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Antagonism of corticotropin-releasing factor CRF_1 receptors blocks the enhanced response to cocaine after social stress

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ABSTRACT

Numerous studies have shown that social defeat stress induces an increase in the rewarding effects of cocaine. In this study we have investigated the role played by the main hypothalamic stress hormone, corticotropin-releasing factor (CRF), in the effects that repeated social defeat (RSD) induces in the conditioned rewarding effects and locomotor sensitization induced by cocaine. A total of 220 OF1 mice were divided into experimental groups according to the treatment received before each social defeat: saline, 5 or 10 mg/kg of the nonpeptidic corticotropin-releasing factor CRF_1 receptor antagonist CP-154,526, or 15 or 30 μg/kg of the peptidic corticotropin-releasing factor CRF_2 receptor antagonist Astressin$_2$-B. Three weeks after the last defeat, conditioned place preference (CPP) induced by 1 mg/kg of cocaine was evaluated. Motor response to 10 mg/kg of cocaine was also studied after a sensitization induction. Blockade of corticotropin-releasing factor CRF_1 receptor reversed the increase in cocaine CPP induced by social defeat. Conversely, peripheral corticotropin-releasing factor CRF_2 receptor blockade produced similar effects to those observed in socially stressed animals. The effect of RSD on cocaine sensitization was again blocked by the corticotropin-releasing factor CRF_1 receptor antagonist, while peripheral CRF_2 receptor antagonist did not show effect. Acute administration of Astressin$_2$-B induced an anxiogenic response. Our results confirm that CRF modulates the effects of social stress on reinforcement and sensitization induced by cocaine in contrasting ways. These findings highlight CRF receptors as potential therapeutic targets to be explored by research about stress-related addiction problems.

1. Introduction

Drug addiction can be considered a multifactorial disorder of chronic relapse as a result of the interaction of biological and environmental factors, characterized by a loss of control over use of the drug (Kalivas and Volkow, 2005; Koob, 2010; Koob and Volkow, 2009; Volkow et al., 2015). It has been repeatedly demonstrated that adverse life experiences can render individuals more prone to addictive substances of abuse and make them more vulnerable to relapse after periods of detoxification (Le Moal, 2009; Miczek et al., 2008; Sinha et al., 2011). Thus, stress is considered a risk factor that can influence all stages of drug addiction, as it plays a role in initiation, maintenance, escalation of intake and relapse (Burke and Miczek, 2015; Kalivas and Volkow, 2005; Koob, 2010; Sinha et al., 2011; Logrip et al., 2011, 2012).

Social interaction is known to be the main source of stress in human beings (Dickerson and Kemeny, 2004; Tamashiro et al., 2005). An animal model of social stress should closely mimic real-life situations in human life (Neisewander et al., 2012); in this context, social defeat in an agonistic encounter between rodents is a model of ecological validity for recreating experiences such as bullying, physical abuse or subordination stress (Björkqvist, 2001; Lu et al., 2003; Miczek et al., 2008; Tornatzky and Miczek, 1993). After being exposed to repeated social defeat, rodents show a range of depression-like symptoms such as anhedonia, social withdrawal and metabolic syndrome (weight gain and insulin and leptin resistance) (Meerlo et al., 1996; Von Frijtag et al., 2000). It has repeatedly been shown that exposure to different procedures of social defeat increases the rewarding and reinstating effects of psychostimulant drugs, such as cocaine, in the self-administration (SA) and conditioned place preference (CPP) paradigms (Aguilar et al., 2013; Miczek et al., 2008; Neisewander et al., 2012). Defeated animals also show an enhanced sensitivity to cocaine-induced hyperactivity (Nikulina et al., 1998; Nikulina et al., 2004) and dopaminergic cross-sensitization, with an augmented behavioral response to subsequent doses of cocaine after repeated drug exposure (Kalivas et al., 1998; Piazza and Le Moal, 1998; Steketee and Kalivas, 2011). These effects

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are associated with increased dopamine transmission in the corticolimbic system (Steketee and Kalivas, 2011), including projections from the ventral tegmental area to the medial prefrontal cortex and the nucleus accumbens (Pierce and Kalivas, 1997; Steketee and Kalivas, 2011), which are the main structures implicated in the rewarding and motor effects of psychostimulants (Koob, 2009; Sinha, 2008).

These changes in the corticolimbic system may be mediated by the action of neuropeptide corticotropin-releasing factor (CRF), which interacts with two G-protein-coupled corticotropin-releasing factor CRF receptors, type 1 (corticotropin-releasing factor CRF_1 receptor) and type 2 (corticotropin-releasing factor CRF_2 receptor), both positively coupled to adenylate cyclase through stimulatory G-proteins (Binder and Nemeroff, 2010; Hauger et al., 2009; Zorrilla and Koob, 2004, 2010) with actions at central and peripheral levels (Hauger et al., 2006; Heinrichs and Koob, 2004). This factor is known as the principal mediator of a wide range of both acute and chronic neuroendocrine and behavioral responses to stress (Logrip et al., 2011). Corticotropin-releasing factor activates the hypothalamic-pituitary-adrenal axis and stimulates the release of glucocorticoids (Bale and Vale, 2004). In addition, corticotropin-releasing factor axons project to extrahypothalamic areas such as the extended amygdala and ventral tegmental area, thereby modulating dopamine function and causing neuroadaptations in dopamine neurons in the corticolimbic pathway (Haass-Koffler and Bartlett, 2012; Saal et al., 2003; Wanat et al., 2008). This especially relevant during withdrawal (Zorrilla et al., 2014), when corticotropin-releasing factor plays a key role in anxiety-like effects and helps to explain the negative reinforcement processes that drive the compulsivity of addiction (Koob, 2008).

The aim of this investigation was to study the role of both corticotropin-releasing factor receptors in the effects of social stress on the conditioned rewarding effects and locomotor sensitization induced by cocaine. To achieve our objective, we administrated a pretreatment of a peripheral injection of the nonpeptidic corticotropin-releasing factor CRF_1 receptor antagonist CP-154,526 or the peptidic corticotropin-releasing factor CRF_2 receptor antagonist $Astressin_2$-B before each social defeat. It should be noticed that corticotropin-releasing factor CRF_1 and 2 antagonists were injected peripherally. As CP-154,526 crosses the blood brain barrier we expected it to block central and peripheral corticotropin-releasing factor CRF_1 receptors. On the other hand, $Astressin_2$-B acts only on peripheral corticotropin-releasing factor CRF_2 receptors such as those located on the pituitary and other peripheral locations.

2. Material and methods

2.1. Animals

A total number of 220 male OF1 mice (Charles River, France) were delivered to our laboratory at 42 days of age. Experimental mice were housed in groups of four in plastic cages (27 × 27 × 14 cm) during the entire experimental procedure. To reduce their stress levels in response to experimental manipulations, mice were handled for 5 min per day on each of the 3 days prior to initiation of social defeat experiences. Aggressive opponents were individually housed in plastic cages (21 × 32 × 20 cm) for a month prior to initiation of the experiments in order to heighten aggression (Rodrıguez-Arias et al., 1998). All mice were housed under the following conditions: constant temperature; a reversed light schedule (white light on 8:00–20:00 h); and food and water available ad libitum, except during behavioral tests. All procedures were conducted in compliance with the guidelines of the European Council Directive 2010/63/UE regulating animal research and were approved by the local Ethics Committee for Experimentation and Animal Welfare of the University of Valencia in January 2012 (approval ID A1302084466177).

2.2. Drugs

The corticotropin-releasing factor CRF_1 receptor antagonist CP-154,526 (Bio-Gen, Madrid, Spain) was injected intraperitoneally at a dose of 5 or 10 mg/kg 30 min before each social defeat. These doses have previously been shown by other researches to not affect locomotor activity (Przegaliński et al., 2005). A dose of 30 or 15 μg/kg of the corticotropin-releasing factor CRF_2 receptor antagonist $Astressin_2$-B (Bio-Gen, Madrid, Spain) was also injected intraperitoneally 30 min before each social defeat following the procedure developed by Rivier and co-workers (Rivier et al., 2003). For CPP and sensitization studies doses of 1, 10 or 25 mg/kg of cocaine hydrochloride (Alcaliber laboratory, Madrid, Spain) were used. The lowest dose of cocaine was selected on the basis of previous CPP studies showing 1 mg/kg to be a threshold dose (Arenas et al., 2014; Montagud-Romero et al., 2014; Vidal-Infer et al., 2012). All the treatments were adjusted in a volume of 0.01 ml/g of weight. Control groups were injected with physiological saline (NaCl 0.9%), which was also used to dissolve the drugs. In the case of CP-154,526, in order to achieve a complete suspension of the product, the solvent Tween-80 was added with a maximum concentration of 10%. We have previously tested the effect of Tween-80 in a control group and did not observe any effect on the development of CPP (Manzanedo et al., 2004).

2.3. Experimental design

The experimental design is depicted in Table 1. In the first study the role of corticotropin-releasing factor CRF_1 and corticotropin-releasing factor CRF_2 receptors in the effects that social defeat induce on the conditioned rewarding effects of cocaine (1 mg/kg) was evaluated. Mice were divided into ten experimental groups according to the treatment received before each social defeat (RSD) or exploration (EXP): physiological saline, the corticotropin-releasing factor CRF_1 receptor antagonist CP- 154,526 (5 or 10 mg/kg) or the corticotropin-releasing factor CRF_2 receptor antagonist $Astressin_2$-B (15 or 30 μg/kg). The CPP procedure was initiated three weeks after the last social defeat. Ten days after extinction of the CPP, the mice in each group were assigned to a cocaine (25 mg/kg) or saline condition and were injected for three consecutive days with a daily dose of the corresponding treatment. The sensitization study was performed in an additional set of mice 3 weeks after the exploration or RSD experiences. A sample of 68 mice was divided into four experimental groups according to the treatment received before each social defeat (RSD) or exploration (EXP): physiological saline, the corticotropin-releasing factor CRF_1 receptor antagonist CP- 154,526 (10 mg/kg) or the corticotropin-releasing factor CRF_2 receptor antagonist $Astressin_2$-B (30 μg/kg).

The last study was designed to evaluate the behavioral effect of an acute dose of 30 μg/kg $Astressin_2$-B on the open field and the elevated plus maze (EPM). The mice previously treated with the corticotropin-releasing factor CRF_2 receptor antagonist in the CPP experiment were used in this procedure, which took place after the end of the CPP test.

2.4. Apparatus and procedures

2.4.1. Procedure of social defeat- RSD

Repeated Social Defeat (RSD) procedure consisted of four episodes of social defeat, on post-natal days 47, 50, 53 and 56. Each episode consisted of three phases, which began by introducing the “intruder” (the experimental animal) into the home cage of the “resident” (the aggressive opponent) for 10 min (Tornatzky and Miczek, 1993). During this initial phase, the intruder was protected from attack, but the wire mesh walls of the cage allowed for social interactions and species-typical threats from the male aggressive resident, thus allowing instigation and provocation (Covington and Miczek, 2001). The wire mesh was then removed from the cage to allow confrontation between the two animals for a 5-min period. In the third phase, the wire mesh was