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Role of dopamine neurotransmission in the long-term effects of repeated social defeat on the conditioned rewarding effects of cocaine

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ABSTRACT

Numerous studies report that social defeat stress alters dopamine (DA) neurotransmission in several areas of the brain. Alterations of the mesolimbic dopaminergic pathway are believed to be responsible for the increased vulnerability to drug use observed as a result of social stress. In the present study, we evaluated the influence of DA receptors on the long-term effect of repeated social defeat (RSD) on the conditioned rewarding and reinstating effects of cocaine. For this purpose, the D1R antagonist SCH 23390 and the D1R antagonist raclopride were administered 30 min before each social defeat and a cocaine-induced CPP procedure was initiated three weeks later. The expression of the D1R and D2R was also measured in the cortex and hippocampus throughout the entire procedure. Mice exposed to RSD showed an increase in the conditioned rewarding effects of cocaine that was blocked by both DA receptors antagonists when a subthreshold dose of cocaine was employed. However, while the vulnerability to reinstatement of the preference induced by 25 mg/kg cocaine-induced CPP was abolished by the D1R antagonist, it was practically unaffected by raclopride. Increases in D2R receptor levels were observed in the cortex of defeated animals after the first and fourth social defeats and in the hippocampus 3 weeks later. Nevertheless, D1R receptor levels in the hippocampus decreased only after the last social defeat. Our results confirm that RSD enhances the conditioned rewarding effects of cocaine and that both DA receptors are involved in this enduring effect of social stress.

1. Introduction

Stressful experiences modify the activity of brain areas involved in the rewarding effects of psychostimulants (Belujon and Grace, 2011; Koob, 2008; Sinha, 2008). A positive association between stress and increased drug intake and relapse to drug use has been described (Sinha et al., 2011). Preclinical studies report a significant association between acute and chronic stress and an increase in motivation to initiate use and augment the consumption of addictive substances (Sinha, 2001; Sinha et al., 2006; Koob and Kreek, 2007; Miczek et al., 2008). Furthermore, repeated exposure to stressors results in a long-term enhancement of dopamine (DA) release in the mesoaccumbens pathway in response to psychostimulant challenge (Sorg and Kalivas, 1991; Wilcox et al., 1986).

Different studies found that social defeat stress alters DA neurotransmission (Tidey and Miczek, 1996; Cabib et al., 2000; Isovich et al., 2001; Razzoli et al., 2011; Shimamoto et al., 2015). Social stressors have been related with increases in extracellular DA release in the shell of the nucleus accumbens (NAcc) (Holly et al., 2015; Han et al., 2015; Piazza and Le Moal, 1998; Tidey and Miczek, 1997), and also in response to cocaine (Miczek et al., 2011) or D-amphetamine (Han et al., 2015). Few studies have investigated the effects of social defeat stress on DA receptors and those to have done it have obtained discrepant results. Increases, decreases or no changes in the levels of D1R and D2R have been found after being exposed to social defeat (Lucas et al., 2004; Rasheed et al., 2010; Bagalkot et al., 2015; Huang et al., 2016; Jin et al., 2015).

In experimental models, acute exposure to different stressful experiences can promote psychostimulant use and increase the escalation of consumption (Shaham et al., 2000, 2003; Sanchez et al., 2003). Social defeat in an agonistic encounter increases vulnerability to acquiring and maintaining cocaine self-administration (Tidey and Miczek, 1997; Covington et al., 2005; Covington and Miczek, 2005), prompts an escalation of cocaine-seeking behavior (Burke and Miczek, 2015; Boyson et al., 2011; Covington et al., 2005; Miczek et al., 2011), and increases the conditioned rewarding effects of cocaine and MDMA (Rodríguez-Arias et al., 2015; García-Pardo et al., 2015; Montagud-Romero et al., 2015). The conditioned place preference (CPP) paradigm has been widely used to study the conditioned rewarding effects of addictive drugs, since contextual stimuli can acquire secondary appetitive properties (conditioned rewarding effects) when paired with a primary reinforcer, thereby highlighting the liability of

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abuse (Tzschentke, 2007). While D1R antagonists block cocaine-induced CPP (Cervo and Samanin, 1995; Pruitt et al., 1995; Baker et al., 1998; Liao, 2008; Nazarian et al., 2004), there is controversial evidence regarding the blockade of D2R; some studies have reported that D2R antagonists do not affect cocaine-induced CPP (Cervo and Samanin, 1995; Pruitt et al., 1995; Baker et al., 1996; Nazarian et al., 2004), while others have shown that they play a role in the reinstatement of cocaine-induced CPP (Badanich and Kirstein, 2012).

The relationship between stress and DA receptors has been demonstrated repeatedly. Physical acute stress can increase the activity of D2R in the NAcc, and induces CPP that can be blocked by either D1R or D2R antagonists (Shen et al., 2010). Moreover, changes in D1R have been observed following social encounters during adolescence or adulthood (Avgustinovich and Alekseyenko, 2010; Novick et al., 2011). While the experience of acute social defeat increases the conditioned rewarding effects of cocaine immediately after the stress (Montagud-Romero et al., 2015), the administration of a D1R antagonist (raclopride) before the stress experience blocks the increase in the rewarding effects of cocaine induced by social stress without affecting the rewarding properties of cocaine in the CPP (Reguilón et al., under review). Equally, intra-mPFC infusion of a D2R antagonist prior to each defeat episode during adolescence has been shown to prevent defeat-induced reductions in mPFC DA turnover in early adulthood (Watt et al., 2014). On the other hand, pretreatment with SCH23390 (D1R antagonist), but not raclopride (D1R antagonist), blocks CRF-induced reinstatement of cocaine-seeking (Brown et al., 2012). Similar dissociation of the selective effects of D1R and D2R antagonists on the reinstatement of cocaine-seeking by central injections of other stress-related neuropeptides (Lopak and Erb, 2005) or intra-VTA injections of a Substance P analogue (Placenza et al., 2004) has also been reported.

The aim of the present study was to evaluate the influence of DA receptors on the long-term effect of repeated social defeat (RSD) on the conditioned rewarding and reinstating effects of cocaine. For this purpose, the D1R antagonist SCH 23390 and the D2R antagonist raclopride were administered 30 min before each social defeat and three weeks later cocaine-induced CPP procedure was initiated. Expression of the D1R and D2R receptors was also measured in the whole cortex and hippocampus brain structures throughout the entire procedure.

2. Material and methods

This study was designed to evaluate the role of DA receptors in the long lasting effects that social defeat induced in the CPP induced by cocaine. Adult mice were exposed to four social defeats and the rewarding effects of cocaine in the CPP were evaluated three weeks later. In the control groups, the D1R antagonist SCH 23390 or the D2R antagonist raclopride was administered before each social defeat or exploration. Three weeks after the last social defeat, cocaine (1 or 25 mg/kg)-induced CPP was initiated. Another set of mice was employed to obtain brain samples and determine levels of D1and D2R after the first and fourth social defeat, and also three weeks later.

2.1. Animals

A total of 289 male OF1 (Charles River, France) arrived at our laboratory at 42 days of age. All mice (except those used as aggressive opponents n = 30) were housed in groups of four in plastic cages (25 × 25 × 14.5 cm) for 8 days before the experiments began. Aggressive opponents were individually housed in plastic cages (23 × 13.5 × 13 cm) for a month prior to experiments in order to heighten aggression (Rodríguez-Arias et al., 1998). While 211 animals were tested in the CPP experiment, an independent set of 48 mice were used in the Western Blot procedure. Mice were housed in controlled laboratory conditions with the temperature maintained at 21 ± 1 °C and humidity at 55 ± 10%. All tests took place during the first few hours of the dark phase of a reversed light/dark cycle (lights off at 08:00 h and on at 20:00 h). Food and water were available ad libitum to all the mice used in this study. 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 committees (University of Valencia).

2.2. Drugs

Animals were injected i.p. with 1 or 25 mg/kg of cocaine hydrochloride (Laboratorios Alcaliber, Madrid, Spain), 0.125 and 0.250 mg/kg of SCH 23390 (Research Biochemical International, Natick, USA), and 0.3 and 0.6 mg/kg of Raclopride (RACL) (Astra Laboratory, Sodertalje, Sweden) 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. These doses were selected on the basis of previous studies (Manzanedo et al., 2001; Vidal-Infer et al., 2012; Arenas et al., 2014; Montagud-Romero et al., 2014).

2.3. Procedure and apparatus

The experimental design is depicted in Table 1.

2.3.1. Repeated social defeat encounters

Animals in the stress/defeated groups were exposed to 4 episodes of social defeat lasting 25 min each on postnatal days (PND) 47, 50, 53 and 56. Each episode consisted of three phases, which began by placing the experimental animal or intruder in the home cage of the aggressive opponent or resident for 10 min. During this initial phase, the intruder was protected from attack by a wire mesh wall that permitted social interaction and species-typical threats from the aggressive resident (Covington and Miczek, 2001). In the second phase, the wire mesh was removed from the cage and a 5-min period of confrontation began. The second phase of each social defeat protocol was video-recorded and ethologically analyzed. Threat and attack behaviors were scored in resident mice and avoidance/flee and defensive/submissive behaviors were evaluated in intruder mice. In the third phase, the wire mesh was replaced for a further 10 min to allow social threats from the resident. The non-stressed exploration groups underwent the same protocol, but without the presence of a "resident" mouse in the cage. Following this last phase, animals were kept in the vivarium for three weeks, after which the behavioral tests began.

In the corresponding groups, physiological saline, SCH 23390 or Raclopride were administered 30 min before each social encounter. Control groups received saline or the DA antagonist 30 min before exploration.

2.3.2. Conditioned place preference

2.3.2.1. Apparatus. For place conditioning, we employed eight identical Plexiglas boxes with two equally-sized compartments (30.7 cm long × 31.5 cm wide × 34.5 cm high) separated by a gray central area (13.8 cm long × 31.5 cm wide × 34.5 cm high). The compartments had different colored walls (black vs white) and distinct floor textures (fine grid in the black compartment and wide grid in the white one). Four infrared light beams in each compartment of the box and six in the central area allowed the recording of the position of the animals and their crossings from one compartment to the other. The equipment was controlled by three IBM PC computers using MONPRE 2Z software (CIBERTEC, SA, Spain).

2.3.2.2. Procedure of the CPP

2.3.2.2.1. Acquisition. Place conditioning, which consisted of three phases, was carried out during the dark cycle following a procedure that was unbiased in terms of initial spontaneous preference (Manzanedo et al., 2001). During the first phase - or preconditioning (Pre-C) - mice were allowed access to both compartments of the