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Research report

Involvement of D1- and D2-like dopamine receptors in the dentate gyrus in the acquisition, expression, and extinction of the morphine-induced conditioned place preference in rats

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ABSTRACT

In the current study, we investigated the role of intra-dentate gyrus (DG) administration of D1 and/or D2 receptor antagonists on the expression, acquisition, and extinction of morphine-CPP. Cannulae were implanted bilaterally into the DG region in male Wistar rats and CPP was induced by the subcutaneous injection of morphine (5 mg/kg) during a 3-day conditioning phase. Three experimental designs were separately employed in the CPP paradigm during the acquisition, expression and extinction phases, and different doses (0.25, 1, or 4 μg/0.5 μl saline) of SCH23390, as a selective D1-like receptor antagonist, and sulpiride (0.25, 1, or 4 μg/0.5 μl DMSO), as a selective D2-like receptor antagonist, were bilaterally microinjected into the DG region. Conditioning scores and locomotor activities were recorded during the test. Results showed that the injection of the antagonists into the DG region dose-dependently attenuated the acquisition and expression of the morphine-induced CPP and sulpiride revealed prominent behavioral results compared to SCH23390 in both mentioned phases. Moreover, the blockade of D1- and D2-like receptors shortened the extinction phase of the morphine-induced CPP but had no effect on the locomotor activity. We found that the dopamine receptors within the DG region are involved in the acquisition and expression of morphine-CPP and have a critical role in the association between a morphine-paired context and the rewarding proprieties of morphine.

1. Introduction

Behavioral evidence shows that drug craving, as a complex phenomenon involving many biological and social factors, can result in drug seeking and relapse to drug abuse even long-time after withdrawal [1]. The development of tolerance and dependence to opiates is a phenomenon that involves learning and memory mechanisms [2]. Research using the conditioned place preference (CPP) model [3,4] has shown that among the involved areas in the psychological dependence on opioids, the mesolimbic dopaminergic pathway, consisting the dopaminergic loop between the hippocampus (HIP) and ventral tegmental area (VTA), plays a prominent role in processing reward associated information [5–7]. The HIP has a prominent role in learning and memory [8–10] and the expression and acquisition (development) of reward-associated learning in response to morphine, cocaine, and nicotine [2,11–13]. Local infusion of morphine into the HIP [14] and methamphetamine into the dorsal HIP induce place preference in the CPP test [15]. Dopamine receptors (DARs) in the HIP influence the expression of synaptic plasticity and HIP-dependent LTP and behavior [6]. During exploratory behaviors, the dentate gyrus (DG) region of the HIP fires at high rates and the reward salience of an external stimulus is signaled by the release of dopamine from the VTA projections to the molecular layer of the DG region [16]. Previous studies have shown that colchicine-induced damage to the DG region suppresses the acquisition and expression of cocaine-induced CPP [5].

DARs subtypes are divided into two major subclasses: D1-like (D1 and D5) and D2-like (D2, D3, and D4) receptors [17]. The morphine-CPP is inhibited by the injection of SCH23390, as a D1 receptor antagonist [18]. Previous experiments showed that the injection of D1 (SKF-38393) and D2 (sulpiride) DARs agonists and antagonists into the central amygdala [19] or dorsal HIP [20] potentiates and inhibits morphine-CPP, respectively [21]. The stimulation of the VTA gives rise

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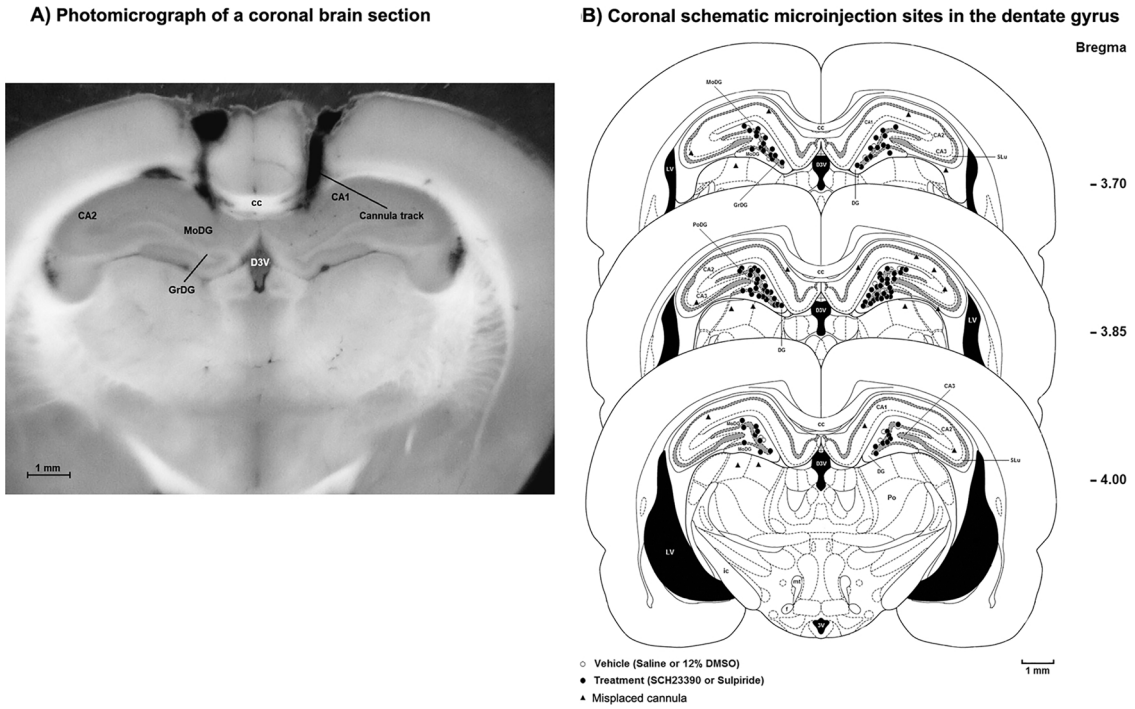

Fig. 1. (A) Photomicrograph of a coronal brain section with the tracks of the guide cannulae visible in both hemispheres from an animal in the extinction group. Infusion sites were 1 mm lower in the area of the dentate gyrus of the hippocampus (B) Three coronal schematic microinjection sites in the dentate gyrus region (○= saline or DMSO microinjection and ●= SCH23390 or sulpiride microinjection and ▲= misplacement). All the microinjections were performed bilaterally. **cc**, corpus callosum; **CA1**, field CA1 of hippocampus; **CA2**, field CA2 of hippocampus; **CA3**, field CA3 of hippocampus; **3 V**, 3rd ventricle; **D3 V**, dorsal 3rd ventricle; **LV**, lateral ventricle; **DG**, dentate gyrus; **SLu**, stratum lucidum of the hippocampus; **GrDG**, granular layer of the dentate gyrus; **MoDG**, molecular layer of dentate gyrus; **PoDG**, polymorph layer of dentate gyrus, **Po**; posterior thalamic nuclear group; **ic**, internal capsule; **mt**, mammillothalamic tract and **f**, fornix. Scale bar is 1 mm.

to state-dependent responses in prefrontal cortical pyramidal neurons [22] and may involve activation of limbic inputs as it does not evoke responses in animals with a ventral hippocampal lesion [23]. Further research indicated that systemic administration of selective D2-like DAR agonists promotes reinstatement [24]. Previous work in our lab showed that intra-CA1 administration of D1 and/or D2 receptor antagonists inhibited the acquisition of morphine-CPP [25]. We have also shown that intra-DG injections of D1- and D2-like receptor antagonists attenuate the morphine-extinguished CPP reinstated by a priming injection of morphine in a dose-dependent manner [26]. In addition, our previous studies emphasised on a role for the DG region in the development of drug abuse and reward processing in addition to its role in memory for place preference [26,27]. Consequently, we hypothesized that the D1- and D2-like receptors within the DG region may be involved in reward-related behaviors and investigated the role of DARs in acquisition, expression, and extinction of morphine-CPP.

2. Materials and methods

2.1. Animals

Adult male Wistar rats (purchased from Pasteur Institute, Iran) weighing 220–280 g were kept in groups of three in cages with free access to chow and tap water. The vivarium was maintained at 12:12 h light/dark cycle and the experiments were conducted during the light part of the circadian cycle. The temperature was controlled at 23 ± 1^{oC}. Different rats were used for the different experiments (please see the design section) and all the experiments were conducted according to 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 University of Medical Sciences (IR.SBMU.PHNS.REC.1396.127), Tehran, Iran. Besides, all efforts were made to minimize animal suffering and reduce the number of animals used to obtain reliable results.

2.2. Stereotaxic surgery

To stereotaxically implant the guide cannulae, the rats were deeply anesthetized with intraperitoneal injection of ketamine (100 mg/kg) and xylazine (10 mg/kg) and were placed in a stereotaxic apparatus (Stoelting, USA). An incision was made along the midline, the scalp was retracted, and the area surrounding bregma was cleaned and dried. Stainless steel guide cannulae were bilaterally implanted 1 mm above the DG region according to the atlas of the rat brain [28]. Stereotaxic coordinates were: 3.85 ± 0.15 mm caudal to bregma; 1.3 mm lateral to midline; 3.4 ± 0.2 mm ventral from the skull surface (Fig. 1A and B). The guide cannulae were anchored to the skull using two stainless steel screws and dental acrylic cement. When the cement was dried and solid, a stainless steel stylet was inserted into each cannula to prevent occlusion during the recovery period (5–7 days). Penicillin-G 200,000 IU/ml (0.2–0.3 ml/rat, single dose, intramuscular) was administered immediately after the surgery.

2.3. Drugs

The following drugs were used in the present study: morphine sulfate (Temad, Iran) and SCH23390 (Tocris Bioscience, UK), a selective D1-like receptor antagonist, were dissolved in sterile saline (0.9%). Sulpiride (Tocris Bioscience, UK), a selective D2-like receptor antagonist, was dissolved in 12% dimethyl sulfoxide (DMSO, Sigma Aldrich, Germany) diluted with normal saline. The rats in separate control groups received either saline or 12% DMSO as a vehicle.