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Synergistic interactions between mirtazapine and prazosin prevent the induction and expression of behavioral sensitization to cocaine in rats

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ABSTRACT

Cocaine abuse and dependence are a global public health problem. To date, no effective therapy has been established to treat cocaine dependence but mirtazapine—as well as prazosin used in preclinical and clinical trials—has been shown to decrease cocaine behavioral effects. Therefore, our hypothesis was that the effectiveness of mirtazapine might improve when used in combination with prazosin. This study investigated the combined effect of mirtazapine and prazosin on cocaine-induced locomotor activity impairment in rats subjected to locomotor sensitization testing. We found that chronic treatment with the mirtazapine-prazosin combination significantly improved the effect of single mirtazapine dosing on cocaine-induced locomotor activity and on the induction and expression of cocaine sensitization. These results suggest that the combined use of mirtazapine and prazosin may be a potentially effective treatment to attenuate induction and expression of locomotor sensitization to cocaine.

1. Introduction

Cocaine abuse and dependence, both chronic brain disorders, have become a global public health problem [1]. Despite significant progress in our understanding of neurobiological changes associated with substance abuse and dependence during the last decade, few pharmacological interventions have proven to successfully treat cocaine dependence [2].

Mirtazapine (MSD REMERON, Schering-Plough-Organon, USA) is an effective noradrenergic and a specific serotoninergic antidepressant with pronounced early-anxiolytic effects in patients with moderate to severe depression [3,4]. Several studies have found that mirtazapine mitigates various behavioral alterations induced by drugs of abuse [5,6]. At the preclinical level, mirtazapine decreases symptom severity during morphine and methamphetamine withdrawal, reduces morphine-induced rewarding effects, inhibits the acquisition of morphine dependence, and attenuates the establishment of conditioned place preference to morphine and methamphetamine in rats [7–11]. Other studies show that mirtazapine has proven to be effective in reducing the reinstatement of methamphetamine self-administration [12] and decreasing the expression of methamphetamine-induced locomotor sensitization [9–11]. In addition, we recently reported that daily dosing of mirtazapine (30 mg/Kg, i.p.) for 30 days during drug-extinction significantly attenuates the induction and expression of locomotor sensitization to cocaine and nicotine, decreases the duration of the cocaine- and nicotine-induced locomotor effect [13–15] and reduce the reacquisition of cocaine self-administration [16]. Human studies have shown that mirtazapine administration reduces benzodiazepine, cocaine, and methamphetamine abuse [5,17]. Double blind, placebo-controlled clinical trials report that mirtazapine significantly improves symptoms of depression, anxiety, and insomnia, minimizing physical and subjective discomfort and dysphoric symptoms during benzodiazepine, methamphetamine, alcohol, and cocaine withdrawal [6,18,19,20], as well as reducing craving [6].

Furthermore, preclinical and clinical trials have found that alpha-1 adrenergic receptors contribute significantly to the behavioral effects of cocaine [21–24]. Prazosin, an antagonist of alpha-1 adrenergic receptors, blocks the acquisition of morphine- or cocaine-induced place preference; reverses tolerance to morphine analgesia; attenuates morphine-withdrawal symptoms in mice; and reduces the reinstatement of cocaine or heroin self-administration in rats [25–29]. Pretreatment with prazosin blocks the acute locomotor response and the development of behavioral sensitization to cocaine and methamphetamine, and significantly reduces hypophagia, locomotor hyperactivity, and Fos expression in the striatum induced by cocaine or amphetamine in rats [23,24,30,31]. In addition, 1 mg/kg doxazosin, another alpha-1 antagonist, blocks the development and expression of cocaine-induced behavioral sensitization in rats [32]. In some clinical trials, doxazosin

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has proven effective to reduce cocaine use and alleviate some of the positive subjective effects of cocaine in cocaine-dependent individuals [33,34].

Some double blind, placebo-controlled studies have found that mirtazapine is not better than placebo at reducing cocaine use in cocaine-dependent patients and that it increases anxiety in patients who are in acute methamphetamine withdrawal [18,35]. Moreover, as shown by preclinical and clinical trials, prazosin significantly reduces cocaine-induced behavioral effects [29,33,36]. Therefore, our research hypothesis was that mirtazapine effectiveness might improve when used in combination with prazosin. This study explored the potential additive or synergistic effects of co-administering mirtazapine and prazosin on cocaine-induced locomotor activity impairment in rats subjected to locomotor sensitization testing. In addition, in order to determine if the behavioral effect of the combination with mirtazapine and prazosin was the result of the pharmacological action of prazosin on mirtazapine, we administered oxymetazoline, an alpha-1 adrenergic agonist, which has demonstrated the ability to reverse the effects induced by prazosin [37,38].

Locomotor sensitization is considering a critical physiological mechanism that reflects the establishing of some of the persistent features of drug abuse and facilitates the expression of drug craving and compulsive drug-seeking behavior [39]. Moreover, the drug-sensitization induces an increase in the salience that result in an increased vulnerability to drug-relapse [40].

Our results indicate that co-administration of mirtazapine and prazosin significantly enhanced the effect of mirtazapine on cocaine-induced locomotor activity during the induction and expression of behavioral sensitization.

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. The study procedures were approved by the Committees on Bioethics and Institutional Laboratory Animal Care and Use, 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 (purity > 98%) 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, prazosin (Minipres, Pfizer), mirtazapine (REMERON, Schering-Plough-Organon), and oxymetazoline (Sigma-Aldrich) were dissolved in sterile saline solution (0.9% NaCl, Sigma Aldrich). The solutions were freshly prepared and maintained at − 20 °C before intraperitoneal (i.p.) administration. Saline (0.9% NaCl) was used as control in all experiments. To determine if co-administration of prazosin and mirtazapine could prevent the locomotor effects of cocaine, mirtazapine was administered 15 min after prazosin and 30 min before cocaine (or saline). The volume injected into each animal depended on its body weight (BW): BW (g)/100 ml.

2.2.1. Dose selection

For this study, the optimal mirtazapine dose (30 mg/kg) was determined in accordance with previous reports. They showed that ≥ 30 mg/Kg mirtazapine does not affect spontaneous locomotor activity [13] or produce sedation, nor does it induce weight gain [41,42], in rats. Additionally, preclinical and clinical trials have reported that 30 mg/Kg mirtazapine decreases cocaine-induced locomotor activity [13], attenuates morphine-induced place preference [7], and reduces morphine and methamphetamine withdrawal symptoms, in rats and humans.

Other authors have shown that 1 mg/Kg prazosin is the optimal dose to decrease behavioral effects caused by cocaine [24,29]. Further, 0.5 mg/kg oxymetazoline has proven to be the optimal dose to decrease the effect of alpha-1 adrenergic antagonists, such as prazosin [37,38].

2.3. Behavioral sensitization procedure

2.3.1. Apparatuses/devices

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 an array of photocell beams (16 × 16) 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).

2.4. Methodology

To estimate spontaneous locomotor activity, the study used a standard protocol [13]. Habituation of the rats to the activity chambers took place during three 30-min sessions. The animals were then randomly assigned to different pharmacological treatment groups. Locomotor activity was recorded for 30 min, and the rats were returned to their home cages after each experimental session had been completed.

2.5. Experimental procedures

The study used 144 male Wistar rats divided into three groups, with each group undergoing a different experiment. For experiments 1 and 2, we used 56 animals further divided into seven experimental groups (n = 8); for experiment 3, we used 32 animals assigned to four groups (n = 8). Each experimental group received a different pharmacological treatment.

2.6. Experiment 1

To determine if chronic co-administration of mirtazapine (30 mg/Kg) and prazosin (1 mg/Kg) prior to daily exposure to cocaine attenuated induction of locomotor sensitization to cocaine, this experiment was divided into three pharmacological phases: phase I, the pre-induction phase, which lasted 30 consecutive days; phase II, induction of locomotor sensitization to cocaine, which lasted 25 days; and phase III, post-induction, which lasted 15 consecutive days (Fig. 1-A).

After a three-day habituation period, the saline (SAL), the prazosin (PRZ), and the mirtazapine (MIR) groups received saline solution (0.9% NaCl, i.p.), prazosin (1 mg/Kg, 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 cocaine-post-induction phases 30 min before saline administration. In contrast, the rats in the PRZini + COC and the MIRini + COC groups received prazosin (1 mg/Kg, i.p.) or mirtazapine (30 mg/kg, i.p.) during both the pre-induction and the induction phases, 15 and 30 min, respectively, before receiving either saline or cocaine. The PRZini + MIRini + COC group received prazosin 15 min before mirtazapine and mirtazapine 30 min before receiving either saline or cocaine in the pre-induction and the induction phases. During post-induction, prazosin and mirtazapine were withdrawn and the three groups received cocaine only. After administration of each treatment, locomotor activity for each