treatment of cocaine dependence. Antidepressant medications have been studied as potential therapeutic drugs to relieve a cocaine dependence disorder. Mirtazapine is an antidepressant implicated in reducing behavioral alterations induced by drugs of abuse. We have reported elsewhere that 30 mg/kg mirtazapine administered for 30 days during cocaine extinction significantly attenuated the induction and expression of cocaine-induced locomotor sensitization and decreased the duration of the cocaine-induced locomotor effect. This study focused on exploring whether different mirtazapine dosing regimens could optimize and/or improve the effect of 30 mg/kg mirtazapine administered for 30 days on cocaine-induced locomotor activity during the expression phase of behavioral sensitization. Our study revealed that the daily dosing regimen with a fixed dose of mirtazapine (30 mg/kg ip) over 60 days improved the decrease in cocaine-induced locomotor activity and behavioral sensitization obtained by dosing of 30 mg mirtazapine for 30 days. In addition, it showed that a dosing regimen of 30 mg/Kg mirtazapine for 30 days managed to reduce cocaine toxicity. These results suggested that dosage of mirtazapine for 30 consecutive days may be an effective therapy.

1. Introduction

Cocaine use is a health problem worldwide (Leeman et al., 2014). Nonetheless, to date, there is no FDA-approved pharmacological treatment for individuals with a cocaine use disorder (Shorter et al., 2015). Evidence has suggested that antidepressant medications may be a treatment option for cocaine abusers (Torrens et al., 2005; Pani et al., 2011).

Mirtazapine, an antidepressant, has a unique pharmacological profile. This includes antagonist activity at the α_2 noradrenergic (NE) receptor and the serotonin (5-HT) 5-HT_{2A} and 5-HT_3 receptors (Croom et al., 2009; de Boer, 1996), as well as the inverse agonist properties of the 5-HT_{2C} receptor (Chanrion et al., 2008).

Some preclinical studies have shown that mirtazapine administration reduces the severity of opioid withdrawal symptoms and morphine-induced rewarding effects, while inhibiting acquisition of morphine dependence, in rats (Kang et al., 2008; Graves et al., 2012b). Mirtazapine administration during methamphetamine withdrawal attenuates methamphetamine-induced locomotor sensitization, motor response patterns generated by methamphetamines and the establishment of conditioned place preference to morphine and methamphetamines in rats (McDaid et al., 2007; Herrold et al., 2009; Voigt and Napier, 2012; Voigt et al., 2011).

An initial open-label clinical trial in humans found that mirtazapine administration (60 mg/day) ended benzodiazepine and cocaine abuse (Zueco-Pérez, 2002). A randomized, double blind, placebo-controlled

Abbreviations: ANOVA, analysis of variance; CPP, conditioned place preference; cm, centimeters; D, dopamine; e.g., for example; FDA, Food And Drug Administration; Kg, kilograms; mg, milligrams; M-100907, [(R-(+)-alpha-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidinemethanol); n, number of animals; NAcc, nucleus accumbens; NaCl, sodium chloride; NE, noradrenergic system; PC, personal computer; PFC, prefrontal cortex; PGR, Office of the Mexican Attorney General; PM, afternoon; SSA, Ministry of Health; VTA, ventral tegmental area; %, percentage; 5-HT, serotonergic system; COC, cocaine group; COC + MIR, cocaine plus mirtazapine group; COC + MIR-15 mg, cocaine + mirtazapine-15 mg group; COC + MIR-30 mg, cocaine + mirtazapine-30 mg group; COC + MIR-60 mg, cocaine + mirtazapine-60 mg group; COC + MIR-15d, cocaine + mirtazapine-15 day group; COC + MIR-30d, cocaine + mirtazapine-30 day group; COC + MIR-60d, cocaine + mirtazapine-60 day group; COC-10 mg, cocaine 10 milligram group; COC-20 mg, cocaine 20 milligram group; COC-40 mg, cocaine 40 milligram group; COC-10 mg + MIR, cocaine-10 mg + mirtazapine group; COC-20 mg + MIR, cocaine-20 mg + mirtazapine group; COC-40 mg + MIR, cocaine-40 mg + mirtazapine group; MIR, mirtazapine group; SAL, saline group

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trial carried out by Colfax et al. for 12 weeks (Colfax et al., 2011) showed that mirtazapine (30 mg/day) reduces methamphetamine use as evidenced by a decrease in the number of methamphetamine-positive urine tests. We have recently reported that daily dosing of mirtazapine (30 mg/Kg, i.p.) for 30 days during cocaine extinction significantly attenuates the induction and expression of cocaine-induced locomotor sensitization and decreases the duration of the cocaine-induced locomotor effect (Salazar-Juárez et al., 2016).

These studies collectively suggest that mirtazapine may be an effective therapeutic option in the treatment of cocaine use disorders. Some double blind clinical trials have shown, however, that the therapeutic effect of an antidepressant or anxiolytic drug depends mainly on the dosing schedule used (treatment dose and duration) (Huzarska et al., 2006).

This study focused on exploring whether different mirtazapine dosing regimens could optimize and/or improve the effect of 30 mg/kg mirtazapine administered for 30 days on cocaine-induced locomotor activity during the expression phase of behavioral sensitization. Our results showed that a dosing regimen of 30 mg/Kg mirtazapine administered for at least 30 consecutive days significantly attenuated the expression of cocaine-induced locomotor sensitization.

2. Experimental procedures

2.1. Animals

This 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 at 21 ± 2 °C and 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 the experimental sessions. All the experiments were conducted during the light phase (between 9:00 AM and 3:00 PM). The study procedures were approved by the Committees on Institutional Laboratory Animal Care and Use and Bioethics, 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 intraperitoneal (i.p.) administration. During the experiment, the solutions were maintained at −20 °C. Saline (0.9% NaCl) was used as control in all experiments. To determine if mirtazapine could prevent the effects of cocaine, it was administered 30 min before cocaine (or saline) administration. The volume injected into each animal depended on its Body Weight (BW): BW (g)/100 ml.

2.2.1. Dose selection

The optimum dose of mirtazapine used in the study (30 mg/kg) was chosen based on previous observations that showed that the dosage of ≥30 mg/Kg of mirtazapine does not affect spontaneous locomotor activity (Salazar-Juárez et al., 2016), does not produce sedation and does not induce weight gain (Salazar-Juárez et al., 2017; Bittolo et al., 2016) in rats. Additionally, preclinical studies and clinical trials have reported that the 30 mg/Kg dose of mirtazapine was able to decrease cocaine-induced locomotor activity (Salazar-Juárez et al., 2016), to attenuate the morphine-induced place preference (Kang et al., 2008) and to reduce the morphine and methamphetamine withdrawal symptoms in rats and humans.

The doses of cocaine were chosen based on previous studies showing that a dose of 10 or 20 mg/kg of cocaine generates a robust increase in cocaine-induced locomotor activity and behavioral sensitization (Zayara et al., 2011; Filip et al., 2004; Perrine et al., 2015), but were not able to generate seizures. The sub-lethal dose of cocaine was selected based on a dose response curve performed in our laboratory, where we found that rats injected with a dose of 40 mg/kg of cocaine induced convulsions in ~50% of the animals but it was not a lethal dose. The literature indicates that doses of ≥75 mg/kg of cocaine are considered lethal doses (Chen et al., 2013; Gaval-Cruz et al., 2008).

2.3. Behavioral sensitization procedure

2.3.1. Apparatus

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

2.3.2. Methodology

To estimate spontaneous locomotor activity, the study used a standard protocol (Salazar-Juárez et al., 2016). Habituation of the rats to the activity chambers took place during three 30-min sessions. Then, they were randomly assigned to different pharmacological treatment groups. At the start of the behavioral recording session, rats were injected with the treatment that was previously assigned and then immediately returned to that activity chamber and locomotor activity was recorded for 30 min, and the rats were returned to their home cages after each experimental session had been completed.

2.3.3. Observation experiments

Acute cocaine toxicity was defined as the occurrence of cocaine-induced convulsions (loss of the righting reflex followed by clonic limb movements) and lethality (cessation of any visible movement and respiration). On the day of activity testing, the rats were transferred from their home cages to the activity chambers and were continuously observed for 30 min thereafter; time to seizure and/or lethality was recorded.

2.4. Experimental procedures

The study used 192 male Wistar rats divided into four groups, and each group underwent a different experiment. For Experiments 1 and 2, we used 48 animals further divided into six experimental groups (n = 8); for Experiment 3, we used 64 animals assigned to eight groups (n = 8); for Experiment 4, 32 animals were used in four experimental groups (n = 8). Each experimental group received a different pharmacological treatment.

2.4.1. Experiment 1: mirtazapine in different doses modified the expression of cocaine sensitization

Chronic dosing with mirtazapine during the extinction phase induced a dose-dependent attenuation of the expression of cocaine-induced locomotor sensitization. This experiment consisted of four phases: phase I, the cocaine-induction phase, which lasted 15 days; phase II, the cocaine extinction phase, lasted 30 days; phase III, for cocaine expression, lasted 25 days; and phase IV, the post-expression phase, which lasted 20 days (Fig. 1-A).

The SAL and the MIR groups received saline solution (0.9% NaCl, i.p.) and mirtazapine (30 mg/kg, i.p.), respectively, during the four phases. The cocaine group (COC) received cocaine (10 mg/kg, i.p.) during the induction, expression, and post-expression phases. During extinction, cocaine was withdrawn, and the group was administered