



# Prior exposure to stress delays extinction but does not modify reinstatement of nicotine-induced conditioned place preference

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## Abstract

Studies in humans suggest that exposure to stress is related to relapse to tobacco use. The reinstatement of conditioned place preference (CPP) provides a simple, noninvasive and easy approach to investigate the mechanisms for drug relapse. The present study investigated whether repeated exposure to stress could change the extinction and reinstatement of nicotine-induced CPP. Adult male Wistar were exposed to restraint-stress for 2 hours/daily for 7 days, while the control-group was left undisturbed during this period. One day after the last stress session the CPP protocol was carried out. Nicotine produced a place preference to the compartment paired with its injections during conditioning (.16 mg/kg, s.c.; four drug sessions). Once established, nicotine place preference was extinguished by alternate exposure to each compartment after a saline injection (four exposures to each compartment). The animals that did not show extinction of CPP were submitted to two other extinction sessions. Following this extinction phase, the reinstatement of place conditioning was investigated following a priming injection of nicotine. Both control and stress groups showed reinstatement of CPP. The percentage of rats from the stress group that extinguished nicotine-CPP in the first and second test was lower as compared to the control group. In conclusion, stress delayed the extinction of the nicotine-induced CPP, but did not modify the reinstatement.

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## Introduction

According to the World Health Organization, cigarette smoking is the leading cause of preventable death worldwide (World Health Organization, 2009). One-third of the world's population smoke tobacco, and half of the smoking population dies from a smoking-related disease. Much evidence suggests that nicotine, which acts at neuronal nicotinic acetylcholine receptors, is the main active component in tobacco responsible for tobacco addiction (Stolerman & Jarvis, 1995; Wonnacott, Sidhpura & Balfour, 2005).

Tobacco addiction is a process that usually begins with the occasional use of the substance and evolves into compulsive use (O'Brien, Volkow & Li, 2006). Moreover, tobacco addiction is associated with high rates of relapse to drug use even after prolonged periods of abstinence (Shalev, Grimm & Shaham, 2002; Fiore, 2000).

Stressful experiences appear to strongly influence the susceptibility to drug-taking behavior (Sinha, Catapano & O'Malley, 1999). Exposure to stressful events has been related to the initiation and maintenance of drug use and relapse (Gawin, 1991; Sinha, 2001; Gordon, 2002; Goeders, 2003; Weiss, 2005). Exposure to stress appears to increase the number of cigarettes smoked and is strongly associated with craving and relapse to tobacco smoking (Cohen & Lichtenstein, 1990; Kassel, Stroud & Paronis, 2003; Niaura & Abrams, 2002).

Stress can increase the reinforcing effects of substances of abuse (Will, Watkins & Maier, 1998; Der-Avakian et al., 2005). Many studies have shown that exposure to stress can facilitate drug-induced conditioned place preference (CPP; Capriles & Cancela, 1999; Del Rosario Capriles & Cancela, 2002). For example, previous stress exposure was shown to increase the intensity of the expression of morphine-induced CPP (Will et al., 1998).

Clinical studies have demonstrated that exposure to stress or simply the presentation of stress-related imagery can induce relapse to drug seeking in humans (Shiffman,

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Read & Jarvik, 1985; Lamon & Alonzo, 1997; Brady & Sonne, 1999; Sinha, 2001; Sinha et al., 1999).

Two animal models have proven especially useful for studying relapse, reinstatement of self-administration (Carroll, 1985; Lê & Shaham, 2002; Lu, Grimm, Shaham & Hope, 2003), and reinstatement of CPP (Mueller & Stewart, 2000; Itzhak & Martin, 2002; Lu et al., 2005; Biala & Budzynska, 2006). The same stimuli that can reinstate self-administration are able to induce the reinstatement of CPP (Aguilar, Rodríguez-Arias & Miñarro, 2009). Preclinical studies have shown that stress can reinstate cocaine, amphetamine, morphine, and heroin self-administration (de Wit & Stewart, 1981; Shaham, Adamson, Grocki & Corrigan, 1997; Buczek, Lê, Wang, Stewart and Shaham, 1999; LeSage, Burroughs, Dufek, Keyler & Pentel, 2004). Similarly, several studies have shown that stress exposure reinstates opioid-, cocaine-, and nicotine-induced CPP (Will et al., 1998, 2004; Der-Avakian et al., 2005; Der-Avakian et al., 2006; Leão, Cruz & Planeta, 2009).

In rats, intermittent footshock reinstates nicotine self-administration up to 15 days after extinction (Buczek, Lê, Wang & Stewart, 1999). We recently showed that exposure to acute restraint stress reinstated nicotine-induced CPP 15 days after the extinction of this behavior (Leão, Cruz & Planeta, 2009). Moreover, exposure to footshock stress prolonged the process of extinguishing morphine-induced CPP (Lu, Ceng & Huang, 2000).

Despite the strong influence of stress on relapse to tobacco use, the effects of prior exposure to repeated stress on extinction and reinstatement of nicotine-induced CPP has not been investigated. Thus, the present study investigated whether repeated stress exposure affects the extinction and reinstatement of nicotine-induced CPP.

## Methods

### *Subjects*

Subjects were adult male Wistar rats weighing 225–250 g from the animal breeding facility of the Universidade Estadual Paulista – UNESP. Groups of four to five animals were housed in plastic cages (32 cm width × 40 cm length × 16 cm height) in a room maintained at  $23 \pm 21^\circ\text{C}$ . Rats were kept on a 12 h/12 h light/dark cycle (lights on at 07:00 h) and were allowed free access to food and water. Each animal was used only in one experimental procedure. All experiments were performed during the light phase between 08:00 h and 17:00 h. Each experimental group consisted of 10 to 12 animals per group.

The experimental protocol was approved by the Ethics Committee for Use of Human or Animal Subjects of the School of Pharmaceutical Science, UNESP (CEP-13/2004), and the experiments were conducted according to the ethical principles of the Brazilian College of Animal Experimentation, which are based on the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals.

### *Drug*

(-) - Nicotine 99% was obtained from Sigma-Aldrich (St Louis, MO, USA). The dose of nicotine was chosen based on previous experiments conducted in our laboratory (Leão, Cruz & Planeta, 2009)

### *Repeated stress paradigm*

The animals were allocated to two groups: control and chronic restraint stress. Animals in the chronic restraint stress group were restrained in plastic cylinders (20.0 cm length × 5.5 cm internal diameter) 2 h daily for 7 days beginning at 10:00 h. The control group was left undisturbed, with the exception of cleaning the cages.

### *Reinstatement of nicotine-induced CPP*

The testing apparatus for the CPP paradigm consisted of Plexiglas boxes with two compartments of equal size (30.0 cm length × 21.0 cm width × 30.0 cm height) separated from a small central gray area (15.0 cm length × 30.0 cm width × 30.0 cm height) by removable guillotine doors. One compartment had white walls and a thin parallel grid floor, and the other compartment had black and white stripes on the walls and a grid with small holes on the floor. The central gray area constituted a “neutral” chamber. The testing boxes were kept in a soundproof room with dim 40 lux illumination.

The CPP reinstatement procedure consisted of the following phases: pre-conditioning, conditioning, post-conditioning, extinction, and reinstatement. This method was similar to that described by Mueller, Perdikaris & Stewart, (2002).

**Pre-conditioning (PRE-TEST):** During this phase, each rat was placed in the neutral compartment with the guillotine doors removed to allow access to the entire apparatus for 15 minutes for 3 days. On day 3, rats were placed in the apparatus and videotaped for 15 minutes to record the time spent in each compartment. Approximately 20% of the animals displayed strong unconditioned aversion (< 15% of session time) or preference (> 85%) for one of the compartments and were thus excluded from the study.

**Conditioning:** Animals were randomly assigned to drug or saline administration. Conditioning was performed using a protocol consisting of eight alternating subcutaneous (s.c.) injections of nicotine (.16 mg/kg) or saline. Injections were administered immediately before confinement to one of the two compartments for 30 minutes. In each group, half of the animals that received nicotine were confined to the preferred compartment, and the other half were confined to the initially non-preferred compartment. Conditioning sessions were conducted twice per day at 4 hour intervals. The control group received saline every day in both compartments. The neutral chamber was never used during conditioning and was blocked by guillotine doors.

**Conditioning test (TEST):** The test was conducted 24 hours after the last conditioning session. Each rat was placed in the neutral compartment with the guillotine

doors removed to allow access to the entire apparatus. The time spent in each compartment was recorded for 15 minutes, similar to the pre-conditioning phase. Nicotine or saline was not injected before the tests.

**Extinction:** Beginning the day after the CPP test, rats underwent extinction by pairing both compartments with saline for 4 days. Twenty-four hours after the last extinction session, the extinction test was performed as described in the conditioning test. The animals that did not show extinction of CPP were subjected to two more extinction sessions until all of the animals exhibited extinction of CPP.

**Reinstatement (REINST):** Twenty-four hours after the last extinction session, drug-induced reinstatement of nicotine-induced CPP was evaluated. Separate groups of rats received a priming injection of nicotine (.16 mg/kg, s.c.) or .9% saline and were then immediately tested for reinstatement of CPP. During this reinstatement test, each rat was placed in the neutral compartment with the guillotine doors removed to allow access to the entire apparatus for 15 minutes, and the time spent in each compartment was measured as described above.

### Statistics

The behavioral data is expressed as means  $\pm$  SEM of CPP score of 10 to 12 animals per group. The conditioned score is expressed by the ratio between the time spent in the drug-paired and the time spent in both compartments (drug and saline paired), (i.e. total time minus time spent in the neutral chamber) multiplied by 100.

Levene tests for homogeneity of variance were performed to the behavioral data. Levene did not show statistically significant differences, indicating the homogeneity of variance.

Thus the reinstatement of CPP was analyzed by three-way ANOVA for repeated measured [Stress (stress and non-stress), treatment (saline and nicotine), and phases (PRE-COND, COND, EXT and REINST)]. The phase was used as repeated-measured. When a significant ( $p < .05$ ) main effect was observed F-tests for contrast analysis were applied.

The  $\chi^2$  test was applied to analyze the percentage of animals that extinguished the CPP across the extinction tests.

## Results

Three-way ANOVA revealed significant differences for the phase ( $F_{3,156} = 10.72$ ;  $p < .001$ ), but not for stress and treatment factors ( $F_{1,52} = 2.54$ ;  $p = .11$ ); ( $F_{1,52} = .0018$ ;  $p < .97$ ; respectively). This analysis detected interaction between treatment and phases factors ( $F_{3,156} = 10.72$ ;  $p < .001$ ). No other interactions were observed among the factors.

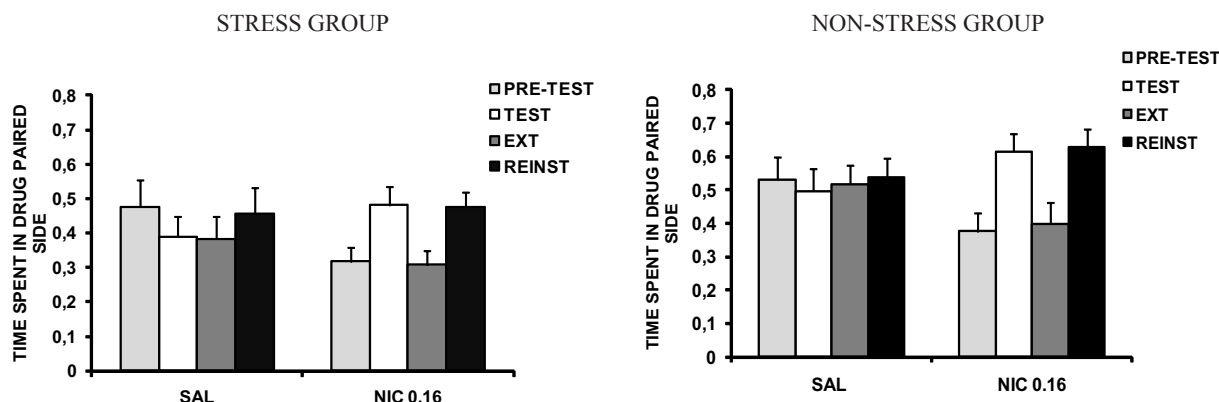
Since ANOVA did not reveal significant differences for the stress factor or interaction between stress and phase factors, the stress factor was not considered for further analysis by the F-Test. The F-Test revealed an increase in the time spent in nicotine-paired compartment in the TEST when compared to PRE-TEST ( $F_{1,52} = 32.86$ ;  $p < .001$ ), indicating that nicotine induced CPP. In addition, no difference was observed comparing PRE-TEST to EXT phases ( $F_{1,52} = .04$ ;  $p = .84$ ). Moreover significant differences in the time spent in nicotine-paired compartment were observed between COND and EXT phases ( $F_{1,52} = 46.55$ ;  $p < .001$ ). Further, significant differences in the time spent in nicotine-paired compartment were detected comparing REINST to PRE-TEST ( $F_{1,52} = 22.68$ ;  $p < .001$ ). No significant differences were observed between COND x REINST phases ( $F_{1,52} = .26$ ;  $p = .60$ ) (Figure 1A and 1B).

No significant differences were observed in the time spent for saline group across phases.

The  $\chi^2_2$  test showed that the percentage of animals that extinguished nicotine-induced CPP in the first and second extinction tests was lower in the stress group as compared to the control one ( $p < .01$ ) (Table 1).

## Discussion

In the present study we investigated whether previous exposure to repeated stress modify the extinction and



**Figure 1.** Acquisition, extinction, and reinstatement of nicotine-induced CPP after a priming injection of nicotine. Bars represent mean  $\pm$  SEM of CPP score ( $n = 10-12$  animals per group). (A) Stress group. (B) Control group. \* $p < .05$ , compared with PRE-TEST; # $p < .05$ , compared with EXT.

**Table 1.** Percentage of animals that extinguished nicotine-induced CPP after the first, second, and third extinction test.

Group	Extinction I	Extinction II	Extinction III
Stress	40%*	60%*	100%
Control	83%	100%	100%

\* $p < .01$ , compared with control group.

reinstatement of nicotine-induced CPP. We observed that the exposure to stress impaired the extinction of nicotine-induced CPP but did not alter the reinstatement induced by a priming injection of nicotine.

The present results showed that previous exposure to repeated stress reduced the percentage of rats that extinguished nicotine-induced CPP after the first and second extinction test when compared to rats that were not exposed to stress, suggesting that previous stress experience can strength the conditioning to nicotine. These findings corroborate those observed by Lu, Ceng & Huang, (2000) showing that the extinction of morphine-CPP is impaired by prior exposure to foot-shock stress.

Conversely, it was demonstrated that stress facilitates the extinction of alcohol self-administration (Funk, Harding, Juzytsch & Lê, 2005). However, there are some differences between the experiments; while we used the CPP procedure Funk, Harding, Juzytsch & Lê, (2005) used the self-administration procedure to access the impact of stress on extinction. Furthermore, they exposed the animals to stress after the acquisition of the conditioned behavior.

The impaired extinction of nicotine-induced CPP in animals prior exposed to stress may be related to the effect of stress on the reinforcing drug properties. In fact, several studies show that both acute and repeated stress can enhance drug reinforcement (Der-Avakian et al., 2005; Goeders & Guerin, 1994; Shaham & Stewart, 1994; Will, Watkins & Maier, 1998). For instance, Capriles & Cancela (1999) showed that a single restraint stress exposure induced an enhancement of D-amphetamine-induced place preference. Furthermore, exposure to uncontrollable stress (inescapable shock) potentiated morphine-CPP. Thus, we could suggest that enhancement of drug reward could have strengthened the conditioning to nicotine making extinction of the conditioned behavior more difficult.

The mesolimbic dopamine systems are critically involved in reward of psychostimulants and nicotine (Di Chiara, 1995; Brunzell, Mineur, Neve & Picciotto, 2009). In this sense, there is evidence that nicotine-induced CPP is coupled to an enhancement of dopaminergic activity (Spina, Fenu, Longoni, Rivas & Di Chiara, 2006). Similarly to drug, stress also increases the activity of the dopaminergic mesocorticolimbic system (Kalivas & Duffy, 1989; Imperato, Puglisi-Allegra, Zocchi, Scrocco,

Casolini & Angelucci, 1990; Marinelli & Piazza, 2002). Moreover, stress can increase drug-induced dopamine release in the NAcc (Pacchioni, Cador, Bregonzio & Cancela, 2007). For instance, it was demonstrated that repeated food restriction stress induced an increased in dialysate dopamine in the nucleus accumbens in response to amphetamine administration (Cadoni, Solinas, Valentini & Di Chiara, 2003).

Regarding reinstatement of nicotine-induced CPP by a priming injection of this drug, we did not observe differences in the group of animals exposed to stress as compared to the control group, i.e., both control and stress groups displayed reinstatement in the same magnitude. These results are in accordance with Funk, Harding, Juzytsch & Lê, (2005) that demonstrated that previous stress exposure did not influence the reinstatement of cocaine self-administration. However, we cannot completely rule out the possibility the stress can alter the reinstatement of nicotine-CPP because in our study we used only one priming dose of this drug.

Even though the effects of stress on potentiating drug-induced reinstatement of CPP was not evidenced in this study, recently we have reported that the exposure to one episode of restraint stress previously to the reinstatement test was able to reinstate nicotine – induced CPP one and 15 days after extinction test (Leão, Cruz & Planeta, 2009), suggesting that although stress did not alter nicotine-induced relapse it can promote relapse by itself.

Overall, stress impaired the extinction of nicotine-induced CPP, but did not modify the reinstatement. Our findings add pre-clinical evidence that exposure to stress can difficult the abstinence to tobacco.

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