Behavioural Brain Research 231 (2012) 111–115

Contents lists available at SciVerse ScienceDirect

Behavioural Brain Research

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

Research report

Role of D1/D2 dopamine receptors in the CA1 region of the rat hippocampus in the rewarding effects of morphine administered into the ventral tegmental area

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ARTICLE INFO

Article history:
Received 26 January 2012
Received in revised form 27 February 2012
Accepted 28 February 2012
Available online 6 March 2012

Keywords:
Dorsal hippocampus
Ventral tegmental area
Morphine
Dopamine antagonists
Conditioned place preference
Rat

ABSTRACT

Considerable evidences show that the VTA, as a major source of dopamine neurons projecting to cortical and limbic regions, has a major role in cognitive and motivating aspects of addiction. The current study assessed the ability of the selective D1 receptor antagonist SCH 23390 and D2 receptor antagonist sulpiride administrated into the CA1 region of hippocampus (dorsal hippocampus) to alter the rewarding effects of intra-VTA administration of morphine using the conditioned place preference (CPP). After bilaterally implantation of cannulae into the CA1 and/or VTA in adult male Wistar rats weighing 210–310 g, dose–response effects of different doses of intra-VTA morphine (0.03, 0.1, 0.3, 1 and 3 μg/side) on CPP paradigm were evaluated and animal displacement, conditioning score and locomotor activity were recorded by Ethovision software. In the next experiments, SCH 23390 (0.02, 0.05, 0.2 and 0.5 μg/side) or sulpiride (0.25, 0.75, 1.5 and 3 μg/side) were injected into the CA1, 5 min after intra-VTA injection of morphine during 3 days conditioning phase. Our results showed that intra-VTA morphine dose-dependently induces CPP in rats. Moreover, the blocking D1 and D2 receptors in the dorsal hippocampus decreased intra-VTA morphine-induced CPP significantly ($P < 0.01$). Intra-CA1 administration of these antagonists alone, in all doses, could not induce CPP. We suggest that D1 and D2 receptors in the CA1 region of hippocampus have a key role in the development of CPP induced by morphine at the level of the VTA. It seems that there is an interaction between dopaminergic and opioidergic systems in these areas in reward circuit.

1. Introduction

There is an emerging consensus that drug addiction is a form of maladaptive learning. Drugs of abuse usurp the neuronal circuitry involved in motivation and reward, leading to aberrant engagement of learning processes. Considerable evidence from animal models and recently from human beings shows that most drugs of abuse converge on a common circuitry in the brain. These regions include the ventral tegmental area (VTA), nucleus accumbens (NAc), hippocampus, hypothalamus and several regions of frontal cortex, such as prefrontal cortex [1]. Among these areas, the VTA, as a major source of dopamine (DA) neurons' projecting to cortical and limbic regions has a major role in cognitive and motivating aspects of addiction [2]. Opiates are known to interact with DA systems by suppressing GABA inhibitory input to DA neurons in the VTA, thereby augmenting DA release [3,4]. On the other hand, recent reports support the view that the hippocampus is also involved in addiction to opiates and other drugs. Some studies suggest that the hippocampus is important for reward-related learning tasks, such as conditioned place preference (CPP), which is used in animal studies to evaluate preferences for environmental stimuli been associated with a positive or negative reward [5–10]. It has been shown that drug-seeking behaviors without using the environmental cues modulate the hippocampus functions. Vorel et al. indicated that addictive memory induced by electrical stimulation of hippocampus induced drug-seeking behaviors and no need to existence of environmental cues [11].

The hippocampus receives dopaminergic input which comes from both the substantia nigra and the VTA [12]. The distribution of input is uneven being particularly strong in the subiculum, hilus, and the stratum lacunosum-moleculare of the CA1 region. It has been shown that activation of the VTA leads to dopamine release in the hippocampus and seems to have a pivotal role in hippocampal plasticity [13,14]. In contrast, the hippocampus is indirectly connected to the VTA via a polysynaptic pathway involving the subiculum, NAc, and ventral pallidum. Hippocampal activation leads to novelty-associated VTA-dopamine release, which could, in turn, affect target structures such as the hippocampus itself

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doi:10.1016/j.bbr.2012.02.050

[15]. Dopamine is a predominant catecholamine neurotransmitter in the central nervous system, which plays an important role in controlling a variety of functions, such as locomotor activity, cognition, and reward [16]. It exerts its influence by activating two group-specific receptors, namely D1-like and D2-like, both of which belong to the family of G-protein coupled receptors [16]. These two types of receptors are found in both the hippocampus [16] and the VTA [17]. In addition, localization studies indicate that, within the hippocampus, DA receptors are mostly located in the dorsal part (CA1). This is in line with histological studies showing predominance of DA neuron innervations in the dorsal hippocampus [18]. Considerable evidence from animal models indicates that the intact hippocampus moderates the effect of reward, probably by opposing catecholamine mechanisms [13,15,19]. Indeed, hippocampal damage is found to influence dopaminergic ascending systems as assessed by behavioral and biochemical methods [20,21]. Although the hippocampus plays a critical role in memory encoding and is involved in drug addiction, little is known about the role of hippocampus in reward-related behaviors. Therefore in the present study, we tried to evaluate the role of dopamine D1/D2 receptors located in the rat dorsal hippocampus (CA1) in conditioned placed preference induced by morphine in the ventral tegmental area.

2. Materials and methods

2.1. Animals

Two hundred and eight adult male albino Wistar rats (Pasteur Institute, Tehran, Iran) weighting 220–310 g were used in these experiments. Animals were caged in groups of 2–3 at 23 ± 1 °C, 60% humidity, and maintained in a 12 h light/dark cycle (light on 07:00) with standard laboratory food and water freely available in their home cages. Each animal was used only once and killed immediately after the experiment. 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) and were approved by the Research and Ethics Committee of Shahid Beheshti University of Medical Sciences.

2.2. Stereotaxic surgery

Experimental animals were prepared with guide cannula implantation (23 guage needle) at least 8–10 days before their use. The rats were anesthetized with intraperitoneal (i.p.) injection of ketamine 10% (100 mg/kg) and xylazine 2% (10 mg/kg) and cannula were stereotaxically (stereotaxic apparatus, Stoelting, USA) implanted in the dorsal hippocampus (CA1) and VTA. The related coordinates was determined from Paxinos and Watson [22] as 3–3.5 mm (depending on body weight) posterior to the bregma, ±1.8–2 mm lateral to the midline, and −2.8 to −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). The guide cannulae were secured in place using two stainless steel screws anchored to the skull and dental acrylic cement. They were sealed with occluding stylette in recovery period (8–10 days).

2.3. Drugs

Morphine sulfate was obtained from TEMAD (Tehran, Iran) and dissolved in physiological saline. SCH 23390 and sulpiride were purchased from Tocris Bioscience (Bristol, UK). All drugs were prepared immediately before use.

2.4. Conditioning place preference apparatus and paradigm

2.4.1. Apparatus

The testing apparatus consisted of three wooden compartments [5,6,9]. 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 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.

2.4.2. Behavioral testing

Conditioned place preference consisted of a 5 day schedule with three distinct 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 to entire apparatus for 10 min. Each animal displacement was recorded.

2.4.2.2. 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 morphine and another with 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. For testing, 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 using the Ethovision software (Version XT7), a video tracking system for automation of behavioral experiments (Noldus Information Technology, the Netherlands) in order to calculate the conditioning score as the preference criteria; the time spent in the drug-paired side minus the time spent in saline-paired side on the post-conditioning (test) day. No injection was given in the acquisition tests on post-conditioning day (test day). Total distance traveled for each animal was also recorded in control and experimental groups.

2.5. Experimental design

2.5.1. Effect of intra-VTA administration of morphine on conditioned place preference paradigm

In this experiment, we determined a dose–response function for morphine place conditioning. Five doses of morphine sulfate (0.03, 0.1, 0.3, 1 and 3 μg/side) were administrated into the VTA during three days of conditioning session (acquisition). In control group, animals received saline (0.3 μl/side) instead of morphine. CPP scores and locomotor activity were measured during 10 min period on the test day. All control and experimental groups were consisting of 8 animals.

2.5.2. Effect of D1 receptor antagonist, SCH 23390, pretreatment on the acquisition of intra-VTA morphine-induced place preference

Ten groups of animals were used (8 rats in each group) in this set of experiments. In experimental groups, animals received different doses of SCH 23390 (0.02, 0.05, 0.2 and 0.5 μg/side) into the CA1 region of hippocampus, prior to intra-VTA administration of morphine (1 μg/0.3 μl) during the conditioning sessions. In control group, animals received saline (0.5 μl/side) instead of SCH 23390. On the other hand, in respective SCH 23390-control groups ($n = 8$ in each group), animals received different doses of SCH 23390 (0.02, 0.05, 0.2 and 0.5 μg/side) or saline (0.5 μl) as a vehicle into the CA1, prior to intra-VTA administration of saline (0.3 μl) during the conditioning sessions.CPP scores and locomotor activity were measured 24 h after the last day after conditioning session (post-conditioning day), with no preceding injection.

2.5.3. Effects of D2 receptors antagonist, sulpiride, pretreatment on the acquisition of morphine-induced place preference in the VTA

In this set of experiments, to evaluate the role of D2 receptors within the dorsal hippocampus in morphine-induced CPP in the VTA, five groups of animals ($n = 8$ in each group) received different doses of sulpiride (0.25, 0.75, 1.5 and 3 μg/side) or DMSO (0.5 μg/side) into the CA1 region of hippocampus, prior to intra-VTA administration of morphine (1 μg/0.3 μl) during the acquisition period (conditioning sessions). Moreover, in respective sulpiride-control groups (8 rats in each group), animals received different doses of sulpiride (0.25, 0.75, 1.5 and 3 μg/side) or DMSO (0.5 μl) as a vehicle into the CA1, prior to intra-VTA administration of saline (0.3 μl) during the conditioning sessions.CPP scores and locomotor activity were measured on the test day (post-conditioning day), with no preceding injection.

2.6. Statistics

Data are expressed as mean ± SEM (standard error of mean). In order to compare the conditioning scores or locomotor activity obtained in all control and experimental groups, one-way analysis of variance (ANOVA) and randomized blocks model followed by post hoc analysis (Dunnett's or Newman–Keuls test) were used, as needed. *P*-values less than 0.05 were considered to be statistically significant.

2.7. Histological verification

After completion of the experiments, rats were sacrificed and the cannulae sites were confirmed. Animals were deeply anesthetized with ketamine and xylazine. Then, they were transcardially perfused with 0.9% saline and 10% formaldehyde solution prior to sectioning. The neuroanatomical location of cannulae tips were confirmed using the rat brain atlas [22]. The data reported here are only from animals in which the placements of cannulae tips were histologically verified.