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Context-dependent effects of rimonabant on ethanol-induced conditioned place preference in female mice

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ABSTRACT

Background: The CB1 receptor antagonist rimonabant has been previously found to prevent behavioral effects of drugs of abuse in a context-dependent manner, suggesting an important role of endocannabinoid signaling in drug-induced environmental conditioning. The aim of the present study was to evaluate the effects of rimonabant on ethanol-induced conditioned place preference (CPP) in female mice.

Methods: Animals were conditioned with saline or ethanol (1.8 g/kg) during 8 sessions, and subsequently treated with either saline or rimonabant (1 or 10 mg/kg) in the CPP environment previously associated with saline (unpaired) or ethanol (paired) for 6 consecutive days. Animals were then challenged with ethanol (1.8 g/kg) in the ethanol-paired environment and ethanol-induced CPP was quantified on the following day.

Results: While treatment with 1 mg/kg rimonabant in the saline-associated environment had no effects on the subsequent expression of ethanol-induced CPP, it blocked the expression of CPP to ethanol when paired to the ethanol-associated environment. When given in the ethanol-paired environment, 10 mg/kg rimonabant induced aversion to the ethanol-associated environment. The same aversion effect was observed for 10 mg/kg rimonabant when given in the saline-associated environment, thereby potentiating the expression of ethanol-induced CPP. Importantly, rimonabant did not induce CPP or conditioned place aversion on its own. Controlling for the estrous cycle phase showed no influences of hormonal cycle on the development and expression of ethanol-induced CPP.

Conclusions: Our data suggest that rimonabant reduces the rewarding properties of ethanol by abolishing drug-environment conditioning in the CPP paradigm in a context-dependent manner.

1. Introduction

Alcohol (ethanol) use disorder is a major global public health concern, representing the 5th leading risk factor for premature death and disability (World Health Organization, 2015). According to the most recent Global status report on alcohol and health, 3.3 million deaths (5.9% of all global deaths) every year result from alcohol misuse (World Health Organization, 2014). Importantly, alcohol use and lifetime prevalence of alcohol dependence among women has been increasing markedly during the past decades (Green et al., 2017; Grucza et al., 2008; Wilsnack et al., 2013). Evidence indicates that women are more vulnerable to alcohol-related harm (World Health Organization, 2014), placing them at risk of negative outcomes and highlighting the need for research focusing on the effects of alcohol in female subjects.

Alcohol consumption increases dopamine availability in the mesolimbic system (Koob and LeMoal, 2001), and the endocannabinoid system has been shown to modulate this effect (Bossong et al., 2015; Colombo et al., 2005). Special attention has been given to drugs targeting the cannabinoid 1 (CB1) receptor due to its wide distribution in the brain. Studies show that the behavioral effects of alcohol are modulated by an interaction between CB1 receptors and opioid receptors (Colombo et al., 2005; Hungund and Basavarajappa, 2000). A previous study from our group has shown that the CB1 receptor antagonist rimonabant (SR 141716) blocked the expression and development of acute and long-term behavioral effects of ethanol in male mice (Marinho et al., 2015). Several studies have also shown that CB1

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receptor blockade decreases alcohol intake and self-administration in male rodents (Arnone et al., 1997; Dyr et al., 2008; Femenia et al., 2010; Freedland et al., 2001). Although females seem to be more vulnerable than males to the effects of ethanol and show higher ethanol consumption than males (Hungund et al., 2003), few studies have investigated the role of CB1 receptors on the effects of ethanol in female rodents. Among these studies, it has been shown that ethanol consumption is decreased more markedly in female than in male CB1 knock-out mice compared to wild-type animals (Hungund et al., 2003; Naassila et al., 2004), suggesting that CB1 receptors might play a major role on ethanol-induced behaviors in females.

Studies suggest that the effects of CB1 receptor on drug abuse seem to be modulated by drug-environment conditioning (Gerdeman et al., 2008). Among the behavioral animal models of drug addiction, the conditioned place preference (CPP) paradigm is the main model for studying the interactions between drug effects and contextual cues (Tzschentke, 2007; van der Kooy, 1987). Studies have shown that lifelong depletion of CB1 receptors in CB1 knockout mice attenuates ethanol-induced CPP (Houchi et al., 2005; Thanos et al., 2005). However, in a recent study conducted with male mice administration of the selective CB1 receptor antagonist PF 514273 had no effects on the acquisition or expression of ethanol-induced CPP when given before the conditioning or test sessions, respectively (Pina and Cunningham, 2014). Thus, it remains unknown whether CB1 antagonism plays a major role in ethanol-induced CPP and if that effect would be different among males and females.

The present study investigated the effects of treatment with rimonabant on ethanol-induced CPP after the acquisition of drug-environment conditioning in female mice. In order to evaluate the influence of the treatment environment on the effects of rimonabant, the CB1 antagonist was administered either in the non-drug-paired environment or in the ethanol-paired environment. Finally, because studies suggest that estrous cycle hormonal fluctuations can influence the outcomes of behavioral studies (ter Horst et al., 2011), we evaluated the influence of estrous cycle on ethanol-induced CPP in free-cycling female rats to control for possible confounders.

2. Material and methods

2.1. Animals

Three-month-old Swiss female mice from our own colony were used. Animals weighing 35–40 g were group housed (5–7 per cage) in polypropylene cages (32 × 42 × 18 cm) under controlled temperature (22–23 °C) and light (12 h light, 12 h dark; lights on at 6h45a.m.) conditions. Food and water were available *ad libitum* throughout the experiments. Animals were maintained according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals (8th Edition, revised 2011) and in accordance with the Brazilian Law for Procedures for Animal Scientific Use (#11794/2008). The Institutional Ethical Committee of UESC approved the experimental procedures (protocol #028/2013).

2.2. Drugs

Absolute ethanol (Merck®) was diluted in 0.9% saline (Sal) solution. Rimonabant (Sanofi-Aventis®) was dissolved in a solution of Sal + 1% Tween 80 + 3% propylene glycol, which was used as vehicle solution (Veh). Drugs and vehicle solutions were administered intraperitoneally at 10 ml/kg of body weight. The selected dose range of rimonabant and ethanol was based on previous studies from our group (Marinho et al., 2014, 2015; Oliveira-Lima et al., 2015). Doses of rimonabant were chosen based on their ability to prevent acute and long-term behavioral effects of ethanol in mice (Marinho et al., 2015).

2.3. Vaginal cytology

The 4–5 days estrous cycle in adult female mice consists of 4 stages: proestrus, estrus, metestrus and diestrus. For simplicity, we combined proestrus and estrus (estrogenic phase) and metestrus and diestrus (progestogenic phase) because of the similarities in hormone profiles. The estrous cycle was tracked by vaginal smears always at 10:00 to 11:00 h. Smears were done by vaginal lavage using a blunt tipped disposable 100 µl pipette and ~0.3 ml physiological Sal. The material collected was then applied to a slide and air-dried. Cytology was then examined under a light microscope. Criteria for stage of cycle were as follows: progestogenic phase (metestrus and diestrus) – presence of abundant leucocytes and a few nucleated epithelial cells and cornified cells (irregular cells without nuclei); estrogenic phase (proestrus and estrus) – predominance of nucleated epithelial cells with a few cornified cells and/or predominant presence of large cornified cells (Antunes et al., 2006; Caligoni et al., 2009).

2.4. Conditioned place preference (CPP)

The CPP apparatus consisted of 2 conditioning compartments of equal size (40 × 20 × 20 cm): 1 black with white vertical bands in the walls and a black wooden floor and 1 white with black horizontal bands in the walls and a dark (red) smooth floor, both connected by a central choice compartment (40 × 10 × 15 cm) that was accessible by sliding doors. The CPP procedure consisted of the following phases: Experiments 1 and 4 – pre-conditioning test, conditioning, post-conditioning test; Experiments 2 and 3 – pre-conditioning test, conditioning, post-conditioning test, treatment, ethanol reexposure and post-treatment test.

2.4.1. Pre-conditioning test

In order to establish if animals showed a preference for either of the compartments, a pre-conditioning test was conducted (Day 1) in which animals were placed in the center of the apparatus with the door open with free access to each compartment for 15 min. No injection was administered on the day of the pre-conditioning test.

2.4.2. Conditioning

An unbiased design was used because mice showed no preference for either of the compartments in the pre-conditioning test. Therefore, animals were randomly assigned to an experimental group and a 'drug-paired compartment' in a counterbalanced fashion, with the "black" compartment as the drug-paired one for half of the animals and the "white" compartment for the other half. One "drug-paired compartment" and one "Sal-paired compartment" were defined for all animals. The conditioning trials were performed during 8 consecutive days (Days 2–9). During the conditioning sessions, the doors remained closed so the animals would be confined to one of the conditioning compartments. Animals received an i.p. injection of Sal in the even days and ethanol (1.8 g/kg) (Experiments 1, 2 and 3) or rimonabant (0.3, 1.0, 3.0 or 10.0 mg/kg) (Experiment 4) in the odd days. Five (Eth) or 30 (Rim) min after injection, mice were confined to the assigned drug- or Sal-paired compartment for 10 min.

2.4.3. Post-conditioning test

Twenty-four hours after the last conditioning session (Day 10), animals were placed in the center of the apparatus with the door open with free access to each compartment for 15 min. No injection was administered on the day of the post-conditioning test.

2.4.4. Treatment

For 6 consecutive days (Day 11–16), animals received daily i.p. injections of Veh or rimonabant (1 or 10 mg/kg) and, 30 min after injection, were confined to the assigned ethanol- or Sal-paired compartment for 10 min.

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