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Short communication

Potentiation of the expression of cocaine-induced sensitization by a conditioned stressor

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HIGHLIGHTS

- A footshock-conditioned odor cue potentiated the expression of behavioural sensitization to a cocaine challenge.
- A footshock-conditioned odor cue did not, itself, elicit cross-sensitization to the unconditioned stressor or to cocaine.
- This represents a novel examination of the effects of a conditioned stressor on the expression of sensitization.

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ABSTRACT

Repeated exposures to physical stressors cross-sensitize to the locomotor activating effects of psychostimulants in rodents. In the present study, we examined the effect of a conditioned stressor on expression of cocaine-induced sensitization in rats. We determined whether a mint odor cue previously paired with footshock stress (FS) would elicit a sensitized locomotor response in cocaine pre-exposed rats. Rats were given once daily injections of cocaine (30 mg/kg, i.p.) or saline for 6 days in activity monitoring chambers. Subsequently, and in a different and distinct context, equal numbers of rats in each drug condition were exposed to 10 min of brief, intermittent FS or no FS, either in the presence or absence of the mint odor cue. Upon re-exposure to the activity chambers (in which cocaine exposures had been given), all rats previously exposed to cocaine showed robust conditioned locomotion. In response to a cocaine challenge (10 mg/kg, i.p.), cocaine relative to saline pre-exposed rats showed a sensitized locomotor response. Finally, in those cocaine pre-exposed rats that had been given prior odor-FS pairings, concurrent delivery of the cocaine challenge and presentation of the odor cue markedly potentiated the expression of sensitization. To our knowledge, this is the first report of a facilitation of cocaine-induced locomotor sensitization by a conditioned stressor.

1. Introduction

Stress is a major factor contributing to cocaine relapse in humans, and can evoke strong craving in cocaine users [1,2]. In animal studies, exposure to various forms of physical and pharmacological stress have likewise been found to enhance intravenous cocaine self-administration (e.g., [3]), and to induce reinstatement of cocaine seeking after prolonged drug-free periods (e.g., [4,5]).

It is well known that during drug use, associations are formed between the pharmacological actions of the drug (including perceived reward or relief), and contextual cues experienced simultaneously (such as items, people, or places). Strong desire for the drug can then be triggered by re-exposure to drug-associated contextual cues, a phenomenon referred to as 'conditioned craving' [6,7]. Such conditioned craving has been reliably modeled in laboratory animals, and has been extended to an examination of the combined effects of cues and stressors on drug-related responses. For example, the presentation of acute footshock (FS) with previously cocaine-paired cues enhances cocaine-seeking behavior upon reinstatement [8].

The extent to which stress-conditioned cues can come to control drug-related responses has been the subject of relatively limited study. There is good reason to think, however, that such condi-

Abbreviations: FS, footshock; PE, pre-exposure; HAB, habituation.

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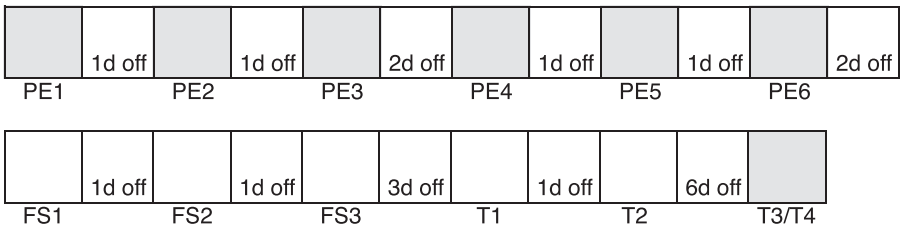

Fig. 1. Experimental timeline: All rats were given a habituation session (HAB) followed by 6 days of drug pre-exposure (PE1–PE6: 30 mg/kg, i.p.) with 1–2 days off between exposures. Two days after PE6, 3 sessions of footshock-mint odor conditioning were given (FS1–FS3). Three days later, a test for conditioned locomotion (T1) was administered, followed two days later by a test for conditioned locomotion in the presence of the mint odor cue (T2). Six days after T2, a subset of rats were given a test for behavioral sensitization to a cocaine challenge (T3) and another subset of rats were given a test in response to simultaneous delivery of a cocaine challenge and presentation of the mint odor cue (T4). Shaded cells indicate days on which cocaine injections were administered.

tioned stressors could serve to modify aspects of drug experience. In studies of behavioural sensitization, for example, it has been shown that stress can cross-sensitize to the locomotor activating effects of psychostimulants, and that conditioning factors can powerfully influence the expression of that sensitization (e.g., [9–11]). Likewise, it has been shown that acute or repeated stress can both augment drug-induced mesocorticolimbic dopamine transmission and the locomotor activating effects of psychostimulants (e.g., [12,13]). However, the effects of prior cocaine exposure on expression of sensitization by a conditioned stressor are not known.

Thus, the objective of the present study was to examine the effect of a conditioned stressor, a mint odor cue paired with repeated FS stress, on the expression of cocaine-induced sensitization in rats. Wistar rats were acquired from Charles River Canada (St.-Constant, QC) and pair-housed in a humidity-controlled vivarium on a 12 h light-dark cycle. Standard rat chow and water were freely available. All rats were allowed at least 1 week of acclimatization to the vivarium before the start of experimental procedures. All procedures were in accordance with the guidelines of the Canadian Council on Animal Care and were approved by the University of Toronto Animal Care Committee.

A flowchart of the experimental phases is provided in Fig. 1. A total of 6 pre-expsoure (PE) sessions, with 48–72 h between sessions, were given over the next 14 days (Fig. 1a; PE1–PE6). In each of these sessions, rats were injected with either cocaine (30 mg/kg, i.p.) or saline (1 ml/kg, i.p.) prior to placement in an activity chamber (26 cm × 48 cm × 21 cm), where distance travelled was monitored for 30 min (Ethovision, Noldus Information Technology, Inc., Leesburg, VA).

Starting 3 days later, stress conditioning occurred via pairings of intermittent FS with exposure to a peppermint extract odor cue. A total of 3 stress conditioning sessions were administered over 6 days, with 48 h between sessions (Fig. 1b; FS1–FS3). An equal number of rats from each PE condition were assigned to each of 4 FS groups (n = 16/group): (1) FS plus odor, (2) FS plus no odor, (3) no FS plus odor, and (4) no FS plus no odor. This procedure was carried out in standard Plexiglas chambers (30.5 cm × 24.1 cm × 21.0 cm) that had steel rod floors equipped to deliver intermittent FS stress (Med. Associates, Inc., St Albans City, VT). Each chamber was enclosed in a sound-attenuating cubicle. For rats exposed to the odor cue, a cotton ball containing five drops of peppermint extract was placed inside the enclosed cubicle immediately before the start of the session. Administration of FS occurred over a 10 min period; each FS (0.9 mA) was 0.5 s in duration and delivered once every 10–70 s, on a random variable schedule.

Three days later, all rats were given a test for conditioned locomotion (Fig. 1b; T1). For this test, rats were placed back in the activity chambers (in which PE sessions had been carried out), and activity was recorded for 30 min; no injections were given in this test. Forty-eight hours later, a test for cross-sensitization to the FS-conditioned odor cue was given (Fig. 1b; T2). For this test, the upper walls of the activity chambers were swabbed with the mint extract prior to placement of rats in the chambers for 30 min. All rats were exposed to the mint odor but, again, no injections were given. In the next test, given 2 days later, a subset of rats from each PE/FS condition (n = 6 per each of 8 conditions) was given a test for sensitization to a cocaine challenge. (Fig. 1b: T3). Here, all rats, irrespective of condition, were injected with 10 mg/kg, i.p. cocaine and placed in the activity chambers for 30 min. No mint odor was introduced in this test. Finally, in a last test (given on the same day as, but after, T3), a second subset of rats from each PE/FS condition (n = 10 per each of 8 conditions) was exposed simultaneously to both the odor cue and a cocaine challenge (Fig. 1b: T4). For this test, the upper walls of all chambers were swabbed with the mint extract; subsequently all rats were injected with cocaine (as in T3) and placed in the activity chambers for 30 min. Thus, all rats were exposed to both cocaine and mint odor.

Fig. 2 shows the mean (±SEM) distance traveled (cm) on Days 1 though 6 of the PE phase. Cocaine relative to saline rats were more active on each day, corresponding to a significant main effect of PE [$F(1, 117) = 376.339$, $p < .001$].

Fig. 3a shows the mean (±SEM) distance traveled (cm) by the rats during T1, the test for conditioned locomotion. As expected, cocaine relative to saline pre-exposed rats exhibited significantly higher levels of activity upon re-exposure to the locomotor chamber [Main Effect PE: $F(1, 119) = 20.841$, $p < .0001$]. There were no overall effects of FS or odor, or interactions between any factors. Thus, cocaine pre-exposed rats exhibited strong locomotor conditioning, irrespective of their history of FS.

The test (T2) for cross-sensitization to the FS-conditioned odor cue (see Fig. 3b) revealed a significant main effect of PE [$F(1, 118) = 25.49$, $p < .0001$], but no significant main effects of FS or odor,

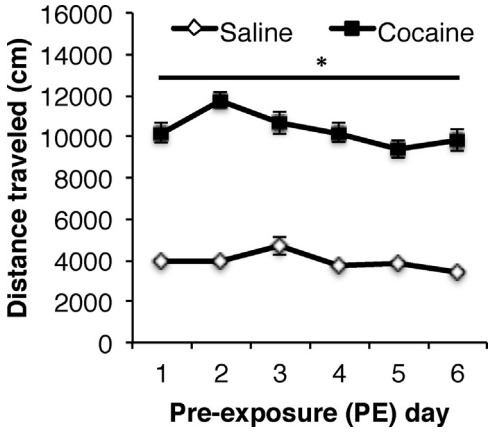

Fig. 2. Mean total distance travelled (cm) ± SEM by cocaine (n = 64) and saline (n = 64) pre-exposed rats, during 30 min sessions on Days 1–6 of drug pre-exposure (PE). Cocaine different than Saline, $p < .001$.