Neuroscience Letters 556 (2013) 10–14

Contents lists available at ScienceDirect

Neuroscience Letters

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

Involvement of dopaminergic receptors of the rat nucleus accumbens in decreasing the conditioned place preference induced by lateral hypothalamus stimulation

Abbas Haghparast[a,*], Alireza Omranifard[a], Reza Arezoomandan[a], Mohadeseh Ghalandari-Shamami[a], Zahra Taslimi[a], Abbas Ali Vafaei[b], Ali Rashidy-Pour[b,**]

[a] Neuroscience Research Center, Shahid Beheshti University of Medical Sciences, P.O. Box 19615-1178, Tehran, Iran
[b] Laboratory of Learning and Memory, Research Center and Department of Physiology, School of Medicine, Semnan University of Medical Sciences, Semnan, Iran

HIGHLIGHTS

- Intra-accumbal D1 receptors involve in place preference induced by LH stimulation.
- Blockade of D2 receptors in the NAc could decrease the LH stimulation-induced CPP.
- Intra-accumbal D1/D2 receptor antagonists alone could not induce place conditioning.

ARTICLE INFO

Article history:
Received 9 July 2013
Received in revised form 29 August 2013
Accepted 26 September 2013

Keywords:
Reward
Lateral hypothalamus
Nucleus accumbens
Dopamine receptor
Conditioned place preference
Rat

ABSTRACT

Our previous study showed that chemical stimulation of the lateral hypothalamus (LH) by carbachol can produce conditioned place preference (CPP) in rats. Also, it has been indicated that orexin activates the mesolimbic dopamine projecting neurons to the nucleus accumbens (NAc) and promotes the development of reward in rodents. Therefore, in this study, we tried to determine the role of intra-accumbal D1 and D2 dopamine receptors in the development (acquisition) of reward-related behaviors induced by chemical stimulation of the LH. Eighty-eight adult male Wistar rats were unilaterally implanted by two separate cannulae into the LH and NAc. For chemical stimulation of LH, carbachol (250 nmol/0.5 μl saline) was microinjected once daily during 3-days conditioning phase (acquisition period) of CPP paradigm. In the next experiments, different doses of D1 receptor antagonist, SCH23390 (0.25, 1 and 4 μg/0.5 μl saline) or sulpiride (0.25, 1 and 4 μg/0.5 μl DMSO) as a D2 receptor antagonist were unilaterally microinjected into the NAc, 5 min prior to LH stimulation. One-way ANOVA showed that intra-accumbal administration of SCH23390 or sulpiride can decrease the development of LH stimulation-induced CPP in the rats. However, this decrease is more effective after blockade of the D2 dopamine receptor in the NAc. It seems that the dopaminergic system in this area is involved in place preference induced by LH stimulation.

1. Introduction

Orexins (also known as hypocretins) are neuropeptides made in hypothalamic neurons that have recently been shown to be involved in many behavior such as feeding, reward, stress, pain, arousal, maintenance of waking, narcolepsy/cataplexy and arousal [13,14,23,27]. Orexinergic neurons in lateral hypothalamus (LH) are involved in reward processing and addictive behaviors [3]. Experimental evidence indicates that chemical stimulation of LH by carbachol can produce conditioned place preference (CPP) in rats [27]. In a previous study, we have shown administration of orexin into the ventral tegmental area (VTA) could induce CPP and blockade of D1/D2 receptors in the nucleus accumbens (NAc) inhibited this effect of orexin [26]. Considerable evidences show that the VTA, as a major source of dopamine projecting neurons to cortical and limbic regions, has a major role in cognitive and motivating aspects of reward and addiction [16,28]. Projecting neurons from the VTA to NAc are essential for rewarding effects of drug addiction and it is indicative of important role of mesolimbic system in the reward system [28].

* Corresponding author. Tel.: +98 21 2243 1624; fax: +98 21 2243 1624.
** Co-corresponding author. Tel.: +98 231 3354186; fax: +98 231 3354186.
E-mail addresses: haghparast@yahoo.com (A. Haghparast), rashidy-pour@sem.ums.ac.ir (A. Rashidy-Pour).

0304-3940/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.neulet.2013.09.062

The NAc receives dopaminergic input from the VTA and glutamatergic input from regions such as the prefrontal cortex (PFC), amygdala, and hippocampus. NAc has critical role in behavior of motivational and reward system [7,16]. It had been shown that increased activity of dopamine neurons in the VTA could increase dopamine release in the NAc [17,19], and drug reward and natural reward are related with increased intrasynaptic levels of dopamine in the NAc [11]. So, dopamine receptors located in this area have an important role in motivation and reward, and these functions are mediated by activating two group-specific receptors, D1- and D2-like receptors [20]. While administration of dopamine receptors agonists into the NAc induce place preference [8], intra-accumbal injection of dopamine receptors antagonists or lesion of dopaminergic terminals in this area suppress the rewarding effect of morphine, amphetamine or cocaine [8,16]. Also, several studies have shown that intra-NAc injection of D2-like antagonist or D1-like agonist precipitates signs of somatic opiate withdrawal [8]; in addition morphine cannot induce place preference in mice without intra-accumbal D2 receptors [18]. As for the role of intra-accumbal D1/D2 dopamine receptors in rewarding processes and also the rewarding effect of LH; the interaction between these systems are unknown. Therefore, in the present study, we tried to examine the role of intra-accumbal D1 and D2 dopamine receptors in the development of CPP induced by microinjection of carbachol, as a cholinergic agonist and chemical stimulator agent, into the LH in rats.

2. Materials and methods

2.1. Animal

Animals were housed in groups of four per cage and brightness plan of animal house was a 12/12 h light/dark cycle with free access to food and tap water. Eighty-eight adult male albino Wistar rats (Pasteur Institute, Tehran, Iran) weighing 200–280 g were used in these experiments. The animals were randomly assigned to different experimental groups. Each animal was used only once. Rats ware accustomed to their new environment and handled for one week before the experimental procedure was started. All experiments were executed in accordance with the guide for the care and use of laboratory Animals (National Institutes of Health Publication No. 80-23, revised 1996) and were approved by the Research and Ethics Committee of Shahid Beheshti and Semnan Universities of Medical Sciences.

2.2. Drugs

The following drugs were used in the present study: carbachol (Sigma–Aldrich, USA) as a cholinergic agonist, and SCH23390 (Tocris Bioscience, Bristol, UK) as a D1 receptor antagonist, were dissolved in normal saline as a vehicle. Sulpiride (Tocris Bioscience, Bristol, UK) as a D2 receptor antagonist was dissolved in 10% dimethyl sulfoxide, DMSO (Sigma–Aldrich, Germany) as a vehicle. Control animals received either saline or 10% DMSO.

2.3. Stereotaxic surgery

All surgical procedures were conducted under Ketamine-Xylazine (100 mg/kg Ketamine-10 mg/kg Xylazine) anesthesia. Animals were placed into the stereotaxic device (Stoelting, USA), the scalp was retracted, and the area surrounding bregma was cleaned and dried. In addition, lidocaine with epinephrine (0.2 ml) was injected in several locations around the incision. Stainless steel, 23-gauge guide cannulae were unilaterally implanted 1 mm above the intended site of injection (LH and NAc) according to atlas of rat brain [29]. Stereotaxic coordinates for the LH (cannulae 23-gauge, 12 mm) were AP =3 mm caudal to bregma, Lat = ±1.6 mm and DV = 8.8 mm ventral from the skull surface, and 1–1.3 mm anterior to the bregma, ±0.8 mm lateral to the sagittal suture and 6.8–7 mm down from top of the skull unilaterally for the NAc (cannulae 23-gauge, 11 mm, guide cannula was 1 mm above the appropriate injection place). The guide cannulae were secured in place using two stainless steel screws anchored to the skull and dental acrylic cement. After the cement was completely dried and hardened, two stainless steel stylets were used to occlude the guide cannulae during recovery period. Penicillin-G 200,000 IU/ml (0.2–0.3 ml/rat, single dose, intramuscular) was administered immediately after surgery. Animals were individually housed and allowed to recover for 5–7 days before experiments.

2.4. Microinjection procedure

Microinjections were performed by 30-gauge injector cannulae (1 mm below the tip of the guide cannulae). Polyethylene tubing (PE-20) was used to attach injector cannula to the 1-μl Hamilton syringe. Drug solutions or vehicles unilaterally were slowly administered in a total volume of 0.5 μl/rat over a period of 60 s into the nuclei. Needles were left in place for an additional 60 s to facilitate diffusion of the drugs and prevented drug backflow, and then the stylets were reinserted into the guide cannulae. During the infusion procedure, the experimenter loosely held the animals.

2.5. Conditioning place preference apparatus and paradigm

CPP paradigm was used to evaluate the effects of intra-NAc administration of dopamine D1 and D2 receptors antagonists on the intra-LH carbachol-induced place preference. This paradigm has been described in our previous works in detail [9,12,27]. However, in this study, it is explained briefly.

2.5.1. Apparatus

The testing apparatus is consisted of three wooden compartments. Two compartments were identical in size (30 cm × 30 cm × 40 cm) but different in shading and texture. Compartment A was white with black horizontal stripes 2 cm wide on walls and also had a textured floor. Compartment B was black with vertical white stripes 2 cm wide and also had a smooth floor. The third compartment (C) was a red tunnel (30 cm × 15 cm × 40 cm). It protruded from the rear of two large compartments and connected the entrances to them.

2.5.2. Behavioral testing

CPP consisted of a 5-day schedule with three distinct phases: pre-conditioning, conditioning and post-conditioning. This method (unbiased design) was similar to that used in previous studies.

Pre-conditioning phase. During this phase (day 1), each animal was placed in compartment C with the guillotine door removed to allow access to entire apparatus for 10 min. Each animal displacement was recorded. In the experimental setup used in this study, the animals did not show any preference for either of the compartments.

Conditioning phase. This phase started 1 day after pre-conditioning phase. It consisted of six, 30-min sessions (three saline and three drug pairing) in a 3-day schedule. These sessions were conducted twice each day (from day 2 to day 4) with a 6-h interval. On each day, separate groups of animals received a conditioning session with drug (administration of carbachol in to the LH) and another with saline. During 30-min session intervals for drug/saline, the animals were confined to one compartment by closing the removable wall. Treatment compartment and order of presentation of drug/saline were counterbalanced for either group.