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Research report

Forced swim stress but not exogenous corticosterone could induce the reinstatement of extinguished morphine conditioned place preference in rats: Involvement of glucocorticoid receptors in the basolateral amygdala

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HIGHLIGHTS

- Forced swim stress could significantly induce the reinstatement to morphine.
- Corticosterone as a main stress hormone couldn't induce the morphine reinstatement.
- Glucocorticoid receptor blockade in the BLA inhibit the stress-induced reinstatement.

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ABSTRACT

Addiction is a common psychiatric disease and stress has an important role in the drug seeking and relapse behaviors. The involvement of basolateral amygdala (BLA) in the effects of stress on reward pathway is discussed in several studies. In this study, we tried to find out the involvement of glucocorticoid receptors (GRs) in the BLA in stress-induced reinstatement of extinguished morphine-induced conditioned place preference (CPP) in rats. The CPP paradigm was done in adult male Wistar rats weighing 220–320 g, and conditioning score and locomotor activity were recorded by Ethovision software. Animals received effective dose of morphine (5 mg/kg) daily, during the 3-day conditioning phase. In extinction phase, rats were put in the CPP box for 30 min a day for 8 days. After extinction, animals were injected by corticosterone (10 m/kg) or exposed to forced swim stress (FSS) 10 min before subcutaneous administration of ineffective dose of morphine (0.5 mg/kg) in order to reinstate the extinguished morphine-CPP. To block the glucocorticoid receptors in the BLA, after stereotaxic surgery and placing two cannulae in this area bilaterally, animals received GR antagonist mifepristone (RU38486; 0.3, 3 and 30 ng/0.3 μl DMSO per side) prior to exposure to FSS then each animal received ineffective dose of morphine (0.5 mg/kg) as drug-induced reinstatement. The results revealed that physical stress (FSS) but not exogenous corticosterone can significantly induce reinstatement of extinguished morphine-CPP, and intra-BLA mifepristone prevents the stress-induced reinstatement. It can be proposed that stress partially exerts its effect on the reward pathway via glucocorticoid receptors in the BLA.

1. Introduction

Drug addiction can be considered as a chronic recurrent brain disease characterized by relapse. Clinical researches have indicated that life stress is not only a risk factor in the development of addiction but also a relapse trigger to drug abuse [1,2]. Exposure to stress increases drug seeking behavior and the risk of addictive drug use in human and animal models of drug addiction by the mechanisms that are not completely understood yet. The high rate

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of relapse to opioid use after detoxification is a major clinical problem and remains the primary challenge in treating drug abuse [3]. The reinstatement model is currently used in many laboratories to investigate mechanisms underlying relapse to drug seeking behavior. Indeed, reinstatement in the laboratory animals is induced by conditions that are reported to provoke relapse in humans such as drug priming, presence of drug-associated cues and stress. Stress is known to increase the rewarding effects of opiates [4–6] and has an established role in relapse [7,8]. Stress can play a more effective role in reinstating drug-seeking behavior than re-exposure to the drugs [9]. Previous studies have confirmed the effect of environmental stressors on opiates and psychostimulants reinforcement, reinstatement and discrimination in rats. Stress reliably reinstates heroin seeking after prolonged drug-free periods [7,10,11].

It has been shown that foot-shock stress reinstates heroin-seeking behavior in heroin-experienced and 6-weeks heroin-free animals [12]. The relapse phenomenon can also be investigated by using a conditioned place preference reinstatement approach in which the ability of stimuli to re-establish the extinguished preference for the previous cocaine and morphine-paired environment is examined [13,14]. In mice, the extinguished morphine-induced conditioned place preference can be reinstated by administration of a priming injection of morphine [15,16] or exposure to different stressors such as social stress [14] or forced swim stress [17]. A response to the stress begins with the activation of hypothalamic-pituitary-adrenal (HPA) axis which then leads an increase in glucocorticoid (GC) release. The binding of GCs to the glucocorticoid receptors (GRs) mediate adaptation to stress and regulate termination of the stress response through negative feedback at of the HPA axis level [18]. Chronic stress or impaired GR feedback have been proposed as the leading cause for dysregulation of the HPA axis activity.

Since the basolateral amygdala (BLA) is critical for stimulus-reward learning and cue-induced reinstatement, we suggest that the BLA neurons encode the cue-reward association which then endows the cue with the power to motivate responding to a reward. Studies in humans and rodents suggest that the effect of stress on the emotional processing and memory formation are mediated by the amygdala (AMY) [19]. Specifically, the BLA has been suggested as the locus for memory storage of stressful experiences [20]. GCs enhance the consolidation of emotionally arousing experiences and this requires arousal induced noradrenergic activation of the BLA circuits [21], presumably via a cAMP-dependent protein kinase pathway [22]. The BLA also acts as a critical gateway in mediating stress effects on the other aspects of memory formation, via sending projections to structures such as the prefrontal cortex (PFC) and hippocampus [19]. We hypothesized that the GRs in the BLA have a crucial role in stress conditions, and to test the hypothesis; we investigated the role of the GRs in the BLA. Therefore, in this study, we tried to examine the role of forced swim stress (FSS) and exogenous corticosterone in the stress-induced reinstatement of morphine seeking behavior. For this purpose the paradigm of conditioned place preference (CPP) has been used to study the relapse phenomenon in the rats.

2. Materials and methods

2.1. Animals

Eighty seven adult male albino Wistar rats (Pasteur Institute, Tehran, Iran) weighing 220–320 g were used in these experiments. Animals were housed in groups of three per cage in a 12/12 h light/dark cycle (light on between 7:00 a.m. and 7:00 p.m.) with free access to chow and tap water. The animals were randomly allocated to different experimental groups and used only once. Rats were habituated to their new environment and handled for 1 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 Hormozgan and Shahid Beheshti Universities of Medical Sciences.

2.2. Drugs

In the present study the following drugs were used: morphine sulfate (Temad, Iran) that was dissolved in sterile saline (0.9%), and RU38486 or mifepristone, as a GR antagonist and corticosterone (Sigma-Aldrich, Germany) dissolved in 12% dimethyl sulfoxide (DMSO). Control animals received either saline or 12% DMSO.

2.3. Stereotaxic surgery

Rats were anesthetized by intraperitoneal injection of Xylazine (10 mg/kg), Ketamine (100 mg/kg), and placed into stereotaxic device (Stoelting, USA). An incision was made along the midline, 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. Two stainless steel guide cannulae (23-gauge; 11 mm length) were bilaterally implanted 1 mm above the BLA with these coordinates: 2.8 mm posterior to bregma, ±4.5 mm lateral to the sagittal suture and 8.7 mm down from top of the skull according to the atlas of rat brain [23]. Cannulae were secured with jewelers' screws and dental acrylic cement. After the cement was completely 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) were administered immediately after surgery. Animals were individually housed and allowed to recover for 5–7 days before experiments.

2.4. Intra-BLA injections

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. For RU38486/vehicle microinjection, the animals were gently restrained by hand; the stylets were removed from the guide cannulae and replaced by 30-gauge injector cannulae. The RU38486 solutions or vehicle (12% DMSO) were administered slowly in a volume of 0.3 μl/side over a period of 60 s. Injection needles were left there for an additional 60 s to facilitate diffusion of the drugs, and then the stylets were reinserted into the guide cannulae. All microinjections were bilaterally performed in the BLA.

2.5. Place conditioning apparatus and paradigm

A three-compartment CPP apparatus (30 cm × 30 cm × 40 cm) was used in these experiments [23]. Place conditioning was conducted using an un-biased procedure. The apparatus was made of Plexiglas which was divided into two equal sized but different textured compartments by means of a removable wall, but distinguishable by texture. To provide the tactile difference between the compartments, one of the compartments had a smooth floor while the other compartment had a net-like floor. Two preference compartments were differently striped black and white on their walls. The null compartment was a red tunnel (30 cm × 15 cm × 40 cm) connecting the two preference compartments. In this apparatus, rats showed no consistent preference for none of the large compartments, which supports our unbiased CPP paradigm. This paradigm took place in five consecutive days, which consisted of three distinct phases: pre-conditioning, conditioning