Research report

Activation of cannabinoid receptors elicits antidepressant-like effects in a mouse model of social isolation stress

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ARTICLE INFO

ABSTRACT

Social isolation stress (SIS) paradigm is a chronic stress procedure able to induce profound behavioral and neurochemical changes in rodents and evokes depressive and anxiety-like behaviors. Recent studies demonstrated that the cannabinoid system plays a key role in behavioral abnormalities such as depression through different pathways; however, there is no evidence showing a relation between SIS and the cannabinoid system. This study investigated the role of the cannabinoid system in depressive-like behavior and anxiety-like behavior of IC animals. For this purpose, NMRI mice were treated with WIN55, 212-2 (non-selective cannabinoid receptor agonist) and AM-251 (cannabinoid receptor type 1 antagonist) and AM-630 (cannabinoid receptor type 2 antagonist). We found that behavioral abnormality followed by SIS was mitigated after administration of WIN55, 212-2. Also, depressive-like effects induced by SIS were significantly increased following administration of AM-251 and AM-630. Co-administration of cannabinoid receptor antagonists (AM-251 and AM-630), significantly reversed the antidepressant effect of WIN55, 212-2 in IC animals. Our findings suggest that the cannabinoid system is involved in depressive-like behaviors induced by SIS. We showed that activation of cannabinoid receptors (type 1 and 2) could mitigate depression-like behavior induced by SIS in a mouse model.

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1. Introduction

Evidences from clinical and pre-clinical studies have demonstrated that early life exposure to environmental and social stressors plays a pivotal role in the development of psychiatric disorders such as depression (Lupien et al., 2009; Pechtel and Pizzagalli, 2011). In this regards, it has been shown that social isolation stress (SIS) paradigm is a chronic stress procedure able to induce profound behavioral and neurochemical changes in rodents and evokes depressive and anxiety-like behaviors (Fone and Porkess, 2008; Weiss et al., 2004; Nestler and Hyman, 2010; Koob et al., 1989). Glutaminergic system, nitrergic system, hypothalamic-pituitary-adrenal (HPA) axis are pathways known to mediate the impacts of SIS on psychopathologies like depression (Weiss et al., 2004; Haj-Mirzaian et al., 2015; Amiri et al., 2014).

The cannabinoid system comprises the cannabinoid receptors (CB1 and CB2 receptors) and represents an important neuromodulator in the central nervous system (CNS) (Devane et al., 1992; Dinh et al., 2004; Gong et al., 2006; Matsuda et al., 1990; Sugiura et al., 1995). Recent studies demonstrated that the cannabinoid system exerts its antidepressant effects through different pathways including the modulation of HPA axis function (Weidenfeld et al., 1994), regulating the release of neurotransmitters (Domenici et al., 2006; Takahashi and Castillo, 2006) and the modulation of neuroinflammation (Walter and Stella, 2004).

Although, antithesis evidence has shown different effects for cannabinoids on behavior, overall, effects of cannabinoids depend on the doses and time of administration as well as experimental

conditions (Rodriguez Bambico et al., 2009; Witkin et al., 2005); however, the exact mechanisms modulated by the cannabinoid system are still unknown. Therefore, further investigations are needed to clarify the mechanisms underlying the antidepressant-like effects of these pharmacological agents targeting the cannabinoid system. Previous reports have determined that cannabinoid receptor (CBR) agonists can reverse the depressive state in animals exposed to chronic mild stress; however, there is no evidence showing that cannabinoid agonists have beneficial effects in depression following SIS paradigm (Segev et al., 2014).

Considering the above-mentioned points, we tried to demonstrate the impact of the cannabinoid system on depressive-like behaviors induced by SIS. The aim of our study is to investigate the effects of drugs acting on CB1 and CB2 receptors (CB1R and CB2R) on depressive-like behavior in SIS mice using WIN55,212-2 (non-specific agonist) and AM630 (CB2R antagonist) and AM251 (CB1R antagonist). For this purpose, we used SIS paradigm as a chronic stress model. Behavioral experiments to measure depressive-like behavior including forced swimming test (FST), splash test and open field-test (OFT) were used in order to verify our hypothesis.

2. Materials and methods

2.1. Animals and housing conditions

Male NMRI mice (Pasteur Institute, Tehran, Iran) weighing 10–12 g on postnatal day (PND) 21–24 were used in this study (animals used in this study were at adolescence period) (Spinelli et al., 2013). Animals were housed under standard laboratory conditions as temperature at 22 ± 2C, humidity at 50, 12-h light–dark cycle, and free access to food and water ad-lib for a period of 28 days in two opposing conditions: social condition (SC) or isolated condition (IC). Socially conditioned mice were located (6 per cage) in Plexiglas boxes (25 cm × 25 cm × 15 cm) and IC animals were placed individually in Plexiglas boxes (24 cm × 17 cm × 12 cm) (Amiri et al., 2015). The cages of IC animals were cleaned weekly by a same experimenter to diminish handling and social interaction. All experiments were conducted during the period between 10:00 a.m. and 02:00 p.m. Each mouse was used only once in each tests. Each experimental group contained 6–8 animals. All experiments were carried out in accordance with National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals (NIH publication #80-23) and institutional guidelines for animal care and use (Department of Pharmacology, School of medicine, Tehran University of Medical Sciences).

2.2. Drugs

AM-251 (CB1R antagonist), AM-630 (CB2R antagonist) and WIN55, 212-2 (non-selective agonist of CBR) were purchased from Sigma (Sigma, St Louis, MO, USA). AM-251 and AM-630 were dissolved in saline and WIN55, 212-2 dissolved in dimethyl sulfoxide (DMSO) and further diluted with 5% Tween-80 and 90% saline (0.9% NaCl). Final DMSO concentration was 5%. Injections were carried out through intraperitoneal (i.p.) route in a constant volume of 5 ml/kg body weight. DMSO, Tween-80 and saline solutions were used as vehicle (Vehicle: 1:1:18 of DMSO, Tween-80 and saline, respectively).

AM-251 (0.2 and 0.5 mg/kg) and AM-630 (0.2 and 0.5 mg/kg) were administrated 30 min before behavioral tests (Kruk-Slomka et al., 2015; Ostadhadi et al., 2016) and WIN55, 212-2 (1, 3 and 5 mg/kg) was administered 60 min prior to the behavioral tests (Bambico et al., 2007). Doses and time of administrations of each drug were chosen based on our pilot study and pervious published reports (Haj-Mirzaian et al., 2016a; Haj-Mirzaian et al., 2016c; Weiss et al., 2004).

2.3. Experiment design and treatments

In the first part of study, the effects of SIS on depressive-like behaviors were investigated using previously validated behavioral tests including forced swimming test (FST), open-field test (OFT) and splash test. On the next step, the possible effects of CBR agonist/antagonists on IC mice were assessed. To do this, mice (IC and SC) were treated with the sub-effective doses of AM-630 (0.2 and 0.5 mg/kg, i.p., 30 min prior to the tests), AM-251 (0.2 and 0.5 mg/kg, i.p., 30 min prior to the tests) and WIN55, 212-2 (1, 3 mg/kg and 5 mg/kg, i.p., 60 min prior to the tests). After administration of drugs, behaviors of animals were evaluated using aforementioned behavioral tests. To exclude the possible impact of saline and vehicle administrations, mice were treated with 5 ml/kg physiological saline as well as vehicle before carrying out behavioral tests.

2.4. Open-field test (OFT)

Just before the FST, the locomotor activity of animals was evaluated using the open-field test (Haj-Mirzaian et al., 2016a; Kaster et al., 2005; Haj-Mirzaian et al., 2016b), in order to rule out the possibility that changes in duration of immobility are not the result of modifications in motor activity. OFT was used to elucidate the locomotor activity in response to SIS (Walsh and Cummins, 1976). The apparatus of OFT was made of white opaque Plexiglas (50 cm × 50 cm × 30 cm) and was faintly illuminated. Each animal was placed gently on the central zone (30 cm × 30 cm) and behaviors were recorded using a camera for a 5 min period and were analyzed by Ethovision software version 8 (Noldus, Netherlands). The surface of the apparatus was cleaned with 70% ethanol after each experiment. Each animal was used in only one experiment. The distance moved and the numbers of rearings were evaluated.

2.5. Forced swimming test (FST)

FST was carried out by using the method of Porsolt et al. (Porsolt et al., 1977a; Porsolt et al., 1977b; Haj-Mirzaian et al., 2016c). Mice were separately placed in an open cylinder-shaped flask (diameter 10 cm, height 25 cm), containing 19 cm water at $23 \pm 1\,°C$. Mice were allowed to swim for 6 min and the period of immobility was recorded throughout the last 4 min of the test. Each mouse was considered immobile when it ceased struggling and stayed floating motionless in the water, making only those movements necessary to keep its head above water.

2.6. Splash test

This test was used to evaluate self-care and motivational behaviors. In this test, grooming activity time of mice, which can be considered as an indirect measure of palatable solution intake, was measured. A 10% sucrose solution was squirted on the dorsal coat of animals in their home cage and mice were videotaped for 5 min. The total grooming activity time was recorded for 5 min after the sucrose vaporization (Detanico et al., 2009). Grooming activity consists of nose/face grooming, head washing and body grooming.

2.7. Statistical analysis

Comparisons between the groups were assessed using t-test and one-way ANOVA followed by Tukey's post hoc test using GraphPad Prism 6 software (San Diego, CA, USA). P values less than 0.05 were considered statistically significant.