Progress in Neuro-Psychopharmacology & Biological Psychiatry 51 (2014) 65–71

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Basolateral amygdala CB1 cannabinoid receptors mediate nicotine-induced place preference

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ARTICLE INFO

Article history:
Received 27 October 2013
Received in revised form 10 January 2014
Accepted 16 January 2014
Available online 24 January 2014

Keywords:
Basolateral amygdala
CB1 cannabinoid receptors
Nicotine
Rat(s)
Reward

ABSTRACT

In the present study, the effects of bilateral microinjections of cannabinoid CB1 receptor agonist and antagonist into the basolateral amygdala (intra-BLA) on nicotine-induced place preference were examined in rats. A conditioned place preference (CPP) apparatus was used for the assessment of rewarding effects of the drugs in adult male Wistar rats. Subcutaneous (s.c.) administration of nicotine (0.2 mg/kg) induced a significant CPP, without any effect on the locomotor activity during the testing phase. Intra-BLA microinjection of a non-selective cannabinoid CB1/CB2 receptor agonist, WIN 55,212-2 (0.1–0.5 μg/rat) with an ineffective dose of nicotine (0.1 mg/kg, s.c.) induced a significant place preference. On the other hand, intra-BLA administration of AM251 (20–60 ng/rat), a selective cannabinoid CB1 receptor antagonist inhibited the acquisition of nicotine-induced place preference. It should be considered that the microinjection of the same doses of WIN 55,212-2 or AM251 into the BLA, by itself had no effect on the CPP score. The administration of a higher dose of AM251 (60 ng/rat) during the acquisition decreased the locomotor activity of animals on the testing phase. Interestingly, the microinjection of AM251 (20 and 40 ng/rat), but not WIN55,212-2 (0.1–0.5 μg/rat), into the BLA inhibited the expression of nicotine-induced place preference without any effect on the locomotor activity. Taken together, these findings support the possible role of endogenous cannabinoid system of the BLA in the acquisition and the expression of nicotine-induced place preference. Furthermore, it seems that there is a functional interaction between the BLA cannabinoid receptors and nicotine in producing the rewarding effects.

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1. Introduction

Nicotine, the principal psychoactive component of tobacco, is responsible for addictive properties of cigarettes (Goniewicz and Delijewski, 2013). Several studies have demonstrated that mesolimbic dopaminergic pathways, which originate from the ventral tegmental area (VTA) and project to forebrain structures such as the nucleus accumbens (NAc) and the prefrontal cortex, play a critical role in reinforcing effects of drug abuse, including nicotine (for review see Mark et al., 2011). Neurotoxic lesion in mesolimbic dopamine (DA)-containing neurons or pretreatment by dopamine antagonist attenuates intravenous self-administration as well as reward preference of nicotine in animal models (Corrigall et al., 1992; Pak et al., 2006). Moreover, nicotine modulates reward pathways through nicotinic acetylcholine receptors (nAChRs) in the VTA (Mansvelder et al., 2002). Activation or desensitization/inactivation of these ionotropic pentameric receptors is important in nicotine addictive properties (for review see Changeux, 2010). For example, the blockade of nAChRs in the VTA decreased systemic nicotine-evoked DA release in the NAc (Gotti et al., 2010) and also intravenous self-administration of nicotine- induced rewarding effect in rats (Kenny and Markou, 2006).

Recent evidence indicated that the motivation effect of nicotine in reward circuitry is modulated by the endocannabinoid system (Forget et al., 2005). It is well recognized that there are functional and structural interactions between nicotine and cannabinoid receptors (López-Moreno et al., 2008). Available data suggest that co-abuse of nicotine and cannabinoid share pharmacological properties such as antinociception (Valjent et al., 2002), anxiety-like behavior (Biala et al., 2009), learning and memory (Alijanpour and Rezayof, 2013). Cannabinoid influences physiological functions in the central nervous system (CNS) via well characterized CB1 cannabinoid receptors (Litvin et al., 2013; McLaughlin et al., 2013). These receptors belong to the G-protein coupled receptor family (Shim et al., 2013). Neuroanatomical studies have reported a high density of CB1 cannabinoid receptors in the neurons of brain regions such as the NAc, the VTA and the amygdala reflecting reward motivational behaviors (Mackie, 2005).

Abbreviations: AM251, N-(piperidin-1-yl)-5-(4-isodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide; ANOVA, Analysis of variance; BLA, Basolateral amygdala; CB, Cannabinoid; CNS, Central nervous system; CPP, Conditioned place preference; DA, Dopamine; DMSO, Dimethyl sulphoxide; NAc, Nucleus accumbens; nAChRs, Nicotinic acetylcholine receptors; s.c, Subcutaneous; VTA, Ventral tegmental area; WIN 55,212-2, WIN55,212-2 mesylate.

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0278-5846/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pnpbp.2014.01.010

The amygdala complex anatomically divides into more than a dozen nuclei and has a critical role in mood and emotional behavior (for review see Sah et al., 2003). The basolateral nucleus (BLA), one of the important nuclei of the amygdala, has connectivity with reward circuitry and is well known to be necessary in reward pathways that play a central role in reward seeking behavior, emotion and reward-associated memory (Heinrichs et al., 2013; Wassum et al., 2012). It seems that there is an overlapping distribution of CB1 cannabinoid receptors and nACh receptors in the BLA (McDonald and Mascagni, 2001; Zhu et al., 2005). Previous studies have suggested a possibility of functional interactions between these two systems that regulate emotional responses, cognition (Pessoa, 2010) and reward (Kodas et al., 2007) in this region of the brain. These findings suggested that the endocannabinoid system modulates cortico-limbic circuitry for motivational properties of nicotine. Previous reports indicated that drug abuse has a dual motivational effect that conditioned place preference (CPP) paradigm which is widely used to evaluate both reinforcing and aversive effects of drug abuse including nicotine and cannabis in laboratory animals (Brielmaier et al., 2008; Cheer et al., 2000). It has been shown that systemic administration of CB1 receptor antagonists such as rimonabant (Fang et al., 2011) and AM251 (Budzyńska et al., 2009) inhibited nicotine-induced place preference. Nicotine-induced CPP also inhibited by a selective CB2 receptor antagonist, SR144528 (Ignatowska-Jankowska et al., 2013), indicating that CB1/CB2 receptors play a critical role in nicotine reward and may be a target for relapsing nicotine addiction. Considering that previous studies suggested that the specific brain circuits may be involved in the functional interaction between nicotine and cannabis in rewarding processes (for review see Vlachou and Panagis, 2014) and also that the basolateral amygdala (BLA) is a key component of the reward circuit (Stuber et al., 2011; Wassum et al., 2012), the present study was designed to investigate the role of CB1 receptors of the BLA in mediating nicotine reward. Therefore, this study highlights whether the acquisition and expression of nicotine-induced CPP could be affected by intra-BLA microinjections of CB1-receptor agonist and/or antagonist.

2. Materials and methods

2.1. Subjects

Male Wistar rats (Pasteur Institute; Tehran, Iran) weighing 240–280 g, at the time of surgery, were used. Each cage contained four animals and they could access water and food freely except during the time of experiments. The animals were kept under a 12-h light–dark cycle (lights on at 07:00 h) and controlled temperature (22 ± 2 °C). For adaptation to the laboratory conditions all animals were allowed to adapt for at least 1 week before surgery and before starting the experiments. Besides, each animal was handled for 5 min every day. All experiments were done during the light phase of the cycle. Each group of experiments contained six animals and each animal was analyzed once. All procedures for the treatment of animals were approved by the Research and Ethics Committee of the School of Biology, University of Tehran and were done in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23). Moreover, all efforts were made to minimize the number of animals used and limiting their suffering.

2.2. Surgery and drug microinjection

Under deep anesthesia (50 mg/kg of ketamine and 5 mg/kg of xylazine), the animals were placed in a stereotaxic frame. The animals were bilaterally implanted with 22-gauge guide steel cannulas into the basolateral nucleus of the amygdaloid complex (BLA) according to the atlas of Paxinos and Watson (2007). Stereotaxic coordinates for the BLA were AP: −2.8; ML: ±4.6; DV: −8.6. The guide cannulas were anchored by jeweler's screws, and the incision was closed with dental cement. Stainless steel stylets (27 gauge) were placed in the guide cannulas in order to prevent clogging until each animal was given the BLA injections. All animals were allowed a seven day recovery period from surgery to clear the anesthetic effects. During the recovery period, rats were handled about 5 min each day prior to the behavioral testing.

For drug injection, the stylets were gently removed from the guide cannulas and replaced by 27-gauge injection needles. Considering that the guide cannulas were implanted 1 mm above the BLA, the injection needles were 1 mm longer than those. Each injection unit was connected by polyethylene tubing to 2 μl Hamilton syringes. The left and right BLA were injected with a 0.3 μl solution on each side (0.6 μl/rat) over a 60 s period. The injection needles were left in place an additional 60 s to allow diffusion. The stylets were subsequently reinserted into the guide cannulas.

2.3. Drugs

In the present study, the drugs were nicotine hydrogen tartrate (Sigma, Poole, Dorset, UK), WIN55,212-2 mesylate (Tocris Cookson, Bristol, UK) and AM251 (N-(piperidin-1-yl)-5-(4-isodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide; Tocris, Bristol, UK). Nicotine was dissolved in sterile saline and then the pH of the solution was adjusted to 7.2 with NaOH (0.1 normal solution). Nicotine was injected subcutaneously (s.c.) at a volume of 1 ml/kg. WIN55,212-2 and AM251 were dissolved in dimethyl sulphoxide (DMSO; up to 10% v/v) and sterile 0.9% saline and a drop of Tween 80, which also was used as DMSO (10% DMSO; 0.6 μl/rat) or vehicle respectively. WIN55,212-2 and AM251 were injected into the BLA at a volume of 0.6 μl/rat. In the experiments where the animals received one or two injections, the control groups also received one or two saline or vehicle injections. The time intervals of drug administrations and the drugs' doses were based on our pilot experiments and previous studies (Rezayof et al., 2011; Walters et al., 2006).

2.4. Conditioned place preference apparatus

The place preference apparatus and procedure were conducted as described previously, using a minor modification of a procedure according to Carr and White (1983), and with minor modification. Briefly, two large conditioning compartments A and B (40 × 30 × 30 cm) were connected by a communicating tunnel (compartment C: 40 × 15 × 30 cm) that differ in color and flour texture. The compartment A was white with black horizontal stripes 2 cm wide on the walls and also had a textured floor. The other compartment (B) was black with vertical white stripes 2 cm wide and also had a smooth floor. Compartment C was painted red and this smaller tunnel allows animals access to both compartments. It had removable wooden partition that separated it from the other compartments and could be opened allowing animals entrance into each of the two compartments (A and B).

2.5. Place conditioning

In this experiment, we used the unbiased procedure of CPP paradigm. The experiments took place on 5 consecutive days involving three distinct phases: pre-conditioning (introduction session), conditioning (acquisition sessions) and post-conditioning (testing session).

2.5.1. Pre-conditioning

On day 1, each animal was placed into the compartment C and the guillotine door was removed. The animal was allowed to move freely between the compartments for 15 min. The time spent by the animals in each compartment was computed to assess any baseline preferences for A or B compartment prior to nicotine administration. In the particular experimental setup used in this study, the animals did not show an unconditioned preference for either of the compartments. Therefore, the animals were randomly assigned to one of two groups for place

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