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Long-term effects of repeated social stress on the conditioned place preference induced by MDMA in mice

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ABSTRACT

Previous studies have demonstrated that social defeat stress increases the rewarding effects of psychostimulant drugs such as cocaine and amphetamine. In the present study we evaluated the long-term effects of repeated social defeat (RSD) on the rewarding effects of ±3,4-methylenedioxymethamphetamine (MDMA) hydrochloride in the conditioned place preference (CPP) paradigm. Adolescent and young adult mice were exposed to four episodes of social defeat (on PND 29–40 and PND 47–56, respectively) and were conditioned three weeks later with 1.25 or 10 mg/kg i.p. of MDMA (experiment 1). The long-term effects of RSD on anxiety, social behavior and cognitive processes were also evaluated in adult mice (experiment 2). RSD during adolescence enhanced vulnerability to priming-induced reinstatement in animals conditioned with 1.25 mg/kg of MDMA and increased the duration of the CPP induced by the 10 mg/kg of MDMA. The latter effect was also observed after RSD in young adult mice, as well as an increase in anxiety-like behavior, an alteration in social interaction (reduction in attack and increase in avoidance/flee and defensive/submissive behaviors) and an impairment of maze learning. These results support the idea that RSD stress increases the rewarding effects of MDMA and induces long-term alterations in anxiety, learning and social behavior in adult mice. Thus, exposure to stress may increase the vulnerability of individuals to developing MDMA dependence, which is a factor to be taken into account in relation to the prevention and treatment of this disorder.

1. Introduction

Many people take addictive drugs and do it for different reasons, in different ways and in different contexts (Everitt, 2014). Addiction can be defined as a chronic, relapsing brain disease characterized by a compulsion to seek and take drugs, loss of control over intake, and the emergence of a negative emotional state when access to the drug is prevented (Koob, 2013). The factors that might predispose individuals to lose control over drug use are gradually being defined (Belin et al., 2008; Dalley et al., 2007; Dilleen et al., 2012) leading to the identification of endophenotypes of drug addiction and related neuropsychiatric disorders (Ersche et al., 2010; Everitt, 2014). Adverse life experiences may render individuals more prone to abuse addictive substances and more vulnerable to relapse into drug-seeking after periods of detoxification (Caprioli et al., 2007; Le Moal, 2009; Miczek et al., 2008; Sinha et al., 2011). In experimental animals, it has been demonstrated that exposure to stressors (i.e., social defeat stress, social isolation, maternal separation, immobilization stress, footshock stress, etc.) and activation of neural and hormonal stress mechanisms can produce behavioral and neurochemical adaptations that render animals more vulnerable to the initiation, maintenance and escalation of drug consumption and to the reinstatement of this behavior after extinction (Burke and Miczek, 2014; Koob, 2010; Logrip et al., 2011, 2012; Rodríguez-Arias et al., 2013; Sinha, 2008; Sinha et al., 2011).

Exposure to different procedures of social defeat, considered a stressor of ecological and ethological validity in rodents (Neisewander et al., 2012; Tornatzky and Miczek, 1993), increases the rewarding and reinstating effects of psychostimulant drugs, such as cocaine and amphetamine, in the self-administration and conditioned place preference (CPP) paradigms (for a review see Aguilar et al., 2013; Burke and Miczek, 2014; Miczek et al., 2008; Neisewander et al., 2012). No studies have evaluated the influence of stress on the rewarding effects of ecstasy (±3,4-methylenedioxymethamphetamine, MDMA), with the exception of a previous work carried out in our laboratory in which we observed that exposure to acute social defeat undermined the rewarding effects of MDMA in the CPP paradigm in adult mice (García-Pardo et al., 2014). It is not clear if these results, which diverge from those observed with psychostimulants, were due to differences in the drug tested (MDMA vs cocaine or amphetamine) or in the procedure of social defeat stress. Although MDMA is a less effective reinforcer than

Abbreviations: CPP, Conditioned preference place; MDMA, 3,4 methylenedioxymethylamphetamine; DA, Dopamine; RSD, Repeated social defeat; Pre-C, Pre-conditioning; Post-C, Post-conditioning; PND, Postnatal day; Ado, Adolescent; YA, Young Adult; Ctr, Control; CRF, Corticotrophin release factor; BDNF, Brain derived neurotrophic factor.

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other drugs of abuse, it induces rewarding and reinstating effects in the self-administration and CPP paradigms, which are mainly due to the activation of dopamine (DA) and serotonin neurotransmission (Roger-Sánchez et al., 2013; Schenk, 2009). On the other hand, specific features of the procedure of acute social defeat stress may explain the reduction of MDMA-induced CPP. Firstly, as mice experienced social defeat immediately before each conditioning session with MDMA, the adverse experience of social defeat could reduce the rewarding properties of MDMA. Secondly, only the short-term effects of social defeat stress are evaluated (48 h after the last stress exposure). Thus, in the present study, we aim to evaluate, for the first time, the long-term effects of social defeat exposure on the rewarding effects of MDMA. It is important to note that an increase in the rewarding effects of psychostimulants is generally observed after the absence (for 10 days or more) of repeated social defeat stress in a resident–intruder paradigm (Boyson et al., 2011, 2014; Cruz et al., 2011; Han et al., 2015; Miczek et al., 2008, 2011; Quadros and Miczek, 2009; Yap et al., 2015). Similarly, in a recent study we have demonstrated that mice exposed to intermittent repeated social defeat (RSD) during adolescence display an increase in ethanol consumption and motivation to drink in adulthood. Moreover, we have observed that RSD during adolescence induces depression-like symptoms and social subordination behavior in mice during adulthood, without affecting anxiety-like behavior in the elevated plus maze or cognitive performance in the passive avoidance and Hebb–Williams tests (Rodríguez-Arias et al., 2014). In contrast to this last work, the majority of studies of the effects of RSD on drug vulnerability have been performed in adult mice. However, it is essential to test the effects of social defeat stress in adolescent animals, since adolescence is a highly vulnerable developmental period and adolescent rodents are more vulnerable to stressors than younger or older counterparts (Buwalda et al., 2011; Romeo, 2010; Stone and Quartermain, 1998; Vázquez, 1998).

Thus, in the present work we have evaluated the long-term effects of intermittent RSD on the CPP induced by MDMA in adolescent or young adult mice. We hypothesized that exposure to intermittent RSD stress would induce a long-term increase in the vulnerability of the animals to the rewarding effects of MDMA. In experiment 1, we evaluated the rewarding effects of a low (1.25 mg/kg) and a high (10 mg/kg) dose of MDMA in mice pre-exposed (3 weeks before the initiation of CPP procedure) to four episodes of social defeat stress during adolescence (PND 29–38) or early adulthood (PND 47–56). Corticosterone levels were determined immediately or 30 min after the first and last episodes of RSD, or three weeks after, at the initiation of the CPP procedure. Additionally, we evaluated the long-term effects of this regime of intermittent RSD stress on the behavioral profile of mice (anxiety, social interaction, and cognitive performance). Three weeks after the last social defeat, the behavior of mice in the plus maze, passive-avoidance task, social interaction test and Hebb–Williams maze was evaluated (experiment 2). This experiment was performed only in young adult mice, since the effects of intermittent RSD on these behaviors in adolescent mice have previously been studied (Rodríguez-Arias et al., 2014). In this way, we set out to evaluate if the changes observed in the rewarding effects of MDMA in socially defeated mice are related with behavioral or cognitive alterations induced by RSD.

2. Materials and methods

2.1. Animals

Male OF1 mice (Charles River, Barcelona, Spain) arrived at our laboratory at 21 or 42 days of age (early and late adolescents, respectively). 70 adolescent and 84 young adult mice were employed as experimental subjects in experiment 1, and 30 young adult mice were employed in experiment 2. 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. 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 the behavioral tests. Adult mice used as resident aggressive opponents (n = 85) were individually housed in plastic cages (21 × 32 × 20 cm) for a month prior to experiments in order to induce heightened aggression (Rodríguez-Arias et al., 1998). All mice were housed under the following conditions: constant temperature; a reversed light schedule (white lights on 19:30–07:30 h); and food and water available ad libitum, except during behavioral tests. Procedures involving mice and their care were conducted according to national, regional and local laws and regulations, which are in compliance with the Directive 2010/63/EU.

2.2. Apparatus

2.2.1. Place conditioning boxes

For place conditioning, we employed eight identical Plexiglas boxes with two equal-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).

2.2.2. Elevated plus maze

To evaluate the effects of RSD on anxiety-like behaviors, an elevated plus maze (EPM) was employed. The apparatus consisted of two open arms (30 × 5 × 0.25 cm) and two enclosed arms (30 × 5 × 15 cm). The junction of the four arms formed a central platform (5 × 5 cm). The floor of the maze was made of black Plexiglas and the walls of the enclosed arms of clear Plexiglas. The open arms had a small edge (0.25 cm) to provide additional grip for the animals. The entire apparatus was elevated 45 cm above floor level.

2.2.3. Inhibitory avoidance apparatus

For the passive avoidance test, a step-through inhibitory avoidance apparatus for mice (Ugo Basile, Comerio-Varese, Italy) was employed. This cage, made of sheets of Perspex, is divided into two compartments (15 cm × 9.5 cm × 16.5 cm each one). The safe compartment is white and illuminated by a light fixture (10 W) fastened to the cage lid, whereas the "shock" compartment is dark and made of black Perspex panels. The two compartments are divided by an automatically operated sliding door at floor level. The floor is made of 48 stainless steel bars with a diameter of 0.7 mm and situated 8 mm apart.

2.2.4. Hebb–Williams maze

To perform the Hebb–Williams maze, we used a maze constructed with black plastic and measuring 60 cm wide × 60 cm long × 10 cm high. It contains a start box and a goal box (both 14 cm wide × 9 cm long) positioned at diagonally opposite corners. The maze contains cold water at a wading depth (15 °C, 3.5 cm high), while the goal box is stocked with fresh dry tissue. Several maze designs are produced by fixing different arrangements of barriers to a clear plastic ceiling. This apparatus allows the cognitive process of routed learning and the motivation of water escape to be measured.

2.3. Drugs

Animals were injected intraperitoneally with 1.25 or 10 mg/kg of MDMA (±3,4-methylenedioxymethamphetamine hydrochloride, racemic mixture; Agencia Española del Medicamento, Ministerio de Sanidad, Política Social e Igualdad, Madrid, Spain) in a volume of 0.01 ml/g of weight. Physiological saline (NaCl 0.9%) was used to dissolve the drug. The doses of MDMA we administered were selected on