Available online at www.sciencedirect.com
ScienceDirect
European Journal of Pharmacology 582 (2008) 78–87
www.elsevier.com/locate/ejphar

Morphine sex-dependently induced place conditioning in adult Wistar rats

Manizheh Karami [a,b,*], Mohammad Reza Zarrindast [c]

[a] Department of Biology, Faculty of Basic Sciences, Shahed University, Tehran, Iran
[b] Basic Sciences Research Centre, Shahed University, Tehran, Iran
[c] Department of Pharmacology, School of Medicine and Iranian National Centre for Addiction Studies, Tehran University of Medical Sciences, Tehran, Iran

Received 19 May 2007; received in revised form 28 November 2007; accepted 11 December 2007
Available online 23 December 2007

Abstract

The present study was conducted to investigate the potential sex-differences in morphine-induced conditioned place preference. A 3-day unbiased conditioning procedure was used to establish conditioned place preference in adult male and female Wistar rats (weighing 200–250 g). The effect of morphine on locomotor activity of subjects was also studied. Naloxone (0.5–2 mg/kg, i.p.), a selective antagonist of mu-opioid receptor or sulpiride (0.5–2 mg/kg, s.c.), a selective antagonist of dopamine D_2 receptor was administered, during conditioning, to indicate the receptor-mediated mechanisms governing upon possible sex-differences to the opioid response. Results show that morphine (0.5–10 mg/kg, s.c.) differently produced a significant place preference in female and male Wistar rats. Although, the opioid maximum response in both sexes was observed at 7.5 mg/kg, but, it was found that female rats acquired conditioned place preference at a lower dose (0.5 mg/kg, s.c.) of morphine compared to male rats. Moreover, the increase in morphine-induced response at higher doses (5–10 mg/kg, s.c.) was more pronounced in females than the males, indicating that female Wistar rats are more sensitive to the place conditioning induced by morphine. Also, the females were more sensitive to locomotor activation induced by morphine at least at one dose (7.5 mg/kg). Animals' body-weight at 10 mg/kg of opioid was increased, the effect that was not dependent to sex. The results also demonstrate that naloxone (1 and 2 mg/kg, i.p.) induced a significant place preference in two sexes with no significant effect on animals' locomotor activity. The antagonist in males but not in females showed a significant effect on animals' body-weight. Naloxone (0.5–2 mg/kg, i.p.) prior-administration to morphine, during conditioning, attenuated the opioid response in two sexes. The attenuation of the morphine response was more pronounced in males than the other sex at the higher dose (2 mg/kg) of the antagonist. In addition, the preadministration of naloxone, during morphine conditioning, both attenuated the drug-induced hyperactivity in females and decreased the animals' body-weight, albeit more effectively in females than the males. Sulpiride injections (1 and 2 mg/kg s.c.), during the conditioning period, induced a significant aversion in males but not in females with no significant effect either on locomotor activity or body-weight in both sexes. When sulpiride (0.5–2 mg/kg, s.c.), during conditioning, was morphine pre-injected, the antagonist at higher doses significantly attenuated the opioid response in males, reflecting the involvement of dopamine D_2 receptor in sex-dependent morphine-conditioned place preference. Prior-injections of sulpiride to morphine produced a significant effect on locomotor activity of females. The effect of the antagonist preinjections on body-weight was also observed in males. Present results indicate sex-differences both in reinforcing and locomotor activity effects of morphine in Wistar rats.

Keywords: Sex-difference; Morphine; Naloxone; Sulpiride; Place conditioning; Locomotor activity; Body-weight; (Wistar rat)

1. Introduction

Sex-dependent differences in reward effects induced by opiates have been previously described (Elman et al., 2001; Lynch et al., 2000; Miaskowski and Levine, 1999). Moreover, evidence indicates that sex plays a role in morphine efficacy (Miaskowski and Levine, 1999; Randall et al., 1998) as sex-related differences have been shown for the effect of morphine on locomotor activity (Kavaliers and Innes, 1987), cardiovascular system (Cruz and Rodriguez-Manzo, 2000), temperature (Quock et al., 1985), stimuli discrimination (Craft et al., 1998; Craft et al., 1996), physical dependence (Cicero et al., 2000; Craft et al., 1999), and analgesia (Boyer et al., 1998; Cicero

* Corresponding author. Department of Biology, Faculty of Basic Sciences, Shahed University, Tehran, Iran.
E-mail addresses: Karami34@khayam.ut.ac.ir, karami@shahed.ac.ir (M. Karami).

0014-2999/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2007.12.010

et al., 1996; Cicero et al., 1997; Cicero et al., 2000; Krzanowska and Bodnar, 1999; and see Kest et al., 2000 for review). According to the previous findings female rats expend much greater efforts in an operant conditioning task to obtain morphine or heroin reinforcement (Cicero et al., 2003). Cicero et al. (2003) also postulated that the mu-opiate agonists including morphine serve as reinforcing agents in females over a broader dose range than males.

Place conditioning is a simple and an effective method to assess the rewarding properties of drugs (Karami et al., 2002; Zarrindast et al., 2002; Bardo and Bevins, 2000; Tzschentke, 1998; van der Kooy, 1987; Wise, 1987; Mucha et al., 1982). Russo et al. (2003) demonstrated sex-differences in the acquisition and/or expression of place conditioning induced by cocaine in Sprague–Dawley rats. Female Sprague–Dawley rats have been shown to be more sensitive to cocaine in the conditioned place preference paradigm (Nazarian et al., 2004). Furthermore, the age and the sex-differences in morphine-induced conditioned place preference in Sprague–Dawley rats have also been shown previously (Randall et al., 1998). But, little is known whether a conditioned place preference establishment in Wistar rats is based on a sex-difference. Investigators have shown that there are strain-dependent differences in the rewarding effects induced by morphine in rats (Semenova et al., 1995; Shoaib et al., 1995; Suzuki et al., 1992; Sudakov et al., 1990). The present study aims to determine the reinforcing effects of morphine in male and female Wistar rats in the unbiased conditioned place preference task. Evidence shows that morphine administrations stimulate or depress locomotor activity in Sprague–Dawley rats (Craft et al., 2006), the effect that may interfere with reinforcing effect of the drug (Van Ree et al., 1999); we further survey on the effect of three morphine pairings on locomotor activity of subjects during conditioned place preference testing. Additional study was also made to elucidate the changes of body-weight of conditioned animals.

It has been found that the majority of morphine-central actions are mediated by mu-opioid receptors (Zheng-xiong and Stein, 2002). Stimulation of mu-type receptors induces place preference in experimental animals (Tzschentke, 1998; Van Ree et al., 1999). Naloxone, a pure narcotic antagonist was shown to antagonize the opioid effect by competing for the same receptor sites (Wang et al., 2005). Evidence shows that infusion of naloxone into ventral tegmental area or periaqueductal gray blocked morphine place preference development (Olmstead and Franklin, 1997b). After systemic injection of naloxone, on the contrary, has been shown that the expression of morphine-conditioned place preference in both mice and rats increased (Neisewander et al., 1990). Therefore, in the present experiment response to naloxone in the same procedure was investigated in the subjects.

It has been reported a sex-related differentiation of dopamine neurons in feminized site in laboratorial animals' brain (Simerly et al., 1997). Findings show that dopamine release, and subsequently dopamine D_2 receptor activation are essential for rewarding effects of morphine (Manzanedo et al., 2005). In order to evaluate more the possibly sex-dependent involvement of dopamine (DA) system in morphine-conditioned place preference in Wistar rats, the interaction of sulpiride, a selective dopamine D_2 receptor antagonist to morphine in the conditioned place preference process was also studied.

2. Materials and methods

2.1. Subjects

Adult male and female rats (age-matched, weighing 200–250 g, Wistar, Pasteur Institute of Iran, Tehran, Iran) were housed in standard plastic cages in groups of 2 in a controlled colony room (temperature 22±3 °C). They were maintained on a 12-h light/dark cycle (lights on at 07.00 a.m.) with food and water ad libitum. The experiments were carried out during the light phase of the cycle. Each animal was tested once. 7–8 animals were used per group. Animals' body-weight was recorded on day of experiment. At the end of each experiment, the rats were killed with overdose chloroform. The experiments were conducted according to a protocol approved by Ethics Committee of Shahed University.

2.2. Drugs

Morphine sulphate (Temad, Co., Tehran, Iran) and (±) sulpiride (Sigma Chemical Co., U.S.A.) were prepared freshly in sterile 0.9% NaCl solution, and were injected subcutaneously (s.c.). The injection volume of naloxone hydrochloride (Tolid-Daru Co., Tehran, Iran) was 1 ml/kg for all groups. Vehicle injections were 0.9% physiological saline.

2.3. Apparatus

A two compartment conditioned place preference apparatus (30×60×30 cm) was used in these experiments. Place conditioning was conducted using an unbiased procedure, with design previously described (Karami et al., 2002; Zarrindast et al., 2002); the apparatus was divided into two equal-sized compartments. In the middle of the apparatus a removable wall was designed. Both compartments were colored white but were differently striped black (vertical vs. horizontal). The compartments were also distinguishable by texture and olfactory cue. To provide the tactile difference between the compartments, one of the compartments had a smooth floor, while the other compartment had a nylon white mesh floor. A drop of vinegar was placed at the right corner of the compartment with a textured floor, to provide the olfactory cue difference between the compartments.

2.4. Experimental procedure

The experiment consisted of three phases.

2.4.1. Pre-conditioning (familiarization)

On day 1 (before conditioning phase), animals received one habituation session. They were placed in the middle line