Brain Research Bulletin 137 (2018) 217–224

Contents lists available at ScienceDirect

Brain Research Bulletin

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

Research report

Role of the orexin receptors within the nucleus accumbens in the drug priming-induced reinstatement of morphine seeking in the food deprived rats

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ARTICLE INFO

Keywords:
Reward
Orexin
Nucleus accumbens
Stress-induced reinstatement
Drug priming-induced reinstatement
Food deprivation
Morphine
Rat

ABSTRACT

Orexin plays a key role in mediating stress-induced drug relapse. However, the role of different types of orexinergic receptors that modulate stress-induced drug seeking remains unknown. The nucleus accumbens (NAc) has an important role in the reward system and receives orexinergic projections of the lateral hypothalamus. In addition, orexin interacts with other receptors that are involved in drug reinstatement. Therefore, in the present study, the role of orexin receptors in the NAc in morphine priming- induced reinstatement and the effect of food deprivation (FD) on drug reinstatement were examined. The extinguished morphine preference rats were tested for reinstatement following the 24-h FD condition after conditioning was induced. In the other groups, the animals were given intra-accumbal administration of SB334867 (01, 1 and 10 nM/0.5 µl DMSO) as an orexin-1 receptor antagonist and TCSOX229 (1, 5 and 25 nM/0.5 µl DMSO), as an orexin-2 receptor antagonist. The results showed that the blockade of two types of orexin receptors in the NAc remarkably attenuated the effect of FD on the drug reinstatement; however, they were more effective in FD condition. These findings indicate that the NAc is a brain area within which orexin has a fundamental role in the effect of stress on morphine-induced reinstatement and the effect of food deprivation- on the reinstatement of morphine.

1. Introduction

Drug addiction is a chronic, recurrent brain disease characterized by relapse (Koob and Volkow, 2010). The identification of brain mechanisms that is responsible for vulnerability to relapse, is crucial for the effective treatments development of drug addiction (Georgiou et al., 2015). Studies suggest that exposure to stressors such as social stress (Al-Hasani et al., 2013; Manvich et al., 2016), forced swim stress (Ebrahimian et al., 2016; Karimi et al., 2014), REM sleep deprivation (Karimi-Haghighi and Haghparast, 2017), and foot shock (Nygard et al., 2016) increases the probability of reinstating drug-seeking behavior. However, the mechanisms by which stress systems may effect reinstatement of drug-seeking behaviors remain unclear. Food deprivation is considered an environmental stressor and there is evidence that acute and chronic food deprivation facilitate the maintenance of drug-reinforced behavior (Carroll, 1985) and potentiate opiate reinstatement (Carr, 2002; Carr and Simon, 1984; Sadeghzadeh et al., 2015, 2016; Stuber et al., 2002). Moreover, lack of calories has been shown to raise cigarette smoking, and the risk for relapse (Cheskin et al., 2005; Hall et al., 1992).

Orexin-A and −B (hypocretin-1 and −2) are peptides produced in neurons residing in the lateral and dorsomedial hypothalamus and perifornical area (Sakurai et al., 1998). They have been shown to be important in reward and addiction biology (Aston-Jones et al., 2009; Bonci and Borgland, 2009), that heavily innervate many areas of the mesolimbic 'reward pathway' including the ventral tegmental area (Fadel and Deutch, 2002; Mahler et al., 2013) and the nucleus accumbens (NAc) (Kotani et al., 2008; Qi et al., 2013) and both of which contain orexin receptors (Chen et al., 2014).

A large body of evidence indicates that orexins are involved in different components of drug addiction, including drug reward (Baimel et al., 2015; Muschamp et al., 2014), drug reinforcement (Borgland et al., 2009; Espana, 2012), drug withdrawal (Bayerlein et al., 2011; Davoudi et al., 2016; Laorden et al., 2012) and drug seeking behaviors (Ebrahimian et al., 2016; Guo et al., 2016; Qi et al., 2013; Smith et al., 2010). Neurons containing orexin are firmly established as regulators of reward seeking specially by interaction with dopamine receptors (Chen et al., 2014; Zhou et al., 2015).

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https://doi.org/10.1016/j.brainresbull.2017.12.008
Received 6 October 2017; Received in revised form 6 December 2017; Accepted 7 December 2017
Available online 16 December 2017
0361-9230/

Some evidence has shown that orexin receptor 1 (OX1R) signaling is more involved in reward seeking (Brown et al., 2016; Cason and Aston-Jones, 2013; Plaza-Zabala et al., 2010; Smith et al., 2009), whereas orexin receptor 2 (OX2R) (Wang et al., 2009) signaling is involved in arousal and stress-related behaviors (Aston-Jones et al., 2010; De Giovanni et al., 2016).

The NAc is the best known for its role in mediating appetitive motivation related to drug relapse and aversive motivation related to stress-like behaviors (Cruz et al., 2010; De Giovanni et al., 2016; Qi et al., 2013). The NAc is one of the most important potential brain areas that receives heavy orexin projections (Azhdari-Zarmehri et al., 2013; Lee and Lee, 2016; Plaza-Zabala et al., 2013b). Also, it has critical role in morphine reinstatement (Qi et al., 2013), and thus is likely to be the potential candidate at which the orexin system may modulate stress-induced drug relapse.

In spite of the close association of the orexinergic system with regulation of stress- and reward-related behaviors, it remains unclear how stress affects drug-seeking behaviors. Therefore, we speculate that stress and drug priming-induced reinstatement may be affected differentially by OX1R and OX2R. The specific goal of the present work is to provide an overview of the role of OX1R and OX2R in the NAc on stress and/or drug priming-induced drug reinstatement with a conditioned place preference paradigm, which is widely used in the studies of drug reinstatement.

2. Materials and methods

2.1. Subjects

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. Moreover, all efforts were made to use the minimum number of animals essential to produce reliable scientific data. One hundred and fifteen adult male albino Wistar rats (Pasteur Institute, Tehran, Iran) weighing 200–250 g were used in our experiment. The animals were housed in a temperature-controlled vivarium under a 12-h light-dark cycle, with food and water available ad libitum. They were adapted to the laboratory conditions and were acclimated to handling for one week before the start of any in vivo studies. The rats were randomly assigned to different experimental groups. Each experimental group was composed of six to eight animals.

2.2. Surgery and infusion procedure

After a week of acclimatization, we anesthetized the rats by ketamine–xylazine (100 mg/kg ketamine–10 mg/kg xylazine) and placed them into stereotaxic device (Stoelting, USA). The stainless steel guide cannulae (23 gauge, Plastics One, Roanoke, VA, USA) were bilaterally implanted into the NAc (AP 1.44 mm; ML ± 1.46 mm; DV7.7 mm) (GaW, 2007). To minimize the damage to the target site by the tips of the cannulae, they were implanted 1 mm above the desired injection site. Two stainless steel screws were attached to the skull to anchor the guide cannula, and dental cement was used to secure the guide cannulae in place. The stainless steel obturator was inserted to prevent clogging and infection. Then, the rats were placed in their home cages to recover for 5–7 days from surgery before the experiments.

For bilateral intra-accumbal microinjection, the rats were held manually while the obturator was removed, and the injection needles (12 mm) (30gauge) were used through the guide cannulae so that they protruded 1 mm beyond the tip. The needles were connected to Hamilton syringes by polyethylene tubing (PE-20) and the drugs were slowly administered by hand in a volume of 0.5 µl over 60 s injectors (30 gauge).

2.3. Drugs

Morphine hydrochloride (Qinghai pharmaceutical, China), SB334867, an OX1R antagonist (Tocris, U.K.), TCSOX229, an OX2R antagonist (Tocris, U.K.), DMSO (Sigma, U.S.), and saline (NaCl0.9%) were used in the experiments. Morphine (5, 1 and, 0.5 mg/kg) were dissolved in saline; SB334867 (0.1, 1, 10 nM) and TCSOX229 (1, 5, 25 nM) was dissolved in DMSO (20%) immediately before use. In separate control groups, animals received either saline or 12% DMSO as a vehicle into the NAc.

2.4. Conditioned place preference paradigm

The conditioned place preference (CPP) is a prevalent method to evaluate motivational properties such as rewarding or aversive effects of drugs in animals.

2.4.1. Apparatus

A three-compartment CPP apparatus (30 cm × 30 cm × 40 cm) was used in these experiments. Place conditioning was conducted using an unbiased procedure (Karimi-Haghighi and Haghparast, 2017; Sadeghzadeh et al., 2015; Sadeghzadeh et al., 2016). The Plexiglas apparatus was divided into two equal-sized compartments with the third section being the null section, which connected the two equal size sections (30 cm × 15 cm × 40 cm). Both compartments had white backgrounds with black stripes with dissimilar orientations (Vertical vs. Horizontal). To provide the tactile difference between the compartments, one of them was floored by a smooth panel while the other had a net floor. In this apparatus, rats did not show any consistent preference for either compartments, an observation that supports our unbiased conditioned place preference paradigm. All compartments were placed in a quiet and isolated room under the similar light and sound condition.

2.4.2. Conditioned place preference protocol

CPP paradigm took place in three distinct phases, including pre-conditioning, conditioning, and post-conditioning.

Preconditioning phase: The rats were transferred from the animal housing room to the test room at least 30 min prior to the start of the experiment, for habituation purpose. To determine the baseline chamber preference − during the pre-conditioning phase on the first day, each animal was placed separately in the start box with the removable door removed and rats were permitted to move freely in all three chambers for 10 min. The distance traveled and the time spent in each compartment were recorded. Each animal that spent ≥80% of the total test time in a compartment was considered to have an initial bias and was excluded from the study. The animals that did not show any preferences for either of the compartments were then randomly chosen for one of the two compartments for place conditioning. Seven to eight animals were used for each group.

Conditioning phase: The conditioning phase started one day after the pre-conditioning session and consists of six, 45-min sessions (three with saline and three with drug pairing) in a three-day schedule. These sessions were conducted twice each day (from day 2 to day 6) within 6-h intervals. For conditioning trials, the animals received morphine (5 mg/kg s.c.) and were immediately confined to their conditioning compartment for 45 min; about 6 h later, the rats were injected with saline and immediately were put in the saline-paired compartment for 45 min.

Post-conditioning phase: This phase was carried out on day 5, following the last conditioning day. In order to determine a conditioning score (CS), as a preference index, the guillotine door was removed so that the rats could access freely the entire apparatus for 10 min. The time spent by each rat in both compartments was recorded by a 3CCD camera (Panasonic Inc., Japan) and analyzed using the Ethovision software (Version 7) which is a video tracking system for automation of