Neuroscience Letters 541 (2013) 138–143

Contents lists available at SciVerse ScienceDirect

Neuroscience Letters

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

Intrahippocampal administration of D2 but not D1 dopamine receptor antagonist suppresses the expression of conditioned place preference induced by morphine in the ventral tegmental area

Abbas Haghparast[a,*], Mohammad-Hossein Esmaeili[b,**], Zahra Taslimi[a], Mojtaba Kermani[c], Saeid Yazdi-Ravandi[a], Amir-Mohammad Alizadeh[a]

[a] Neuroscience Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[b] Cellular and Molecular Research Center & Department of Physiology, Qazvin University of Medical Sciences, Qazvin, Iran
[c] Physiology-Pharmacology Research Center, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

HIGHLIGHTS

- Intra-CA1 D2 dopamine receptors are involved in the expression of morphine-induced CPP.
- Blockade of D1 receptors in CA1 had no effect on the expression of morphine-CPP.
- Intra-CA1 injection of D1/D2 receptor antagonists alone could not induce CPP.

ARTICLE INFO

Article history:
Received 18 November 2012
Received in revised form 28 February 2013
Accepted 1 March 2013

Keywords:
Reward
Hippocampus
Ventral tegmental area
Dopaminergic system
Opioidergic system
Expression
Conditioned place preference
Rat

ABSTRACT

The ventral tegmental area (VTA) as a major source of dopamine neurons projecting to cortical and limbic regions has a crucial role in reward and addiction. The current study assessed the role of D1 and D2 receptors within the dorsal hippocampus (CA1) in the expression of conditioned place preference (CPP) by intra-VTA morphine in the rats. In the present study, 160 adult male albino Wistar rats weighing 220–290 g were bilaterally implanted by two cannulae into the CA1 and VTA. The CPP paradigm was done and animal displacement, conditioning score and locomotor activity were recorded. For blocking the dopamine D1/D2 receptors in the dorsal hippocampus, SCH23390 (0.02, 0.05, 0.2 and 0.5 μg per side) or sulpiride (0.25, 0.75, 1.5 and 3 μg per side) were microinjected into the CA1, just 5 min before the CPP test on the post-conditioning day. All animals received intra-VTA morphine (1 μg per side) during 3-days conditioning phase. Our results showed that sulpiride (1.5 and 3 μg) but not SCH23390 in the dorsal hippocampus significantly decreased the expression of CPP induced by intra-VTA morphine ($p < 0.001$). Intra-CA1 administration of these antagonists alone, in all doses, could not induce CPP. We suggest that D2 receptors in the CA1 region of hippocampus have a key role in the expression of CPP induced by morphine at the level of the VTA and there is a relationship between dopaminergic D2 receptors and opioidergic systems in these areas in reward circuit.

1. Introduction

It is now well established that almost all drugs of abuse converge on a common circuitry in the brain which includes the ventral tegmental area (VTA), nucleus accumbens (NAc), hippocampus, hypothalamus and prefrontal cortex [15]. The mesolimbic dopaminergic system is necessary for the acquisition of morphine-induced CPP [35,34]. The hippocampus and the VTA form a dopaminergic loop, which may regulate some kind of information into the long-term memory that affects hippocampal-dependent learning [17]. Dopamine D1 receptors have an important role in functional interaction between the VTA and the hippocampus [22]. Activation of the VTA increases dopamine (DA) release in the hippocampus and seems to have a pivotal role in hippocampal plasticity [11,30]. The VTA is an important site for synaptic modifications involved in learning and memory to associate morphine exposure with a specific environment [9]. It has also been suggested that the VTA is an important area for reward-related learning [35] through the dopaminergic projections to the NAc and hippocampus.

* Corresponding author at: Neuroscience Research Center, Shahid Beheshti University of Medical Sciences, P.O. Box 19615-1178, Tehran, Iran. Tel.: +98 21 2243 1624; fax: +98 21 2243 1624.
** Co-corresponding author at: Cellular and Molecular Research Center & Department of Physiology, Qazvin University of Medical Sciences, Qazvin, Iran. Tel.: +98 281 3336005; fax: +98 281 3336005.
E-mail addresses: Haghparast@yahoo.com (A. Haghparast), Esmail66@yahoo.com (M.-H. Esmaeili).

0304-3940/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.neulet.2013.03.001

Dopamine conducts its action by activating two group-specific receptors, D1-like and D2-like, both of which belong to the family of G-protein coupled receptors [20]. These two types of dopamine receptor are found in both the hippocampus [20] and the VTA [2]. It has been reported that microinjections of D1 antagonists into the VTA can disrupt the development of amphetamine sensitization, suggesting that DA systems within the midbrain mediate the neuroadaptations that are responsible [32]. Evidently, blockade of D1 receptors disrupts morphine induced conditioned place preference, whereas such effect is unseen with the D2/D3 receptors [1,16,28]. Moreover, morphine does not induce place preference in mice lacking D2 receptors [19]. Acute injections of either D1 or D2 receptor antagonists have been reported either not to affect heroin self-administration or to affect only at doses that also affect motor function or response rate [31]. Opiates augment DA release by suppressing GABA inhibitory input to DA neurons in the VTA [9,12].

The hippocampus receives dopaminergic input from the substantia nigra and the VTA [27]. Dopamine receptors in the dorsal hippocampus have an important role in mediating morphine reward [24] and the hippocampal CA1 region receives a dopaminergic input from the VTA [10,11]. Previous studies showed that the hippocampus is important for learning tasks, such as conditioned place preference (CPP), that use positive reinforcement [13,18,24]. Several studies suggest that both D1- and D2-like receptors in the CA1 region of the dorsal hippocampus are involved in reward-related learning and have an important role in the acquisition and expression of morphine-induced place preference [24]. In our previous study, we found that both D1 and D2 receptors have key role in the development of morphine induced CPP at the level of the VTA [4]. Hence, the aim of this work was to identify the effect of inhibition of the dopamine D1/D2 receptors located in the rat dorsal hippocampus (CA1) on expression of condition placed preference followed by morphine administration into the ventral tegmental area.

2. Materials and methods

2.1. Animals

One hundred and sixty adult male albino Wistar rats (Pasteur Institute, Tehran, Iran) weighting 200–300 g were used in these experiments. Animals were caged in group of 3–4 at $23 \pm 1\,^{\circ}C$, 60% humidity, and maintained in a 12-h light/dark cycle (light on 07:00) with food and water freely available. Each animal was used only once. All experiments were executed in accordance with the Guide for the Care and Use of Laboratory Animals (National Institute of Health Publication No. 80-23, revised 1996).

2.2. Stereotaxic surgery

Animals were anesthetized with intraperitoneal injection of ketamine (100 mg/kg) and xylazine (10 mg/kg) and implanted with two ipsilateral chronic indwelling guide cannulae, one inside the VTA and one inside the dorsal hippocampus (CA1). These cannulae were secured in place using two stainless steel screws anchored to the skull and dental acrylic cement. The related coordinates were determined from Paxinos and Watson [33] as 3–3.5 mm posterior to the bregma, ±1.8–2 mm lateral to the midline, and 2.8–3 mm ventral of the dorsal surface of the skull for CA1 and 4.7–5 mm posterior to the bregma, ±0.8–0.9 mm lateral to the midline and 8.2–8.4 mm from the top of skull for the VTA (guide cannulae were 1 mm above the appropriate injection place).

2.3. Drugs

Morphine sulfate was obtained from TEMAD (Tehran, Iran). SCH23390 (D1 receptor antagonist) and sulpiride (D2 receptor antagonist) were purchased from Tocris Bioscience (Bristol, UK). Morphine and SCH23390 were dissolved in physiological saline and Sulpiride was dissolved in dimethyl sulfoxide (DMSO; Sigma–Aldrich, Germany). All drugs prepared immediately before use.

2.4. Conditioning place preference apparatus and paradigm

2.4.1. Apparatus

The testing apparatus consisted of three wooden compartments [3,6,7,21]. Two compartments were identical in size (30 cm × 30 cm × 40 cm) but differed 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 had a smooth floor. The third compartment (C) was a passage painted in red (30 cm × 15 cm × 40 cm). It protruded from the rear of two large compartments and connected the entrances to them.

2.4.2. Behavioral testing

Conditioned place preference consisted of a 5-day schedule with three phases: pre-conditioning, conditioning and post-conditioning.

2.4.2.1. Pre-conditioning phase. During this phase (day 1), each animal was placed in compartment C with the guillotine door removed to allow access apparatus for 10 min. In this phase, we recorded each animal displacement.

2.4.2.2. Conditioning phase. It consisted of six, 30-min sessions (three for 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 morphine and another received saline. During 30-min session intervals for morphine/saline, the animals were confined to one compartment by closing the removable wall. Treatment compartment and order of presentation of morphine/saline were counterbalanced for either group.

2.4.2.3. Post-conditioning or testing phase. This phase was carried out on day 5 (the preference test day), 1 day after the last conditioning session, in a morphine free state. Each animal was tested only once. The removable wall was raised and rat could access the entire apparatus for 10 min. The mean time spent for each rat in both compartments during a 10-min period was recorded by a 3CCD camera (Panasonic Inc., Japan) and analyzed by the Ethovision software (Version XT7, Noldus Information Technology, the Netherlands) in order to calculate the conditioning score as the preference criteria; the time spent in the drug-paired place minus the time spent in saline-paired place. In control and experimental groups, total distance traveled was also recorded.

2.5. Experimental design

Twenty groups of animals were used (8 rats in each group) in these experiments. During the conditioning phase animals received a bilateral microinjection of the morphine sulphate (1 μg per 0.3 μl saline) or saline (0.3 μl) into the VTA [4]. Later on, 5 min prior to start of the trial session, different doses of the SCH23390 or sulpiride were bilaterally microinjected into the CA1 region of hippocampus (0.5 μl per side).