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# Cocaine + nicotine mixture enhances induction and expression of behavioral sensitization in rats

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ABSTRACT

*Background:* Psychoactive substance abuse is a health problem worldwide. Has been reported a high prevalence of use of tobacco and cocaine, either separately or in combination. Clinical and animal studies have suggested that the concurrent use of cocaine and nicotine reinforces the potency of one or both drugs and that nicotine may enhance the reinforcing effects of cocaine. Our study evaluated the combined effects of cocaine and nicotine on locomotor activity during the induction and expression phases of locomotor sensitization—a physiological mechanism that plays an important role in establishing some of the defining characteristics of drug abuse.

*Methods:* We used *Wistar* rats which were dosed with cocaine, nicotine or cocaine and nicotine combination and recorded their locomotor activity in different phases of the experiment.

*Results:* We found that a daily dose of cocaine combined with nicotine enhanced cocaine- and nicotine-induced locomotor activity, as well as induction and expression of locomotor sensitization. Moreover, we found that pretreatment with nicotine enhanced the locomotor sensitization expression.

*Conclusion:* These results suggest that concurrent use of cocaine and nicotine may result in co-abuse of these drugs.

## 1. Introduction

Various clinical studies have reported that nicotine is one of the drugs with the highest prevalence of use among cocaine-dependent smokers (Budney et al., 1993; Higgins et al., 1994) and that cocaine users use tobacco and cocaine concurrently (Wiseman and McMillan, 1996, 1998a; 1998b). According to the National Survey of Drug Use and Health, in 2016, in the United States, 2.4 million people use cocaine, of which 70–80% cigarettes smoke simultaneously (De la Garza et al., 2016; Brewer et al., 2013; Lai et al., 2000). Additionally, these studies also showed that: A) Cocaine-dependent smokers who also smoke cigarettes use cocaine more often than non-smokers do. B) Cocaine smokers have reported an increase in smoking during periods of cocaine use, compared to periods of non-use (Higgins et al., 1994; Roll et al., 1996, 1997). C) Cocaine-dependent people report that, at the end of a period of cocaine use, they smoke more cigarettes than in periods of non-use of cocaine (Nemeth-Coslett et al., 1986; Patkar et al., 2006), and cocaine abusers who smoke cigarettes report that cigarettes enhance and prolong the reinforcing effects of cocaine (Wiseman and McMillan, 1996, 1998a, 1998b; Radzius et al., 1997) suggesting that simultaneous use of nicotine and cocaine relates to an increase in the rate of consumption of both drugs and in the reinforcing effects of one or both drugs. A similar effect occurs among amphetamine **individuals with addiction**, who increase the number of cigarettes they smoke and the ratings of cigarette-smoking satisfaction (Henningfield and Griffiths, 1981).

Studies in rhesus monkey found that concurrent self-administration of cocaine + nicotine increased response rates and reinforcing effects to levels higher than those found with self-administration of cocaine or nicotine alone (Mello and Newman, 2011; Freeman and Woolverton, 2009). In addition, in rats, microdialysis studies have also shown that co-administration of cocaine and nicotine enhances dopamine release in the nucleus accumbens in rats (Zernig et al., 1997; Gerasimov et al., 2000).

This study evaluated the effect of nicotine and cocaine combination on locomotor activity during the induction and expression phases of locomotor sensitization, as well as the effect of pretreatment with either cocaine or nicotine on cocaine + nicotine-induced expression of locomotor sensitization. Locomotor sensitization is considering a critical physiological mechanism that reflects the establishment of some of the persistent features of drug abuse and facilitates the expression of drug craving and compulsive drug-seeking behavior (Robinson and Berridge,

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1993). Moreover, the drug-sensitization induces an increase in the salience that results in an increased vulnerability to drug-relapse (Koob and Le Moal, 2008).

Our hypothesis was that cocaine mixed with nicotine would increase locomotor activity and sensitization. The study results showed that the cocaine and nicotine combination enhanced locomotor activity during the induction and expression phases of locomotor sensitization.

## 2. Experimental procedures

### 2.1. Animals

We used male *Wistar* rats weighing 250–280 g at the beginning of the study. They were housed in groups of four in standard plastic rodent cages (57 cm × 35 cm x 20 cm) in a colony room maintained at a constant temperature (21 ± 2 °C) and humidity (40–50%), on a 12:12-h light/dark cycle (lights on at 7:00 a.m.). The animals had continuous access to rodent chow pellets and water except during the experimental sessions. All the experiments took place during the light phase of the light/dark cycle (between 9:00 a.m. and 3:00 p.m.). The procedures were approved by the Institutional Animal Care and Bioethics Committee, in strict compliance with the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health (NIH).

### 2.2. Drugs

Cocaine hydrochloride (97% purity) was kindly provided by the Mexican government through the relevant regulatory authorization. All the drugs used in experimental animals were under official surveillance (COFEPRIS- LC-0004-2003). Nicotine (nicotine tartrate salt; Sigma-Aldrich) and mecamylamine (Sigma-Aldrich) were purchased after obtaining the required regulatory permission, as per official guidelines (COFEPRIS-2016, Mexico).

Cocaine hydrochloride, nicotine, and mecamylamine were dissolved in sterile saline solution (0.9% NaCl, Sigma-Aldrich), and the cocaine and nicotine mixture were obtained by mixing both drugs in a single bag. The solutions were freshly prepared before their intraperitoneal (i.p.) administration to the animals. All nicotine solutions were adjusted to pH 7.4 using sodium hydroxide (1 M). During the experiments, the solutions were kept at −20 °C. Saline (0.9% NaCl) was used as the control in all the experiments. Nicotine solutions were stored in black bottles to protect them from exposure to light. Mecamylamine was administered 15 min before cocaine + nicotine (or saline) to determine if it could prevent the locomotor effects of the cocaine + nicotine mixture. The volume injected into the animals depended on their body weight (BW) in grams (BW (g)/100 ml).

#### 2.2.1. Dose selection

The optimum dose of cocaine and nicotine were chosen based on previous studies showing that a dose of 10 mg/kg of cocaine and 0.4 mg/kg of nicotine generates a robust increase in cocaine- or nicotine-induced locomotor activity and behavioral sensitization (Salazar-Juárez et al., 2016; Barbosa-Méndez et al., 2017a, 2017b, 2017c). These doses of cocaine or nicotine were not able to generate seizures or lethality (Barbosa-Méndez et al., 2017a, 2017c).

### 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 personal computer. 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 photo-beams were automatically quantified with OABiomed software (1.1) and then analyzed. Locomotor activity was defined as consecutive beam breaks (OMNIALVA, Mexico).

#### 2.3.2. Procedure

Spontaneous locomotor activity was estimated with a standard protocol (Salazar-Juárez et al., 2016). Animals were habituated to the activity chambers in three 30- min sessions and were randomly assigned to different pharmacological treatment groups. Locomotor activity was recorded for 60 min. The rats were returned to their home cages after each experimental session had been completed.

### 2.4. Experimental procedures

The study used 224 male Wistar rats divided into five experiments. For experiments 1 and 2, we used 32 animals further divided into four experimental groups (n = 8); for experiments 3 and 4, we used 56 animals in seven groups (n = 8); for experiment 5, we used 48 animals in six groups (n = 8). Each experimental group received a different pharmacological treatment.

#### 2.4.1. *"Experiment 1: acute dosing of the cocaine + nicotine mixture enhanced induction and expression of sensitization induced by cocaine and nicotine alone"*

This experiment included three pharmacological phases. Phase I, or the cocaine + nicotine-induction phase, which lasted 15 days. Phase II, or the cocaine + nicotine-extinction phase, lasted 20 days. Phase III, or the cocaine + nicotine-expression phase, lasted 25 days. (Fig. 1A).

The SAL group received saline solution (9% NaCl, i.p.) during the three aforementioned phases. The cocaine (COC) and nicotine (NIC) groups received either cocaine (10 mg/kg, i.p.) or nicotine (0.4 mg/kg, i.p.) during the induction and the expression phases. During extinction, cocaine or nicotine was withdrawn and the groups received daily saline only.

The cocaine + nicotine group (COC + NIC) received cocaine (10 mg/kg, i.p.) mixed with nicotine (0.4 mg/kg, i.p.) daily during the induction and the expression phases. In the extinction phase, the rats received saline. After each administration, the locomotor activity of each animal was recorded for 60 min (Fig. 1-A).

#### 2.4.2. *"Experiment 2: acute dosing of the cocaine + nicotine mixture increased the duration of cocaine- and nicotine-induced locomotor activity"*

Experiment 2 characterized the combined effect of cocaine + nicotine on the duration of cocaine- or nicotine-induced locomotor activity. It included two phases: acquisition (10 days) and testing (1 day).

All the animals were subjected to three daily habituation sessions. During the acquisition phase, the SAL, the COC, and the NIC groups received the pharmacological treatments described in Experiment 1. The rats in the COC + NIC group received cocaine (10 mg/kg, i.p.) mixed with nicotine (0.4 mg/kg, i.p.) for 10 days (Fig. 2A).

Upon completion of the acquisition phase, all the rats were placed in the testing box for 30 min without any treatment to determine baseline responses. Then, after each animal/group had received their treatment, locomotor activity was recorded every 30 min, for a total of 240 min.

#### 2.4.3. *"Experiment 3: acute dosing of mecamylamine altered the combined effect of cocaine + nicotine on the expression of sensitization induced by cocaine and nicotine alone"*

This experiment evaluated the effect of mecamylamine (a non-selective antagonist of the nicotinic acetylcholine receptors) on the combination of cocaine and nicotine. The experiment included five pharmacological phases: phase I, or cocaine + nicotine induction, of 10 days; phase II, or cocaine + nicotine extinction, which lasted 20 days; phase III, or cocaine + nicotine expression, which lasted 10 days; and phases IV and V (the antagonist and the post-antagonist phases), both lasting 5 days.

The SAL + SAL, the SAL + COC, the SAL + NIC, and the