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Research report

Inhibitory effects of forced swim stress and corticosterone on the acquisition but not expression of morphine-induced conditioned place preference: Involvement of glucocorticoid receptor in the basolateral amygdala

Ghassem Attarzadeh-Yazdi[a], Sara Karimi[b], Pegah Azizi[b], Saeid Yazdi-Ravandi[b], Soghra Hesam[b], Abbas Haghparast[b,*]

[a] Department of Physiology, Faculty of Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
[b] Neuroscience Research Center, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, P.O. Box 19615-1178, Tehran, Iran

HIGHLIGHTS

- Physical forced swim stress could attenuate the morphine rewarding properties.
- Exogenous corticosterone could reduce the acquisition of morphine-induced CPP.
- Glucocorticoid receptor (GR) blockade in the BLA reversed stress-induced suppression.
- The effect of corticosterone was diminished by intra-BLA RU38486, GR antagonist.

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ABSTRACT

Addiction is a common chronic psychiatric disease which represents a global problem and stress has an important role to increase drug addiction and relapse. In the present study, we investigated the effects of physical stress and exogenous corticosterone on the acquisition and expression of morphine-induced conditioned place preference (CPP). Also, we tried to find out the role of glucocorticoid receptors (GRs) of basolateral amygdala (BLA) in this regard. In the CPP paradigm, conditioning score and locomotion activity were recorded by Ethovision software. Male adult rats received forced swim stress (FSS) as a physical stress or corticosterone (10 mg/kg; ip) as a dominant stress hormone in rodents, 10 min before morphine injection (5 mg/kg; sc) during three conditioning days (acquisition) or just prior to CPP test in the post-conditioning day (expression). In FSS procedure, animals were forced to swim for 6 min in cylinder filled with water (24–27 °C). To evaluate the role of glucocorticoid receptors in the BLA, different doses of mifepristone (RU38486) as a GR antagonist were injected into the BLA (0.3, 3 and 30 ng/side) during 3-day conditioning phase before FSS or injection of corticosterone in morphine-CPP paradigm. The results showed that FSS and corticosterone reduce the acquisition but not expression of morphine-induced CPP. Moreover, blockade of GRs in the BLA could diminish the inhibitory effects of FSS or corticosterone on the acquisition of morphine-induced CPP. It seems that stress exerts its effect on reward pathway via glucocorticoid receptors in the BLA.

1. Introduction

Drug addiction has been conceptualized as a chronic relapsing disorder characterized by compulsive drug-taking behavior with impairment in social and occupational functioning [1]. All drugs of abuse exert their primary rewarding effects on the mesolimbic dopamine reward pathway which consists of dopamine neurons originating in the ventral tegmental area (VTA) and extending to the nucleus accumbens (NAc) and the prefrontal cortex (PFC) [2]. Psychomotor stimulants, such as opiates cause a release of dopamine in the NAc regardless of their mechanism of action [3]. Addiction is a complex disorder, because many factors contribute to the development and maintenance of this neurological disorder. Stress is one of the key factors in facilitating reward associated with initial drug exposure [4,5]. In addition, the link between reward and stress is further exemplified by the phenomenon of cross sensitization, described by Antelman and colleagues [6].

* 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.
E-mail address: Haghparast@yahoo.com (A. Haghparast).

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Stress activates two systems: (i) the sympatho-adrenomedullar system and (ii) the hypothalamic-pituitary-adrenal (HPA) axis, with specific kinetic properties [7,8]. Activation of HPA axis leads to the secretion of corticotropin-releasing factor (CRF) from paraventricular nucleus (PVN) of the hypothalamus to stimulate the output of adrenocorticotropic hormone (ACTH). It subsequently stimulates the secretion of adrenal glucocorticoids ‐ Cortisol in humans and corticosterone in rodents ‐ into the bloodstream [9]. Corticosterone acts as one of the biological system mediating reward and more recent studies confirm the interaction between glucocorticoids and dopaminergic systems. In fact, it has been shown that an increase in the plasmatic level of glucocorticoids is caused to increase dopamine release [10]. Glucocorticoids bind to two types of receptors, mineralocorticoid receptor (MR) and glucocorticoid receptor (GR) [11,12] in the brain. On the other hand, stress changes the dopamine levels in the brain regions receiving dense VTA inputs like the NAc [13] and basolateral amygdala (BLA). Recent evidence implicate the BLA in learning process about rewards and punishments [14]. The amygdala has also been central to ideas about addiction, where it is proposed to mediate craving and the abnormal attribution of motivational significance to drug-associated cues and contexts [15]. Stress hormones released by an experience can modulate memory strength via the BLA, which in turn acts on sites of memory storage such as the cerebral cortex [8]. Several lines of evidence have implicated the BLA as a substrate for stress-related modulation of memory. Glucocorticoids are secreted during emotionally arousing events and have profound effects on learning and memory that are probably mediated by the BLA [16,17]. Many studies have suggested that the complex of amygdala plays a key role in mediating stress effects on behavioral and hippocampal functions [18].

Previous studies have indicated that chronic stress increases ΔFosB levels in the NAc and BLA [19]. The commonality of effects of stress and reward is considered as a major open question in the field of reward. The conditioned place preference (CPP) is one of the most widespread experimental protocols which is used for measuring drug reward in laboratory [20]. There are some works indicating the effect of stress on CPP [21–24]. Therefore, in this study, we tried to elucidate whether physical stress or corticosterone as a dominant stress hormone has any effect on the acquisition and expression of morphine-induced CPP. Besides, the role of glucocorticoid receptors in the BLA in the development of morphine reward-related behaviors in rats has been investigated.

2. Materials & methods

2.1. Animal

Adult male Wistar rats weighing 200–250 g were housed in standard plastic cages in groups of three in a controlled colony room (temperature 22 ± 2 °C). They were maintained on a 12-h light/dark cycle (lights on at 07:00 AM) with food and water ad libitum. The experiments were carried out during the light phase of the cycle. Each animal was tested once. Five to eight animals were used per group. All experiments were performed 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 University of Medical Sciences, Tehran, Iran.

2.2. Drugs

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

2.3. Stereotaxic surgery

The animals were anesthetized by xylazine (10 mg/kg) and ketamine (100 mg/kg) and placed in a stereotaxic apparatus (Stoelting, USA). Two guide cannulae (23-Gauge) with 11 mm length were 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 [25]. Each guide cannula was anchored with a jeweler's screw, and the incision was closed with dental cement. After surgery, dummy inner cannulae that extended 0.5 mm beyond the guide cannulae were inserted into the guide cannulae and left in the place until injections were made. All animals were allowed to recover for one week before behavioral testing began.

2.4. Intracranial injections

The animals were gently restrained by hand and the dummy cannulae were removed from the guide cannulae. Drugs were directly injected into the BLA through the guide cannulae using injector cannulae (30-Gauge, 1 mm below the tip of the guide cannulae). Polyethylene tubing (PE-20) was used to attach the injector cannula to a 1-μl Hamilton syringe. The injection volume was 0.3 μl per side for all groups. Injections were made bilaterally over a 60-s period, and the injection cannulae were left in the guide cannulae for an additional 60 s to facilitate diffusion of the drugs.

2.5. Place conditioning apparatus

A three-compartment CPP apparatus (30 cm × 30 cm × 40 cm) was used in these experiments. Place conditioning was conducted using an unbiased protocol, modified slightly from a design previously described [26,27]. The apparatus was divided into two equal-sized compartments and the third section was the null section which connected two equal-sized sections. Both compartments had white backgrounds with black stripes in different orientations (vertical vs. horizontal). 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. In this apparatus, rats showed no consistent preference for either compartment. In the CPP paradigm, conditioning score and distance traveled were recorded by using a 3CCD camera (Panasonic Inc., Japan) for detecting animal displacement and it was placed 2 m above the CPP boxes and locomotion tracking was measured by Ethovision software (version 3.1), a video tracking system for automation of behavioral experiments (Noldus Information Technology, the Netherlands). In these experiments, on the pre- and post-conditioning phases, each animal was introduced to the compartment for 10 min. Time spent in each compartment of CPP apparatus and total distance traveled were measured during this time. CPP paradigm took place in 5 continuous days, which consisted of three distinct phases: pre-conditioning, conditioning and post-conditioning.

2.5.1. Pre-conditioning phase

On day 1 (pre-exposure), each rat was separately placed into the apparatus for 10 min, with free access to all compartments. Animal displacement was recorded and analyzed on this day (pre-test day). In the experimental setup used in this study, the animals did not show an unconditioned preference for either of the compartments. Animals were then randomly assigned to one of the two groups for