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Mirtazapine attenuates cocaine seeking in rats

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ABSTRACT

Background: Relapse to cocaine use is a major problem in the clinical treatment of cocaine addiction. Antidepressants have been studied for their therapeutic potential to treat cocaine use disorder. Research has suggested that antidepressants attenuate both drug craving and the re-acquisition of drug-seeking and drug-taking behaviors. This study examined the efficacy of mirtazapine, an antidepressant/anxiolytic, in decreasing cocaine seeking in rats.

Methods: We used the cocaine self-administration paradigm to assess the effects of mirtazapine on rats trained to self-administer cocaine or food under a fixed-ratio schedule. Mirtazapine (30 mg/kg, i.p.) was administered during extinction.

Results: Mirtazapine significantly attenuated non-reinforced lever-press responses during extinction. Moreover, the mirtazapine dosed for 30 days during extinction produced sustained attenuation of lever-press responses during re-acquisition of cocaine self-administration, without changing food-seeking behavior. Our results showed that mirtazapine attenuated the re-acquisition of cocaine-seeking responses.

Conclusion: Our study pointed to the efficacy of mirtazapine in reducing the risk of drug relapse during abstinence, suggesting for its potential use as a novel pharmacological agent to treat drug abuse.

1. Introduction

Relapse to cocaine use is a major problem in the clinical treatment of cocaine use disorders. Several clinical reports have shown that relapse to cocaine use may occur after prolonged periods withdrawal. Cocaine relapse is triggered by re-exposure to the drug itself as well as by drug associated cues and stressors that lead to the development of cocaine craving (Kosten et al., 2006; Fox et al., 2005).

In addition, clinical trials have shown that depressive symptomatology during withdrawal may exacerbate the intensity of drug craving, thereby leading to a relapse to drug use (Sofuoglu et al. 2003, 2005). Over the past decades, several antidepressants have been studied for their therapeutic potential to relieve cocaine use disorders (Torrens et al., 2005).

Mirtazapine (REMERON, Schering-Plough-Organon 3770 USA) is an atypical antidepressant approved for the treatment of moderate to severe depression with comorbid anxiety disorders (Croom et al., 2009; de Boer, 1996).

Double-blind, placebo-controlled clinical trials have found that mirtazapine reduces craving (Graves et al., 2012a) and improves depression, anxiety, insomnia, and dysphoria, which appear during alcohol, benzodiazepine, methamphetamine, and cocaine withdrawal (Graves et al., 2012a; Afshar et al., 2012; Chandrasekaran, 2008; Liappas et al., 2004).

However, in other double-blind placebo-controlled study, found that mirtazapine was not superior to placebo in reducing cocaine use in cocaine-dependent patients and increased anxiety in patients who were in acute methamphetamine withdrawal (Afshar et al., 2012; Cruickshank et al., 2008).

In rats, the picture is similar, in some studies mirtazapine has proven to be effective in reducing the reinstatement of methamphetamine self-administration (Graves and Napier, 2011; Graves et al., 2012a) and decreasing the expression of methamphetamine-induced place preference and locomotor sensitization (Herrold et al., 2009; Voigt et al., 2011; Voigt and Napier, 2012). In addition, we recently reported that daily dosing

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with mirtazapine (30 mg/kg, i.p.) for 30 days during cocaine-withdrawal significantly attenuates the induction and expression of cocaine-induced locomotor sensitization; well as decreased the duration of the cocaine-induced locomotor effect (Salazar-Juárez et al., 2016). In other studies, 24 h pretreatment with mirtazapine was not enough to decrease the expression of morphine-induced place preference and locomotor sensitization (Graves et al., 2012b).

Despite some studies suggest that mirtazapine fails to reduce drug abuse (Afshar et al., 2012; Cruickshank et al., 2008); other studies collectively indicate that mirtazapine may effectively alter the behavioral effects of drugs such as cocaine and methamphetamine (Graves and Napier, 2011; Graves et al., 2012a). Studies, however, have not determined the effect of chronic dosing of mirtazapine on persistent seeking in the absence of cocaine or on the re-acquisition of cocaine seeking in rodents— two behavioral patterns that characterize drug abuse liability. In this study, we used the standard intravenous cocaine self-administration pharmacological paradigm, in a fixed-ratio schedule, to evaluate the effect of daily mirtazapine during extinction on the re-acquisition of cocaine seeking in rats. Our results showed that chronic dosing of mirtazapine is an effective pharmacological treatment that reduces cocaine seeking in the absence of cocaine and attenuates re-acquisition of cocaine self-administration.

2. Methods

2.1. Subjects

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 at 21 ± 2 °C and 40–50% humidity, under a 12-h light/dark cycle (lights on at 7:00 a.m.). The animals had free access to water during the experiments. **Rats trained to food self-administration were restricted to 20 g per day of rat chow after daily operant sessions**. The rats were acclimated to the experimental chambers for 2-h over 5 days, before the lever-press training sessions. All the experiments took place during the light phase of the light/dark cycle (9:00 a.m. to 5:00 p.m.). The procedures were approved by the Institutional Animal Care and Bioethics Committee in strict compliance with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals.

2.2. Drugs

Cocaine hydrochloride was kindly donated by the Mexican government under strict regulatory controls. All the drugs used in experimental animals were placed under official surveillance (COFEPRIS- LC-0004-2003, México). Cocaine hydrochloride and mirtazapine (REMERON, Schering-Plough-Organon) were dissolved in sterile saline solutions (0.9% NaCl, Sigma Aldrich) freshly prepared before administration. Mirtazapine was administered 30 min before cocaine or food self-administration. 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-Juarez et al., 2017) in rats. Additionally, in our laboratory, we found that lower doses of mirtazapine (<30 mg/kg) were not able to decrease cocaine-induced locomotor activity, whereas higher doses (>30 mg/kg) were able to significantly decrease locomotor activity induced by different doses of cocaine (unpublished results).

2.3. Self-administration procedure

2.3.1. Apparatus

For each experiment, we used an operant Skinner boxes (30 × 28 × 30 cm; TSE Germany) equipped with a house light, a ventilation fan, a drug-infusion pump, a fluid swivel attached to a counterbalance arm, a light-cue panel above each lever, and a food-pellet dispenser between the two levers. The levers were 9 cm above the grid floor, but only one of them, the retractable (active) lever, was operational during drug delivery. Each experimental chamber was placed into a wooden box with sound-attenuating insulation.

2.3.2. Surgery

For surgery, the rats were anesthetized with ketamine HCl (90 mg/kg, i.p. Sigma Aldrich) and xylazine (5 mg/kg, i.p. Sigma Aldrich). A surgical incision (5 mm) was made above the jugular vein and the vein was located by dissection. For catheter implantation, a connector pedestal (20 ga 300-001; Plastics One, Wallingford, CT, USA) attached to a propylene catheter (0.51 mm ID, 0.94 mm OD; SILASTIC) was glued to a ProLite mesh (2-cm diameter; Silicon Polypropylene Mesh, Wall, USA) with dental cement. The end of the tubing attached to the connector pedestal was inserted subcutaneously into the area of the right jugular vein and then 3.0 cm into the vein. It was secured with silk sutures. The other end of the catheter tubing was implanted subcutaneously between the shoulder blades of the animals.

Wounds were treated with nitrofurazone and antibiotic ointment. Patency of the catheter was maintained by flushing it daily (Sunday through Saturday), after self-infusion sessions, with a mixed solution consisting of 0.1 ml saline solution (0.9% NaCl, Sigma Aldrich)/12.5 IU heparin (Pisa Agropecuaria Mexico)/100 mg/ml gentamicin (Schein Pharmaceuticals, USA). Prior the self-administration sessions, implanted animals received 0.1 ml heparinized saline (10 IU/ml). During the self-administration procedures, the catheters attached to the pedestal guide cannulas were connected to an infusion-pump system (PHM-100, Med-Associates) through a three-channel fluid swivel (TSE System, USA) fixed above the operant-conditioning chamber.

Animals in food self-administration protocols were subjected to the aforementioned surgical interventions in order to perform the intra-jugular catheter implantation.

One week after the jugular vein catheters had been implanted, the rats were daily exposed to either, 2-h cocaine or food self-administration sessions.

2.4. Procedures

2.4.1. Lever-press training

Before surgery, the rats were trained to lever press for 45-mg food pellets (Noyes, Lancaster, NH, USA) under a fixed-ratio 1 (FR1) schedule of daily 2-h sessions/6 days per week, with light stimulus presentation that had indicated food delivery during training (Fig. 1). Food delivery was controlled by a computer software (TSE Systems, Hamburg, Germany). The rats that learned to lever press for 35 food pellets received further catheter-implantation.

2.4.2. Cocaine self-administration training

Rats were trained to self-administer cocaine using a 1 mg/kg cocaine unit dose (30 μl/infusion/30 s), in daily 2-h sessions during 6 days per week. The maximum number of infusions per session was kept up to 35 infusions. During the initial 10 days, rats acquired cocaine self-administration under an FR1 schedule of reinforcement; then rats acquired cocaine self-administration under an FR3