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Dopamine D_2 receptors mediate the increase in reinstatement of the conditioned rewarding effects of cocaine induced by acute social defeat

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ABSTRACT

Social stress modifies the activity of brain areas involved in the rewarding effects of psychostimulants, inducing neuroadaptations in the dopaminergic mesolimbic system and modifying the sensitivity of dopamine receptors. In the present study we evaluated the effect of the dopamine D_1- and D_2-like receptor antagonists (SCH23390 and raclopride, respectively) on the short-time effects of acute social defeat (ASD). Male OF1 mice were socially defeated before each conditioning session of the conditioned place preference (CPP) induced by 1 mg/kg or 25 mg/kg of cocaine plus the corresponding dopamine antagonist. A final experiment was designed to evaluate the effect of the dopamine antagonists on the CPP induced by 3 mg/kg of cocaine with or without a stress experience. Mice exposed to ASD showed an increase in reinstatement of the conditioned reinforcing effects of cocaine that was blocked by all of the dopamine receptor antagonists. Blockade of dopamine D_2-like receptors with raclopride specifically prevented the effects of stress without affecting the rewarding properties of cocaine. However, SCH23390 inhibited cocaine-induced preference in the control groups and even induced aversion in defeated mice conditioned with the lower dose of cocaine. Moreover, the lowest dose of SCH23390 blocked the rewarding effects of 3 mg/kg of cocaine-induced CPP. Our results confirm that the dopamine D_2 receptor is involved in the short-term effects of ASD on the rewarding effects of cocaine. The dopamine D_1 receptor is clearly involved in the rewarding effects of cocaine, but its role in the effects of ASD remains to be demonstrated.

1. Introduction

The mesolimbic dopaminergic system has been implicated in the rewarding effects of drugs of abuse (Koob and Le Moal, 2001; Wise and Koob, 2014), and, specifically, cocaine administration has been shown to increase extracellular concentrations of dopamine in the nucleus accumbens (N Acc) (Dela Peña et al., 2015). However, some elements of the dopaminergic system are also activated by aversive stimuli such as social isolation (Han et al., 2015), foot shocks (Brischoux et al., 2009), and social defeat (Miczek et al., 2011; Tidey and Miczek, 1996). An acute episode of social defeat induces a significant increase in extracellular dopamine in both the medial prefrontal cortex and the N Acc shell, effects that have been shown to be dependent on CRF2, but not on CRF1 receptors (Holly et al., 2015). These findings suggest that social defeat stress can induce neuroadaptations in the dopaminergic mesolimbic system, which may affect vulnerability to drug use. In line with this, socially defeated mice show a greater release of dopamine in the N Acc shell in response to d-amphetamine administration than non-stressed animals (Han et al., 2015). Stress induced by social defeat increases vulnerability to the acquisition and escalation of cocaine self-administration (SA) (Burke and Miczek, 2015), with only four episodes of social defeat having been shown to increase the sub-threshold dose of cocaine SA (Tidey and Miczek, 1997). We have observed that the experience of ASD increases sensitivity to reinstatement of the conditioned rewarding effects of cocaine after a priming dose of this drug (Ribeiro Do Couto et al., 2009; Montagud-Romero et al., 2015) and precipitates reinstatement of cocaine-induced CPP (Titomanlio et al., 2013). Our results suggest that the mesolimbic dopaminergic system is a critical neural link between aversive stressful experiences and rewarding drug-taking. How exactly the activation of mesolimbic dopamine in response to aversive events such as social defeat stress is related to increased cocaine-induced reward remains to be explored.

Few studies have investigated the effects of social defeat stress on dopamine receptors. Changes in D_1 receptors have been observed after social encounters during adolescence or adulthood (Avgustinovich and Alekseyenko, 2010; Novick et al., 2011). Social defeat stress during adolescence decreases the down-regulation of D_2 receptors in the N Acc core induced by amphetamine (Burke et al., 2011). However, other

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authors have failed to observe any change in dopamine receptors in the same conditions (Jin et al., 2015). A recent report has shown that the D_1/D_2 receptor antagonist cis(z)flupenthixol reduces submissive and defensive behavior in defeated animals when injected into the N Acc prior to social defeat (Gray et al., 2015).

These data suggest that dopamine modulates social defeat stress-induced behavioral changes. The aim of the present study was to evaluate the role of dopamine D_1 and D_2 receptors in the increased sensitivity to acquisition and reinstatement of the conditioned rewarding effects of cocaine induced by ASD. The D_1-like antagonist SCH 23390 and the D_2-like antagonist raclopride were administered 30 min prior to an acute episode of social defeat. Immediately afterwards, the rewarding effects of 1 mg/kg dose of cocaine were evaluated in the CPP.

2. Material and methods

2.1. Subjects

A total of 335 male OF1 mice (Charles River, France) were delivered to our laboratory at 42 days of age. All mice (except those used as aggressive opponents) were housed in groups of four in plastic cages (25×25×14.5 cm) for 8 days before the experiments began. Mice used as aggressive opponents were individually housed in plastic cages (23×13.5×13 cm) for a month before the experiments to induce heightened aggression (Rodríguez-Arias et al., 1998) (n=15 adult mice). All mice were housed under the following conditions - constant temperature; a reversed light schedule (lights off at 08:00 h and on at 20:00 h) – and food and water were freely available ad libitum, except during the 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 committees (University of Valencia).

2.2. Drugs

Animals were injected intraperitoneally with 1, 3 or 25 mg/kg of cocaine hydrochloride (Laboratorios Alcaliber, Madrid, Spain); 0.250, 0.125 or 0.062 mg/kg of SCH23390 (Research Biochemical International, Natick, USA); and 1.2, 0.6 or 0.3 mg/kg of raclopride (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. The doses of cocaine were selected on the basis of previous studies showing that 1 mg/kg is a threshold dose (Vidal-Infer et al., 2012; Arenas et al., 2014; Montagud-Romero et al., 2014), 3 mg/kg is an effective dose that induces CPP but not reinstatement (Maldonado et al., 2006), and 25 mg/kg induces a strong CPP that is reinstated after priming with 12.5 mg/kg of cocaine (Rodríguez-Arias et al., 2009). The dopamine antagonist doses have previously been shown to block MDMA-induced CPP (Vidal-Infer et al., 2012).

2.3. Apparatus

For place conditioning, we used eight identical Plexiglas boxes with two equally sized compartments (30.7 cm long ×31.5 cm wide ×34.5 cm high) separated by a grey 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 position of the animals and their crossings from one compartment to the other to be recorded. The equipment was controlled by three IBM PC computers using Monpre 2Z software (Cibertec, SA, Madrid, Spain).

Table 1
Statistical results of the ANOVA performed between the associated and non-associated cocaine compartment of the CPP.

CPP – induced by 1 mg/kg				
Groups	n	gl	F	Sig.
EXP+Saline	11	1.20	1226	0.281
ASD+Saline	11	1.20	0.805	0.380
EXP+SCH 0.250	17	1.32	0.146	0.705
ASD+SCH 0.062	14	1.26	0.025	0.875
ASD+SCH 0.125	15	1.28	0.865	0.360
ASD+SCH 0.250	17	1.32	0.044	0.836
EXP+Raclopride 0.6	11	1.20	0.247	0.625
ASD+Raclopride 0.3	12	1.22	0.960	0.338
ASD+Raclopride 0.6	16	1.30	2987	0.99
CPP – induced by 3 mg/kg				
Group	n	gl	F	Sig.
EXP+Saline	10	1.18	0.593	0.451
ASD+Saline	10	1.18	1791	0.198
EXP+SCH 0.062	11	1.20	3959	0.060
ASD+SCH 0.062	11	1.20	3774	0.066
EXP+Raclopride 0.3	11	1.20	1240	0.279
ASD+Raclopride 0.3	11	1.20	0.797	0.383
CPP – induced by 25 mg/kg				
Group	n	gl	F	Sig.
EXP-Sal-R	18	1.34	0.138	0.713
ASD-Sal-R	16	1.3	0.575	0.454
EXP+Saline	15	1.28	0.011	0.916
ASD+Saline	15	1.28	2076	0.161
EXP+SCH 0.250	14	1.26	0.097	0.757
ASD+SCH 0.250	18	1.34	0.091	0.765
EXP+Raclopride 0.6	17	1.32	0.041	0.840
ASD+Raclopride 0.6	15	1.28	0.848	0.365
EXP+Raclopride 1.2	10	1.18	4086	0.058
ASD+Raclopride 1.2	10	1.18	1589	0.224

2.4. CPP procedure

This paradigm has been widely used to study the conditioned rewarding effects of addictive drugs (Tzschentke, 1998, 2007; Aguilar et al., 2009).

2.4.1. 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 (Maldonado et al., 2006). During the first phase – or preconditioning (Pre-C) – mice were allowed access to both compartments of the apparatus for 900 s per day on 3 consecutive days. On day 3, the time spent in each compartment was recorded. Animals showing a strong unconditioned aversion (less than 33% of session time; i.e. 250 s) or preference (more than 67% of the session time; i.e. 650 s) for any compartment were discarded from the rest of the study. In each group, half of the animals received the drug or vehicle in one compartment, while the other half received it in the other compartment. ANOVA showed there were no significant differences between the time spent in the drug-paired and vehicle-paired compartments during the Pre-C phase (see Table 1). In the second phase (conditioning), which lasted 4 days, animals were conditioned with cocaine or saline. An injection of physiological saline was administered before confining the mice to the vehicle-paired compartment for 30 min. After an interval of 3 h, animals were injected with the corresponding treatment (saline, SCH23390 or raclopride) 30 min before ASD or the exploration session. Cocaine was administered 30 min after the end of ASD or exploration, immediately prior to confining the animal to the drug-paired compartment for a further 30 min. The central area was made inaccessible by guillotine doors during conditioning. In the third phase–or postconditioning (Post-C)–, which took place on day 8, the guillotine doors separating the two