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Short communication

Corticotropin-releasing factor receptor type 1 mediates stress-induced relapse to cocaine-conditioned place preference in rats

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Abstract

Corticotropin-releasing factor (CRF) has been suggested to play an important role in the development of drug dependence and withdrawal. Based on the recent finding that CRF receptor antagonists inhibit the stress-induced relapse to opiate dependence and attenuate anxiety-like responses related to cocaine withdrawal, the present experiment was performed to examine the possible effect of different CRF receptor antagonists on reactivation of cocaine-conditioned place preference induced by cocaine and stress in rats. The results show that a single injection of cocaine (10 mg/kg, i.p.) could reactivate cocaine-conditioned place preference following a 28-day extinction, and pretreatment with i.c.v. 10 μg α-helical CRF, a nonspecific CRF receptor antagonist, significantly attenuated this reactivation of conditioned place preference. However, pretreatment with i.p. 1 or 10 mg/kg CP-154,526 (butyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]-ethylamine), a specific CRF receptor subtype 1 antagonist, and i.c.v. 1 or 10 μg AS-30 ([D-Phe^{11},His^{12}]Svg-(11-40)), a specific CRF receptor subtype 2 antagonist, failed to show the same effects. In addition, a single footshock stress also elicited the reactivation of cocaine-conditioned place preference following a 28-day extinction and pretreatment with α-helical CRF (10 μg, i.c.v.) and CP-154,526 (1 or 10 mg/kg, i.p.) significantly blocked this effect. In contrast, pretreatment with AS-30 at a dose of 1 or 10 μg (i.c.v.) did not affect the stress-induced reactivation of cocaine-conditioned place preference. The present study demonstrated that CRF receptor type 1, but not CRF receptor type 2, mediates the stress-induced reactivation of cocaine-conditioned place preference. These findings suggest that CRF receptor subtype 1 antagonists might be of some value in the treatment and prevention of stress-induced relapse to drug dependence long after detoxification. © 2001 Published by Elsevier Science B.V.

Keywords: CRF (corticotropin-releasing factor); CRF receptor, antagonist; Stress; Cocaine; Conditioned place preference; Relapse

1. Introduction

In individuals with a history of drug abuse, relapse to drug taking, even after prolonged periods of abstinence, is highly probable and remains the most difficult challenge for treatment. In both humans and nonhumans, acute re-exposure to the drug is a potent event for provoking relapse to drug-seeking behavior (Piazza and Le Moal, 1997). In addiction, exposure to stress, an event long thought to be important for relapse in humans, can induce relapse to opiate- and psychostimulant-seeking behavior in rats (Erb et al., 1998; Stewart, 2000).

The mechanisms involved in the effect of stress on reinstatement of drug seeking are not understood, but corticotropin-releasing factor (CRF) plays a critical role in the neurobiological changes of stress that may leave individuals vulnerable to relapse (Sarnyai et al., 1995; Koob and Heinrichs, 1999). CRF is a 41-amino acid peptide initially identified as a hypothalamic factor responsible for stimulating corticotropin (ACTH) secretion from the anterior pituitary (Vale et al., 1981; Cummings et al., 1983). There is evidence that CRF is widely distributed throughout the central nervous system (CNS), where it induces various behavioral changes related to adaptation to stress. These include suppression of food intake, increase in locomotor activity and grooming in familiar environments, induction of aggression, and enhancement of arousal. α-Helical CRF, a nonspecific CRF receptor antagonist, may attenuate these behavioral effects (Koob et al., 1994; DeVries et al., 1998; Basso et al., 1999). Recently, two CRF

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receptor subtypes, CRF receptor subtype 1 and CRF receptor subtype 2, were cloned and characterized in rats (Perrin et al., 1993; Lovenberg et al., 1995). Subsequently, the pharmacological specificity and regional localization of these CRF receptor subtypes have been determined. CRF_1 receptor shows a high affinity for CRF, while CRF_2 receptor shows a lower affinity (Grigoriadis et al., 1996; Radulovic et al., 1999). Both CRF_1 and CRF_2 receptors are widely and heterogeneously distributed in the central nervous system, suggesting distinctive functional roles for each receptor in the CRF-related system (Lovenberg et al., 1995; Jasnow et al., 1999).

There is considerable evidence that CRF is involved in the anxiogenic and aversive effects of withdrawal from abused drugs, such as cocaine (Basso et al., 1999). Evidence also exists that administration of a CRF_1 receptor antagonist attenuates stress-induced reinstatement of drug seeking (Shaham et al., 1998; Lu et al., 2000a). However, the role of CRF_1 and CRF_2 receptors in stress-induced relapse to cocaine dependence remains unclear. In this study, we investigated the possible effects of CP-154, 526 (butyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]-ethylamine), a specific CRF_1 receptor antagonist, and AS-30 ([D-Phe^{11},His^{12}]Svg-(11-40)), a specific CRF_2 receptor antagonist, and their differences in the induction of relapse to cocaine dependence induced by footshock stress.

2. Materials and methods

2.1. Animal and drugs

Male Sprague–Dawley rats (body weight 250–280 g) were housed in the experimental animal center and maintained on a 12-light/dark cycle with access to food and water ad libitum. All animal treatments were strictly in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. The drugs used were α-helical CRF (Sigma, USA), CP-154,526 (Pfizer, USA), AS-30 (Huasheng, China) and cocaine (Qinghai Pharmaceutical, China).

2.2. Intracerebroventricular cannulae

The cannula was implanted 5 days before the experiment under sodium pentobarbital anesthesia (65 mg/kg, i.p.) and affixed to the skull by dental cement. The cannulae (plastic one) consisted of double-guided cannulae, dummy, and cap. The cannulae were placed in the left lateral brain ventricles as follows: −1.0 mm from bregma, +1.4 mm lateral from the midline, and −3.7 mm from dura measured from the tip of the injector (Paxinos and Watson, 1997). The stock solutions were prepared in 10 mM acetic acid. Final dilutions in twofold-concentrated artificial cerebrospinal fluid (CSF) containing NaCl (125.0 mM), KCl (2.5 mM), $MgCl_2$ (0.9 mM), $CaCl_2$ (1.2 mM) and NaH_2PO_4 (1.2 mM), were prepared immediately before the experiments (Murphy and Maidment, 1999). The final pH of the drug solutions was 7.4. Vehicle solutions were prepared by diluting 10 mM acetic acid in artificial CSF in an identical manner. Cannula placement was verified by giving each rat an intracerebroventricular infusion of angiotensin at 25 ng/ml and by observing subsequent drinking behavior. Placements were considered to be accurate if a rat drank within 1 min of the infusion and sustained drinking over 2–3 min (Sakai et al., 1995).

2.3. Procedure

2.3.1. Induction of cocaine-conditioned place preference

Place conditioning was conducted in an apparatus constructed of plexiglas in a two-compartment design (Maldonado et al., 1997). A removable guillotine door separated the compartments. Both compartments were black. One compartment had white stripes on the wall and a textured floor whereas the other had walls with white dots and a smooth floor. Testing and conditioning were performed between 4 and 8 h in the light phase in the presence of white noise. In order to determine base-line preferences (day 0), animals were 'pretested' by randomly placing them in one of the compartments with the door removed for a period of 15 min. Rats that spent more than 500 s in one compartment were excluded. Conditioning was performed using an unbiased, balanced protocol consisting of six alternating days of drug and saline treatment with the guillotine door in place. The chamber in which cocaine was administered was assigned randomly. Thus, each rat was treated for six consecutive days with alternate injection of cocaine–HCl (10 mg/kg i.p., days 1, 3 and 5) and saline (days 2, 4 and 6). After each injection, the animals were immediately confined to the conditioning compartment for 50 min before they were returned to the home cage. On day 7, the door was removed and the rats were placed on the floor of the apparatus and allowed to move freely for 15 min and the time spent in each compartment during the 15-min session was recorded. The place preference to the drug-paired compartment was determined as the time spent by each animal in the drug-paired side in the session.

2.3.2. Reactivation of cocaine-conditioned place preference

After rats had been injected alternately with cocaine and saline for six consecutive days (from days 1 to 6) to induce cocaine-conditioned place preference, they were not given any treatment from days 8 to 35 (a 28-day drug-free period) and were tested for cocaine-conditioned place preference on day 36 (pre-reactivation). On day 37, the animals were given a single injection of cocaine (10 mg/kg, i.p.) or saline and then immediately confined to the previous drug-paired compartment for 50 min (Lu et al., 2000a). Alternatively, some rats received a single intermittent footshock (15 min, 0.5 mA, 0.5 s on with a mean off period of

40 s) or sham stress (control group) outside the box instead of cocaine injection. All animals were tested for cocaine-conditioned place preference on day 38 (post-reactivation), and the reactivation of place preference for the drug-paired compartment was determined as the time spent by the animals in the drug-paired side (Lu et al., 2000b). Our previous study showed that a single injection of the previous drug or this regimen of intermittent footshock could reactivate the conditioned place preference on day 38 again (Lu et al., 2000a). To investigate the effect of stress- and cocaine-induced reactivation of cocaine-conditioned place preference by different CRF receptor antagonists, α-helical CRF (1 and 10 μg, i.c.v.), CP-154,526 (1 and 10 mg/kg, i.p.), AS-30 (1 and 10 μg, i.c.v.), and vehicle were administered 30 min prior to the single injection of cocaine or footshock.

2.4. Data analysis

The time spent in the drug-paired side in the test of conditioned place preference is expressed as mean ± S.E.M. and was analyzed using GB-STAT statistical package. Repeated-measures two-way analysis of variance (ANOVA) with (treatment × test-session) Newman–Keuls post-hoc tests were performed to determine a difference in the time in the drug-paired side between day 0 and the other days. A statistical difference at $P < 0.05$ was considered significant.

3. Results

In our pilot study, we designed a control group of animals that received injection of saline instead of cocaine (days 1, 3 and 5) and saline (days 2, 4 and 6) for six consecutive days. The results showed that these animals did not show place preference for any compartment on day 7 and also did not acquire place preference induced by a single injection of 10 mg/kg cocaine on day 38 (data not shown). However, alternate injection of cocaine (10 mg/kg) and saline for 6 days significantly increased the time spent in the cocaine-paired compartment (cocaine-conditioned place preference) on day 7, which is in agreement with that described previously (Martin-Iverson et al., 1997; Sora et al.,1998). As shown in Fig. 1, this cocaine place preference disappeared on day 36, when the rats spent less than 500 s in the drug-paired side after they were not given any treatment from days 8 to 35 (a 28-day

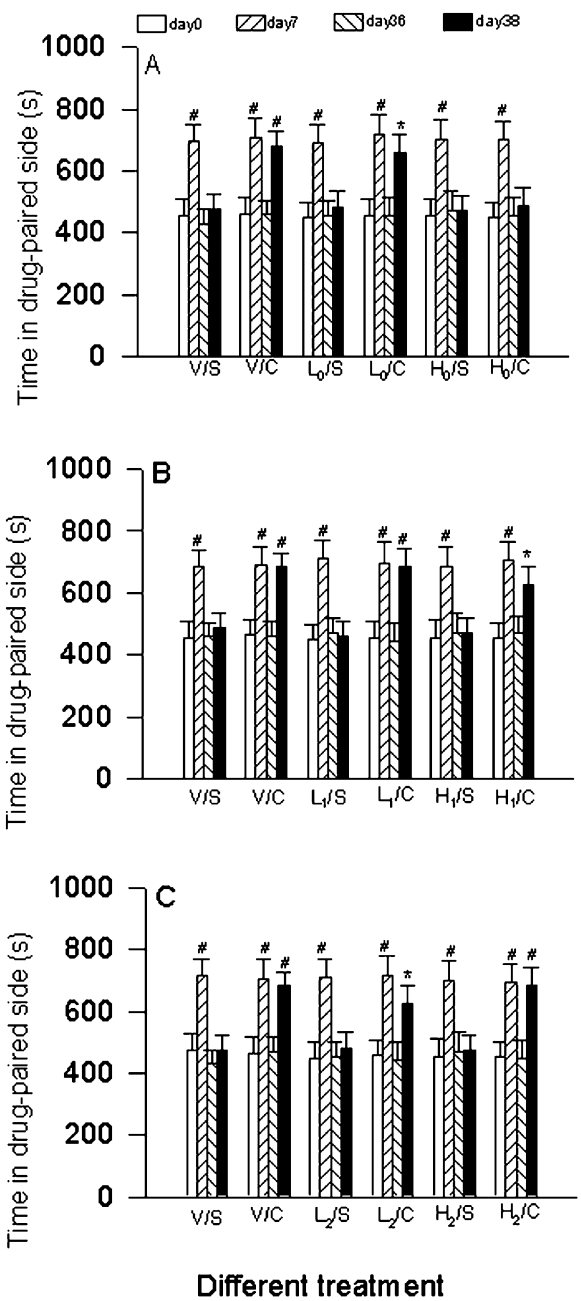

Fig. 1. Effect of pretreatment with the different CRF receptor antagonists on the cocaine-induced reactivation of conditioned place preference. The top panel shows the effect of pretreatment with i.c.v. injection of vehicle (V) and 1 μg (L_0) or 10 μg (H_0) α-helical CRF on cocaine (C)- or saline (S)-induced reactivation of conditioned place preference. The middle panel demonstrates the effect of pretreatment with i.p. injection of vehicle (V) and 1 mg/kg (L_1) or 10 mg/kg (H_1) CP-154,526 on cocaine (C)- or saline (S)-induced reactivation of conditioned place preference. The bottom panel shows the effect of pretreatment with i.c.v injection of vehicle (V) and 1 μg (L_2) or 10 μg (H_2) AS-30 on cocaine (C)- or saline (S)-induced reactivation of conditioned place preference. The animals were treated alternately with cocaine and saline for 6 days (from days 1 to 6) to induce cocaine-conditioned place preference, and then not given any treatment from days 8 to 35 (a 28-day drug-free period). On day 37, these animals received a single injection of cocaine (10 mg/kg) or saline (control group) in order to reactivate the conditioned place preference. The different CRF receptor antagonists or vehicle was administered 30 min prior to the single injection of cocaine or saline. The time spent in the cocaine-paired side by each rat was measured for 15 min on days 0, 7, 36 and 38, respectively. Each column represents the mean with S.E.M. for 10–11 animals. $^{*}P < 0.05$ and $^{\#}P < 0.01$ vs. time spent in drug-paired side on day 0.

drug-free period), and no significant difference in the time spent in the drug-paired side was observed between days 0 and 36. A single injection of 10 mg/kg cocaine reactivated cocaine place preference on day 38 with a significant increase in the time spent in the cocaine-paired side in comparison with that on day 0. However, pretreatment with 10 μg α-helical CRF (Fig. 1A) significantly attenuated the cocaine-induced reactivation of place preference, whereas pretreatment with 1 μg α-helical CRF, 1 or 10 mg CP-154,526 (Fig. 1B) and 1 or 10 μg AS-30 (Fig. 1C) had no significant effect. As shown in Fig. 2, a single footshock stress could also reactivate the cocaine-conditioned place preference following a 28-day drug-free period. Interestingly, pretreatment with 10 μg α-helical CRF (Fig. 2A) and 1 or 10 mg/kg CP-154,526 (Fig. 2B) significantly blocked the footshock-induced reactivation of conditioned place preference, because the rats spent the same time in the cocaine-paired compartment on days 38 and 0 (489.0 ± 58.6 vs. 452.1 ± 48.2, $P > 0.05$; 488.4 ± 65.9 vs. 456.3 ± 49.8, $P > 0.05$; and 465.5 ± 62.8 vs. 452.1 ± 48.2 $P > 0.05$, respectively), whereas pre-administration of 1 μg α-helical CRF did not show the same effect. In addition, pretreatment with 1 and 10 μg AS-30 did not affect the re-acquisition of cocaine-conditioned place preference induced by a single footshock stress (Fig. 2C).

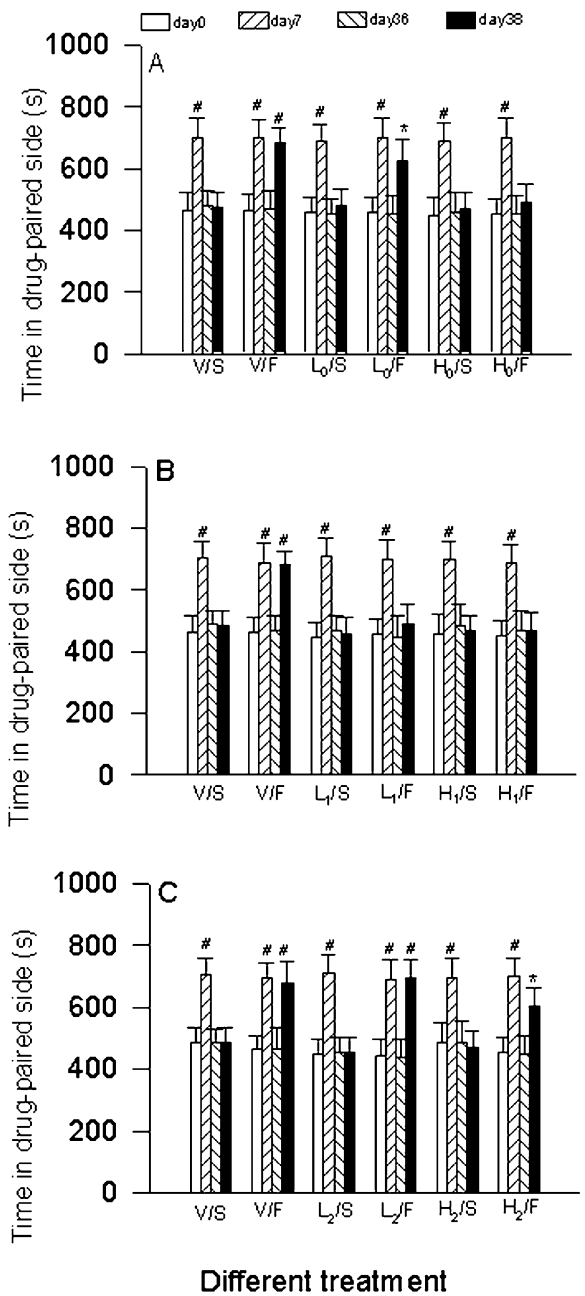

Fig. 2. Effect of pretreatment with the different CRF receptor antagonists on the footshock-induced reactivation of cocaine-conditioned place preference. The top panel shows the effect of pretreatment with i.c.v. injection of vehicle (V) and 1 μg (L_0) or 10 μg (H_0) α-helical CRF on footshock (F)- or sham stress (S)-induced reactivation of cocaine-conditioned place preference. The middle panel demonstrates the effect of pretreatment with i.p. injection of vehicle (V) and 1 mg/kg (L_1) or 10 mg/kg (H_1) CP-154,526 on footshock (F)- or sham stress (S)-induced reactivation of cocaine-conditioned place preference. The bottom panel shows the effect of pretreatment with i.c.v injection of vehicle (V) and 1 μg (L_2) or 10 μg (H_2) AS-30 on footshock (F)- or sham stress (S)-induced reactivation of cocaine-conditioned place preference. The animals were treated alternately with cocaine and saline for 6 days (from days 1 to 6) to induce cocaine-conditioned place preference, and then not given any treatment from days 8 to 35 (a 28-day extinction). On day 37, these animals received a single footshock or sham footshock (control group) to reactivate the cocaine-conditioned place preference. The different CRF receptor antagonists or vehicle was administered 30 min prior to the footshock or sham footshock. The time spent in the cocaine-paired side by each rat was measured for 15 min on days 0, 7, 36 and 38, respectively. Each column represents the mean with S.E.M. for 10–12 animals. $^{*}P < 0.05$ and $^{\#}P < 0.01$ vs. time spent in drug-paired side on day 0.

4. Discussion

Environmental stress has an important effect on the sensitivity of an individual to abused drugs. Studies of drug self-administration in laboratory animals have shown that both physical and psychological stressors facilitate the acquisition of drug self-administration, probably by increasing the reinforcing efficacy of abused drugs. Stressors also facilitate the reinstatement of drug taking even after prolonged periods of withdrawal (Stewart et al., 1984; Piazza and Le Moal, 1997). For example, social isolation, competition in the colony, immobilization, forced swimming and footshock stress increase the propensity to take psychostimulants or opiates (Shibasaki et al., 1991; Erb et al., 1998). In the present study, a single footshock could elicit the reactivation of cocaine-conditioned place preference following a 28-day drug-free period. The results are in agreement with those described previously (Erb et al., 1998), suggesting that stress may interact with drug dependence. It has been shown that cross-sensitization may

develop between stress and chronic drug taking (Deroche et al., 1992), since stress activates the hypothalamic–pituitary–adrenal axis and induces the secretion of corticosterone, which may induce behavioral sensitization by an action on dopaminergic neurons (Deroche et al., 1993). Many stress studies have also shown that the biological status of an individual plays a critical role in determining the propensity for developing drug self-administration and have highlighted the importance of environmental experiences in inducing a drug-prone phenotype (Piazza and Le Moal, 1998). The fact that footshock stress reinstated drug craving in animals following a long-term extinction of drug dependence confirms clinical impressions that stressors can provoke relapse in individuals after long periods of drug abstinence.

After pretreatment with α-helical CRF or CP-154,526, stress-induced reactivation of cocaine-conditioned place preference was significantly attenuated. However, pretreatment with AS-30 had no significant effect. These results extend previous reports on the role of CRF in reinstatement of drug seeking induced by stressors (Shaham et al., 1998), and further clearly demonstrate that only CRF_1 receptor and not CRF_2 receptor mediated this effect. Indeed, the two CRF receptor subtypes have been found to have many differences in their mediation of behavioral and physiological functions (Stecklei and Holsboer, 1999). Mouse mutants in which CRF_1 receptor has been deleted show an impaired emotional response, reduced anxiety-related behavior, and cognitive deficits (Smith et al., 1998; Contarino et al., 1999), whereas the CRF_2 receptor is involved in the effect of CRF on food intake, reproduction, and sexual female behavior (Stecklei and Holsboer, 1999). On the basis of the wide distribution and very different patterns of expression in the CNS of the CRF_1 and CRF_2 receptors, it has been suggested that activation of these two receptors subtype serves different functions in the behavioral effects of CRF and related ligands. The present study provides further evidence that the two CRF receptor subtypes differ in their pharmacology in the brain.

Since CRF is suggested to play a critical role in the development of stress and depression, and because anxiety is recognized as an important result of cessation of chronic drug administration, it is possible to postulate that brain CRF modulates the neurobiological mechanisms that underlie the anxiety and stress associated with drug withdrawal. In fact, some recent evidence demonstrates that CRF receptor antagonists may attenuate the anxiety-like behavior that occurs following cessation of chronic administration of cocaine or opiate (Basso et al., 1999; Iredale et al., 2000). The signs of protracted abstinence such as chronic anxiety and depression, which is one of the main factors contributing to relapse, are an important clinical problem in the treatment of drug dependence (Rasmussen et al., 1996). Thus, inhibition of the protracted abstinence syndrome by CRF antagonist should minimize the possibility of relapse. In our study, the reactivation of conditioned place preference induced by a single injection of cocaine was attenuated by pretreatment with α-helical CRF. However, pretreatment with CP-154,526 or AS-30 did not show the same effect. This suggests that CRF_1 and CRF_2 receptors are not the only receptors involved in the relapse to cocaine dependence, and that the role of the CRF system in stress- and cocaine-induced relapse to drug dependence is not identical. Comprehension of the different neurochemincal events underlying the stress- and drug-induced relapse to drug dependence may therefore throw more light on the biological basis of addiction.

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