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Estrogen pretreatment modulates morphine-induced conditioned place preference in ovariectomized mice

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ABSTRACT

Estrogen is known to modulate the neurotransmission in the brain. The main aim of this study was to investigate the effects of estrogen on the rewarding properties of morphine using conditioned place preference (CPP) paradigm in adult female mice. The possible rewarding effect of estrogen was also examined in ovariectomized mice. Following a 6-day conditioning procedure, sham operated animals showed a significant preference towards the side previously paired with a range of morphine doses (2, 5 and 10—but not 20—mg/kg, SC). However, ovariectomized mice showed decreased CPP compared to gonadally intact mice with a right shift in their morphine dose–response curve. These effects were reversed by chronic daily administration of estradiol benzoate (EB; 20 μg/kg, SC). Furthermore, in ovariectomized mice, EB *per se* was able to induce CPP. In conclusion, our findings indicate that estradiol has a facilitating effect on morphine reward while its deficiency increases the threshold dose of morphine to induce CPP.

1. Introduction

There is substantial evidence demonstrating sex differences in response to opioids in both humans and laboratory animals (Becker, 1999; Mousavi et al., 2007; Craft, 2008). Several effects of acute and chronic exposure to morphine are expressed differently in the two genders including analgesia (Kest et al., 2000; Craft et al., 2004), locomotor activity (Kavaliers and Innes, 1987), alterations in body temperature (Quock et al., 1985), development of tolerance and dependence (Craft et al., 1999b; Cicero et al., 2002), and drug discrimination (Craft et al., 1999a). Moreover, it has been shown that sexual differences play a pivotal role in vulnerability to drug dependence (Lynch et al., 2002; Roth et al., 2004) and are present throughout different stages of addiction from response to first encounters with illicit drugs to development of addiction and relapse to drug-seeking/taking (Becker and Hu, 2008). For instance, women begin to use drugs at a younger age than do men (Griffin et al., 1989), increase the amount of drug use faster (Anglin et al., 1987), and develop dependence to drugs of abuse (such as cocaine, heroin and alcohol) more rapidly (Lex, 1991). In preclinical studies, sex-differences have been demonstrated in the acquisition and/or expression of place preference conditioning induced by cocaine (Russo et al., 2003) and morphine (Karami and Zarrindast, 2008; Cicero et al., 2000).

The exact mechanisms underlying sex differences in addiction are yet to be understood; however, the female ovarian hormone, estrogen, appears to play an important role in this regard (Lynch et al., 2001; Hu and Becker, 2003; Craft et al., 2004; Walf et al., 2007). Previous studies have shown modulatory effects of estrogens on rewarding properties of stimulants (Russo et al., 2003). For instance, it has been shown that removal of the primary source of estrogen by ovariectomy (OVX) attenuates amphetamine-induced hyperactivity, cocaine-induced behavioral sensitization, intravenous cocaine self-administration and cocaine-primed reinstatement of extinguished cocaine-seeking behavior, effects that can be reversed by estrogen replacement therapy (Becker, 1990; Peris et al., 1991; Lynch et al., 2001; Larson et al., 2005). Furthermore, estrous cycle has been shown to be an important factor influencing the level of cocaine-seeking following withdrawal from chronic cocaine self-administration and during cocaine-primed reinstatement (Feltenstein and See, 2007). However, in contrast to psychostimulants, there is not enough evidence regarding the role of estrogen in rewarding effects of opioids such as morphine.

The purpose of the present experiment was to clarify the effects of estrogen on the rewarding effects of morphine in conditioned place preference (CPP) paradigm, which has been widely used to assess the

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rewarding properties of drugs of abuse including opioids (Bardo et al., 1984; Tzschentke, 1998). In this regard, we studied the acquisition of morphine place conditioning in ovariectomized mice with and without estrogen replacement treatment and gonadally intact sham-operated female mice with vehicle. Furthermore, the effect of estrogen on acquisition of CPP was examined to clarify the probable rewarding effect of estrogen.

2. Materials and methods

2.1. Animals

A total of 120 adult female NMRI mice (Pasteur Institute of Iran, Tehran, Iran), weighing 20–25 g at the time of surgery, were used throughout this study. Animals were housed 5–7 per cage in transparent Plexiglas cages in a temperature and humidity controlled colony room under a 12/12 h light/dark cycle (lights on at 7:00 am), with ad libitum access to food and water except during experiments. Subjects were experimentally naïve and each animal was used only once. They were assigned randomly to each treatment group consisting of 6–8 animals. Mice were allowed a week to acclimatize to the laboratory environment before testing began and during this period they were handled, weighed, and habituated to the drug administration procedure. All procedures were performed according to the institutional guidelines for animal care and use. The protocol was approved by the committee of ethics of the Faculty of Sciences, University of Tehran.

2.2. Drugs

The following drugs were used: Morphine sulfate (Temad, karaj, Iran) and 17-β-Estradiol Benzoate (Abureyhan Pharmaceutical, Tehran, Iran). Morphine was prepared freshly in sterile 0.9% NaCl solution to such concentration that requisite doses were administered in a volume of 10 ml/kg and was injected subcutaneously (sc). 17-β-Estradiol Benzoate (EB; 20 μg/kg) dissolved in sesame oil (SO) and was injected daily in a volume of 0.1 ml per animal (sc). This form of estradiol was used because it is metabolized slowly and results in consistent serum levels of estradiol with chronic administration (Frick et al., 2002; Chen et al., 2003; Xu and Zhang, 2006). EB and SO treatments began 2 days prior to commencement of behavioral studies and continued throughout the experiments until animals were sacrificed (Quinlan et al., 2008). Vehicle injections were of appropriate volume of saline and SO.

2.3. Ovariectomy

Anesthesia was induced by intraperitoneal injections of 50 mg/kg of Ketamine Hydrochloride (Rotexmedica, Trittau, Germany) and 10 mg/kg of chlorpromazine (Daroupakhsh, Tehran, Iran) (Niaki et al., 2008). After the onset of anesthesia, the lumbar dorsum was shaved, and the exposed skin was prepared for aseptic surgery by 10% povidone-iodine scrub followed by sterile saline wipe. Surgery was performed based on the method described by Eddy (1986) with modifications (Riazi et al., 2004). In brief, a 1–2 cm incision was made on the midline of the lumbar vertebral line. About 1 cm lateral to midline on each side, paraovarian fat tissue was identified and dissected in order to expose ovaries. Ovaries and associated oviducts were removed bilaterally. Hemostasis was achieved by hemostat pressure for 1–2 min, if needed. Then the skin incision was sutured (5–0 non-absorbable). In sham-operated animals, the paraovarian fat tissue and ovaries were just retracted and replaced. Animals were given 7 days to recover from surgery. EB treatment in half of the OVX mice and SO injection for the remaining half of the OVX mice and all sham-operated animals started 7 days after surgery. All experiments were conducted at the same time.

2.4. General behavioral procedure

The place preference apparatus was made of wood and consisted of two squared-base compartments ($15 \times 15 \times 30$ H cm each). To distinguish two compartments, visual and sensory texture cues were used: the inner surface of one compartment was painted in black with a smooth floor; the other side was white with a textured floor to create equally preferred compartments. Place conditioning was conducted using an unbiased procedure. In this design, animals did not show a significant preference toward any compartment in the pre-conditioning test and drug administration was randomly paired with either of the compartments (Tahsili-Fahadan et al., 2006). The CPP paradigm took place in nine consecutive days, which consisted of three phases: familiarization and pre-conditioning, conditioning and post-conditioning. All trials were done between 10:00 am and 2:00 pm.

2.4.1. Familiarization and pre-conditioning

On the first (i.e., familiarization) and second days (i.e., preconditioning) of trials, each mouse was placed separately into the apparatus for 10 min with free access to both compartments. The time spent in each compartment was recorded on the preconditioning day to determine any individual innate preference for either of the two compartments. Placement in each compartment was considered as placement of the front paws and the head. Animals showing strong unconditioned preference or aversion for any compartment (time spent in either of the two compartments > mean + 2 S.D.) were excluded from the experiment (total of 7 mice).

2.4.2. Conditioning

This phase consisted of six 40-minute conditioning sessions held on 6 consecutive days. Animals were confined to the considered compartment by isolating compartments with a removable partition. The mice received the drugs on days 1, 3 and 5 and their vehicles on days 2, 4 and 6 of the conditioning phase according to the experimental design. Treatment compartments were counterbalanced for all groups.

2.4.3. Post-conditioning

This phase was carried out in the ninth day of the trials (24 h after the last conditioning session) in a drug-free state. As in the preconditioning phase, the partitions were raised and the animals were placed in the apparatus for 10 min with free access to both compartments. The time spent in each compartments was recorded in real time by an observer who was unaware of mice and treatments. Change in preference (CIP) was calculated as the difference (in seconds) between the time spent in the drug-paired compartment on the post-conditioning day and the time spent in the same compartment on the pre-conditioning session.

2.5. Experimental design

2.5.1. Experiment 1: Dose–response effects of place conditioning produced by morphine in female mice

In this experiment, the effect of different doses of morphine sulfate (2, 5, 10 and 20 mg/kg, s.c.) on producing place preference was tested in gonadally intact sham-operated female mice according to the schedule described above. The animals used in this experiment received a daily injection of SO from 2 days prior to start of CPP procedure until the post-conditioning day (during conditioning days, the injections took place 2 h before placement in the CPP boxes). A control group that received saline (10 ml/kg) in all sessions was included to confirm that the injection and conditioning schedule did not affect the time spent in compartments.

2.5.2. Experiment 2: Induction of morphine conditioned place preference in OVX mice

This experiment was carried out to examine the effect of removing the main source of estrogen (ovaries) on induction of CPP by morphine.

Animals received daily injections of SO as described above. Place preference was induced in OVX animals with different doses of morphine (2, 5, 10 and 20 mg/kg) or saline (10 ml/kg) according to the schedule.

2.5.3. Experiment 3: Effect of EB pre-treatment on the acquisition of morphine CPP in OVX mice

This experiment was performed similar to Experiment 2, except that in this experiment the OVX animals received chronic daily injections of EB (20 μg/kg) from 2 days before behavioral experiments until post-conditioning test. During conditioning phase, injections were done 2 h before each conditioning session. Effects of different doses of morphine (2, 5, 10 and 20 mg/kg) or saline on induction of CPP was assessed on post-conditioning test according to the schedule.

2.5.4. Experiment 4: Effect of EB on producing CPP in OVX mice

In this experiment, the possible ability of EB *per se* on producing CPP was investigated in OVX mice. In one group, EB (20 μg/kg) or SO were injected 2 h before conditioning sessions on alternative days according to the schedule described above. In another group, mice were injected with SO 2 h prior to all conditioning sessions and served as a control.

3. Results

3.1. Dose–response curve for place preference conditioning produced by morphine in sham-operated female mice

Dose–response curve for place preference conditioning induced by morphine in female mice for three experimental groups is shown in Fig. 1. A significant dose-dependent effect of morphine on producing CPP in sham-operated animals that received SO chronically (experimental group 1) was seen (One-Way ANOVA, $F_{4,32}=30.98$, $P<0.001$). Post-hoc analyses revealed that the doses of 2, 5 and 10 mg/kg of morphine induced significant place preference ($P<0.001$ for all groups compared to saline-treated animals) in a dose-dependent manner; although animals conditioned with morphine (20 mg/kg) showed a trend towards CPP expression, it was not statistically significant ($P=0.068$). The maximum response was observed with 5 mg/kg of morphine ($P=0.001$ and $P<0.001$ compared to morphine 2 and 10 mg/kg, respectively) as shown in Fig. 1 (left panel).

3.2. Effect of ovariectomy on the acquisition of morphine CPP in mice

Two-way ANOVA indicated a significant effect for morphine treatment on the induction of CPP. In addition, while, OVX by itself did not affect CIP, a significant interaction between morphine treatment and OVX on the induction of morphine CPP was observed (factor morphine, $F_{4,63}=56.13$, $P<0.001$; factor ovariectomy, $F_{1,63}=0.02$, $P=0.8$; and factor morphine × ovariectomy, $F_{4,63}=15.63$, $P<0.001$). Further analysis with Tukey–Kramer's multiple comparison tests in the second experimental groups (Fig. 1, middle panel) indicated that the morphine (2, 5 and 10 mg/kg) produced significant preference toward the drug-paired side in a dose-dependent manner ($P=0.006$, $P<0.001$ and $P<0.001$, respectively in comparison to saline conditioned group). Morphine (20 mg/kg) failed to produce any significant preference for either compartment ($P=0.309$ compared to saline group). The maximum response, however, was observed with 10 mg/

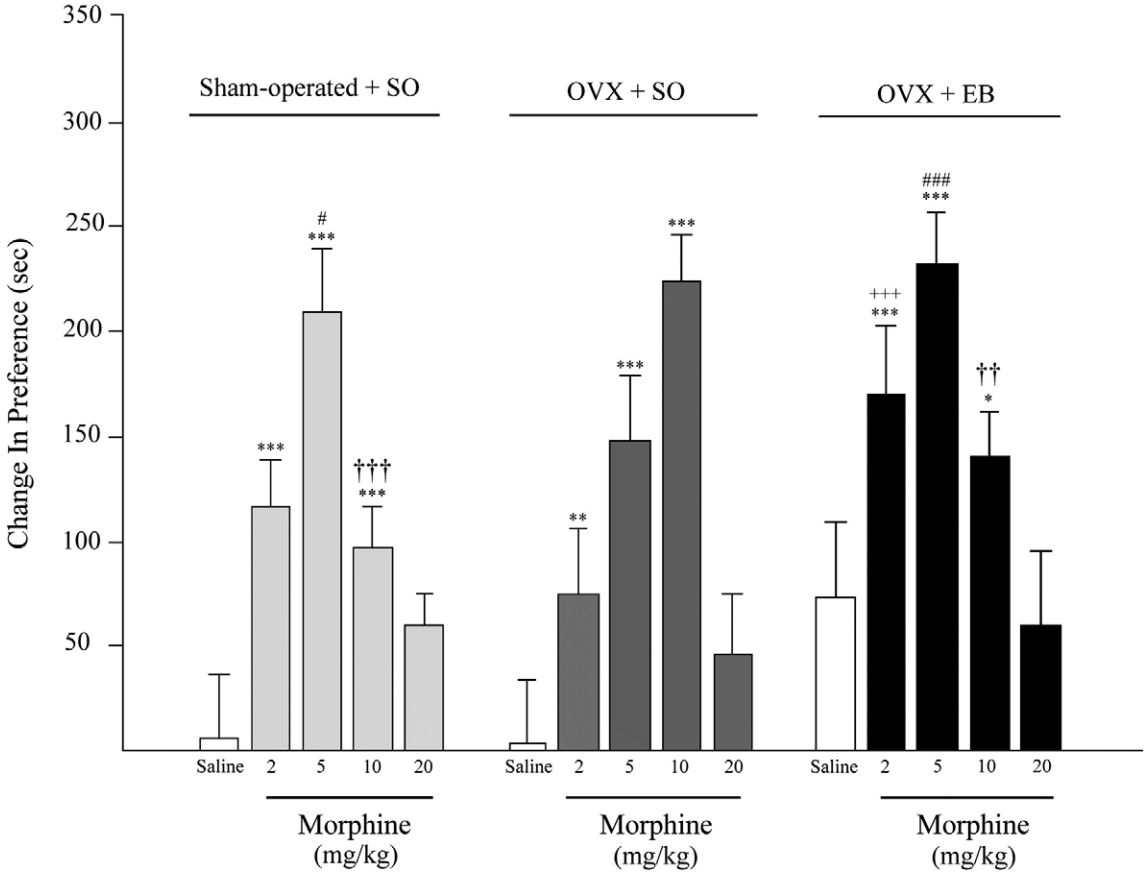

Fig. 1. The effect of different doses of Morphine Sulfate on producing CPP in three experimental groups. Sham-operated (left panel) or ovariectomized (OVX) mice received daily injections of EB (20 μg/kg; right panel) or its vehicle SO (10 ml/kg; middle panel) 2 h prior conditioning sessions. Morphine was injected s.c. immediately before placement in the apparatus on the 1st, 3rd and 5th days of the conditioning phase. Data are expressed as mean ± SEM. * $P<0.05$, ** $P<0.01$ and *** $P<0.001$ compared to saline treated mice in the same experimental group. +++ $P<0.001$different from the OVX + SO mice receiving morphine (2 mg/kg), # $P=0.03$ and ### $P<0.001$ different from the OVX + SO mice receiving morphine (5 mg/kg), †† $P=0.003$ and ††† $P<0.001$ different from the OVX + SO mice receiving morphine (10 mg/kg) (Tukey–Kramer's multiple comparison test).

kg of morphine ($P<0.001$ and $P=0.005$ compared to morphine 2 and 5 mg/kg, respectively).

3.3. Effect of pre-treatment with EB in morphine-induced CPP in OVX mice

A significant effect for pre-treatment with EB in OVX mice was illustrated on the acquisition of morphine CPP (Two-way ANOVA, factor morphine, $F_{4,\ 66}=46.92$, $P<0.001$; factor EB treatment, $F_{1,\ 66}=14.73$, $P<0.001$; and factor morphine × EB treatment, $F_{4,\ 66}=14.06$, $P<0.001$). Post-hoc analyses showed that the doses of 2, 5 and 10 mg/kg of morphine induced place preference ($P<0.001$, $P<0.001$ and $P=0.019$, respectively in comparison to saline control group) as shown in Fig. 1, right panel; however, morphine 20 mg/kg failed to produce CPP ($P=0.984$ compared to saline group). The maximum response was observed with 5 mg/kg of morphine ($P=0.024$ and $P=0.001$ compared to morphine 2 and 10 mg/kg groups, respectively).

3.4. Effect of OVX and EB pre-treatment on the acquisition of place preference conditioning

Ovariectomized mice showed a significant preference for the EB-paired compartment during the post-conditioning test in comparison to OVX mice that received SO during all conditioning sessions by an independent *t* test, 2-tailed ($P=0.005$).

4. Discussion

In the present study we investigated the effects of OVX (i.e., removal of the main source of endogenous estrogen) and estradiol benzoate (EB) replacement therapy on the acquisition of morphine-induced place preference conditioning. In Experiment 1, morphine induced conditioning in gonadally intact sham-operated female mice in a dose-dependent manner. Further results revealed that removal of endogenous estrogen by OVX attenuated rewarding effects of morphine in lower doses, while EB treatment in OVX mice restored and even enhanced the animal's response to rewarding effects of lower doses of morphine. In addition, EB treatment in OVX mice produced CPP for the estrogen-paired side.

Previously significant sex-related differences have been demonstrated for positive reinforcing properties of morphine (Cicero et al., 2000; Karami and Zarrindast, 2008). It is well documented that mesolimbic dopaminergic (DA) projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) play an important role in rewarding effects of drugs of abuse including morphine (Kelley and Berridge, 2002). On the other hand, the gonadal hormone estrogen has been documented to have multiple actions on the mesolimbic DA system including modulating DA synthesis, metabolism, and receptor mRNA expression (Becker, 1999). Considering these, we postulated that estrogen may be involved in sex-dependent rewarding effects of morphine. The CPP paradigm used in this study represents an animal model to assess the rewarding properties of various drug and non-drug treatments including opioids (Bardo et al., 1984). The test is based upon the principle that, when a primary reinforcer is paired with a contextual stimulus, the contextual stimulus can acquire secondary reinforcing properties. These secondary reinforcing properties, which are presumably established due to a Pavlovian contingency, are thought to be capable of eliciting an operant approach response or place preference which results in a significant increase in the time spent in the drug-paired place (Tzschentke, 1998).

Subcutaneous administration of morphine (2, 5 and 10 mg/kg) in the present study induced a significant shift in preference for the environment previously paired with the drug. This is in accordance with previous data in female mice (Sahraei et al., 2004, 2006). Investigators, however, have emphasized that in normal cycling gonadally intact female mice morphine CPP is inducible by lower doses of morphine and the peak of their response to CPP occurs with lower doses in comparison to male mice (Carroll et al., 2004; Sahraei et al., 2006; Karami and Zarrindast, 2008). Accordingly, in the present study the highest preference score in sham-operated animals is seen with 5 mg/kg of morphine rather than higher doses for OVX mice.

The results from this study also revealed that OVX attenuates expression of morphine-induced CPP in lower doses (2 and 5 mg/kg), while enhances CPP in a higher dose (10 mg/kg) of morphine in comparison with gonadally intact female mice. Indeed, OVX has shifted the morphine dose–response curve to the right; and therefore, makes the female animal's response to rewarding effects of morphine more similar to the dose–response curve of morphine-induced CPP in male rodents (Karami and Zarrindast, 2008). Furthermore, our data shows that EB pre-treatment in OVX mice facilitates the induction of morphine CPP by low-doses (2 and 5 mg/kg) of morphine, but did not change the responsiveness of OVX mice to the rewarding effects of higher dose of morphine (10 mg/kg). This suggests that rewarding effects of lower versus higher doses of morphine are differentially modulated by estrogen which is, in part, consistent with recent findings suggesting that estrogen may amplify the rewarding effects of drugs of abuse (Frye and Rhodes, 2006) and that daily EB treatment increases OVX rats' vulnerability to initiate heroin self-administration compared to ovariectomized rats treated with vehicle (Roth et al., 2002). In the latter study, a relatively low dose of heroin (0.0075 mg/kg) was studied which is comparable with low doses of morphine used in the present experiment.

Studies investigating the underlying mechanisms indicate that estrogen may modulate brain opioid peptide and its mRNA levels, opioid receptor density, and opioid receptor-mediated signal transduction (Craft et al., 2004). On the other hand, estrogen is well known to modulate brain dopaminergic (DA) system. For instance, previous studies have shown that OVX decreases basal extracellular DA concentration in striatum (Xiao and Becker, 1997), and striatal DA transporter density (Bossé et al., 1997). Moreover, Striatal DA-stimulated adenylate cyclase activity is lower in OVX rats relative to intact females (Kumakura et al., 1979; Lévesque et al., 1989). Several investigators showed that chronic estradiol treatment in ovariectomized female rats increased striatal D_2 receptor density without modifying its affinity state (reviewed in Di Paolo, 1994; Landry et al., 2002). It also has been shown that ovariectomy decreases D_2 receptor specific binding sites in striatum and NAc, and it could be prevented by chronic estradiol treatment (Le Saux et al., 2005). One possible mechanism is the altered expression of the regulators of G-protein signaling (RGS) by estrogen (Sharifi et. al., 2004). Accordingly, it has been reported that by selectively decreasing the expression of RGS9 mRNA in the shell of the NAc, estrogen may potentiate DA-mediated behaviors. On the other hand, it has been indicated that estrogen has controversial post-synaptical effects on DA receptor expression and DA receptor specific activation (Sharifi et al., 2004).

In the present study, we found that EB alone is able to produce CPP for the estrogen-paired side in OVX mice and this result confirms previous findings showing estradiol-induced CPP in gonadectomized female rats (Walf et al., 2007; Frye and Rhodes, 2006). Nucleus Accumbens (NAc) is considered as the main region enrolled in rewarding effects of estradiol and it has been found that administration of moderate doses of estrogen to OVX rats, which induces CPP, rapidly increases c-*jun* immunoreactivity (Zhou and Dorsa, 1994) and produces moderate levels of estradiol in the NAc (Frye and Rhodes, 2006). Estrogen, in addition to its reinforcing effects, is a well-known factor to augment learning and memory (Xu and Zhang, 2006; Frick et al., 2002). Drug-induced place preference requires memory for the association between environmental cues and the affective state produced by the drug (White and Carr, 1985; Hsu et al., 2002) and estrogen facilitates associative learning (Silverman and Koenig, 2007). Taken together, we could suppose that estrogen's reinforcing effect has an additive influence on morphine-induced reward in OVX mice

treated with EB in this experiment; although it remains as hypotheses until sufficient supportive data are gathered.

In conclusion, we found that the threshold dose of morphine for inducing CPP in OVX mice is higher than sham-operated animals; an effect that could be reversed by exogenous estrogen replacement therapy. Further research is needed to explore the underlying mechanism of estrogen effects on the brain reward system.

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