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The role of alpha-adrenoceptor mechanism(s) in morphine-induced conditioned place preference in female mice

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Abstract

It has been shown that the alpha-adrenergic system is involved in some effects of opioids, including analgesia and reward. Gender differences also exist between males and females in response to alpha-adrenergic agents. This study was designed to determine the effects of alpha-adrenoceptor agonists and antagonists on the acquisition or expression of morphine-induced conditioned place preference (CPP) in female mice. The experiments showed that subcutaneous injections of morphine (0.5–8 mg/kg) induced CPP in a dose-dependent manner in mice. Intraprioneal administration of the alpha-1-adrenoceptor agonist, phenylephrine (0.03, 0.1 and 0.3 mg/kg), and alpha-2 adrenoceptor agonist, clonidine (0.0001, 0.0005 and 0.001 mg/kg), as well as alpha-1-adrenoceptor antagonist, prazosin (0.01, 0.05 and 0.1 mg/kg) or alpha-2 adrenoceptor antagonist, yohimbine (0.005, 0.01 and 0.05 mg/kg) did not induce motivational effects and also did not alter locomotor activity in the animals. In the second set of experiments, the drugs were used before testing on Day 5, to test their effects on the expression of morphine-induced CPP. Intrapritoneal administration of phenylephrine and clonidine decreased the expression of morphine-induced CPP. In contrast, after application of prazosin or yohimbine, the expression of morphine-induced CPP was increased. Administration of lower (0.03 mg/kg) and higher doses of phenylephrine (0.1 and 0.3 mg/kg) during acquisition of morphine CPP decreased and increased the morphine CPP, respectively. Similarly, the administration of prazosin and clonidine decreased while yohimbine increased the morphine CPP. It may be concluded that alpha-adrenoceptor mechanism(s) influence morphine-induced CPP in female mice.

Keywords: Morphine; Alpha-adrenoceptors; Phenylephrine; Clonidine; Prazosin; Yohimbine; Conditioned place preference; Female mice

1. Introduction

Several studies have shown that the alpha-adrenergic and opioid systems can interact in a complex manner. For example, opioids have been shown to inhibit noradrenergic activity in the hippocampus (Matsumoto et al., 1994), cortex (Werling et al., 1987) and the locus ceruleus of the rat (Sklair-Tavron et al., 1994), and also cynomolgus monkeys (Aston-Jons et al., 1992). Morphine also tends to inhibit noradrenaline release from human neuroblastoma cells (Atcheson et al., 1994). There are also reports showing that opioids increase the turnover of norepinephrine (Brazell et al., 1991).

The noradrenergic and opioid systems have been shown to be involved in the development and expression of opioid dependence (for review, see Maldoado, 1997). The rats tolerant to the antinociceptive effects of morphine show cross-tolerance to the effect of norepinepherine (Milne et al., 1985) and alpha-2 adrenoceptor agonist, clonidine (Solomon and Gebhart, 1988). Furthermore, rats tolerant to the antinociceptive effect of clonidine show cross-tolerance to the effects of morphine (Paalzow, 1978). Clonidine also attenuates some of the signs of morphine withdrawal in rats (Kosten, 1994) as well as the signs of morphine withdrawal in humans (Gold et al., 1987). Acute administration of the adrenoceptor antagonist, yohimbine, increases the physical

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effects of morphine withdrawal in rats (Dwoskin et al., 1983), suggesting that alpha-2 adrenoceptors are involved in the development of physical dependence upon opioids (Iglesias et al., 1992). It has also been shown that signs of discriminative-stimulus (Hughes et al., 1996) and development of conditioned opiate withdrawal effects of morphine (Schulteis et al., 1998) may be enhanced by clonidine.

The conditioned place preference (CPP) paradigm has been widely used as a model for studying the reinforcing effects of drugs of dependence and addiction (McBride et al., 1999; Tzschentke, 1998). Considerable evidence indicates that alpha-2 adrenergic agonists and antagonists can induce CPP or conditioned place aversion (CPA; see review, Tzschentke, 1998). Morphine-induced CPP may be related to dopaminergic mechanism(s) (Rezayof et al., 2002). Several studies in mice and rats revealed the existence of interactions between adrenergic and dopaminergic systems (Lategan et al., 1990; Shi et al., 2000; Drouin et al., 2002). It has been also postulated that there is a difference between male and female animals in response to morphine (Cicero et al., 2000) and alpha-adrenergic agents (Luzier et al., 1998; Turner et al., 1999); therefore, in the present study, the effects of alpha-1 and alpha-2 adrenoceptors on the expression and acquisition of morphine CPP in female mice has been studied.

2. Materials and methods

2.1. Animals

Experiments were carried out on female Swiss–Webster mice ($n = 8$ per group) weighing 20–30 g (Pasture Institute, Tehran, Iran). The animals were group housed (eight per cage) at a constant temperature of 22–24 °C, on a 12:12-h light/dark cycle (light period 0700–1900 h). Standard laboratory mouse chow and water were available at all times except during experimentation. The animal Ethics Committee of the Baghyatallah (a.s.) University of Medical Sciences Research Department approved all of the experiments (79/123, Dec. 21, 2000).

2.2. Apparatus

The place conditioning apparatus was similar to that described by De Fonseca et al. (1995) with modifications. It consisted of three interconnected rectangular boxes of 15 × 15 × 20 cm, situated at 120° angles from each other. In the middle, there was a triangular area with a smooth glass floor, from which any of the three compartments was accessible. Each compartment was equipped with a set of different sensory stimuli that made them unique. Compartment A was equipped with a sand floor, plain walls and a small container with a drop of 10% acetic acid. Compartment B contained a soft plastic floor and walls painted with white circles and a small container with a drop of anise extract. Compartment C had a cork floor, alternating white stripes (5 cm wide) painted on the walls and no odor (water). The apparatus was placed in an isolated, dimly illuminated room (100 lx). Each compartment was equipped with four photocells, which allowed us to monitor the position of the animal and to automatically register the time spent in each compartment and the locomotor activity.

2.3. Behavioral testing

Experiments were performed between 0900 and 1800 h. Each place conditioning experiment consisted of a 6-day schedule with three phases: preconditioning, conditioning and testing.

2.3.1. Preconditioning phase

This phase lasts for 2 days. On Day 1 of the preconditioning phase, animals were placed in the middle of the apparatus and they were allowed to freely explore the three compartments for 45 min to explore the entire apparatus. On Day 2 of the preconditioning phase (this section was conducted for determining the preference of the animals), each animal was placed in the middle of the apparatus and was allowed to move freely to the three compartments for 10 min. During this section, the time spent in each compartment was computed and those animals exhibiting unconditioned aversion (< 10% of the session) or preferences (>60% of the session) for any compartment were discarded from the conditioning sessions. The two compartments, which exhibited the most similar time of preference, were chosen for each animal for the conditioning sessions. In one of these compartments, randomly chosen, the animals received drug, whereas in the other, saline was administered. This selection permitted us to avoid the interference of natural preference of the animals for the conditioning drugs.

2.3.2. Conditioning phase

This phase consisted of a 3-day schedule of double conditioning sessions. The first day involved a morning session (0900–1100 h) in which the animals received a single dose of morphine and were immediately placed in one of the compartments chosen as described above for 30 min. This compartment had been isolated from the others using removable panels. In the evening session (1600–1800 h), the animals received a single injection of saline and were placed for 30 min in the other compartment chosen for conditioning experiments. Injection intervals for each animal was 7 h. On the second day of conditioning, the animals received the saline injection in the morning session and morphine administration in the evening session. The third day of conditioning had the same schedule as the first.

2.3.3. Testing phase

On the sixth day of the schedule, the animals were allowed again to freely explore the three compartments for 10 min, exactly as in the preconditioning phase. The time spent in each compartment was computed. We defined the

change in preference as the difference (in seconds) between the times spent in the drug-paired compartment on the testing day and the time spent in this compartment in the preconditioning session. This variable was chosen as an index of drug-induced place preference, as previously described (Hand et al., 1989).

2.3.4. Locomotion

Locomotor activity was measured by means of four infrared LEDs attached to the wall of each compartment during CPP recording in the test day (expression of CPP). The doses which were used in these experiments did not alter locomotor activity.

2.4. Experimental design

In a pilot study, the effects of subcutaneous administration of various doses of morphine (0.5, 1, 2, 4 and 8 mg/kg) on the induction of CPP were investigated. To examine state-dependent learning (as mentioned by Tzschentke, 1998), morphine was administered prior to testing. It was found that the size of the CPP response was not altered. Therefore, all the animals were tested in a morphine-free state. This eliminates the possibility that morphine-induced motor effects might influence the response.

To examine the effects of adrenergic drugs on the acquisition of morphine CPP, the animals received different doses of adrenoceptor agonists 15 and 30 min before morphine injection in the conditioning phase, while in the testing phase, the animals were examined in a drug-free state, but not with morphine.

To examine the effects of adrenergic drugs on the expression of morphine-induced CPP, those animals which conditioned to morphine in the conditioning phase of experiments, received different doses of adrenoceptor agonists and antagonists 15 and 30 min, respectively,

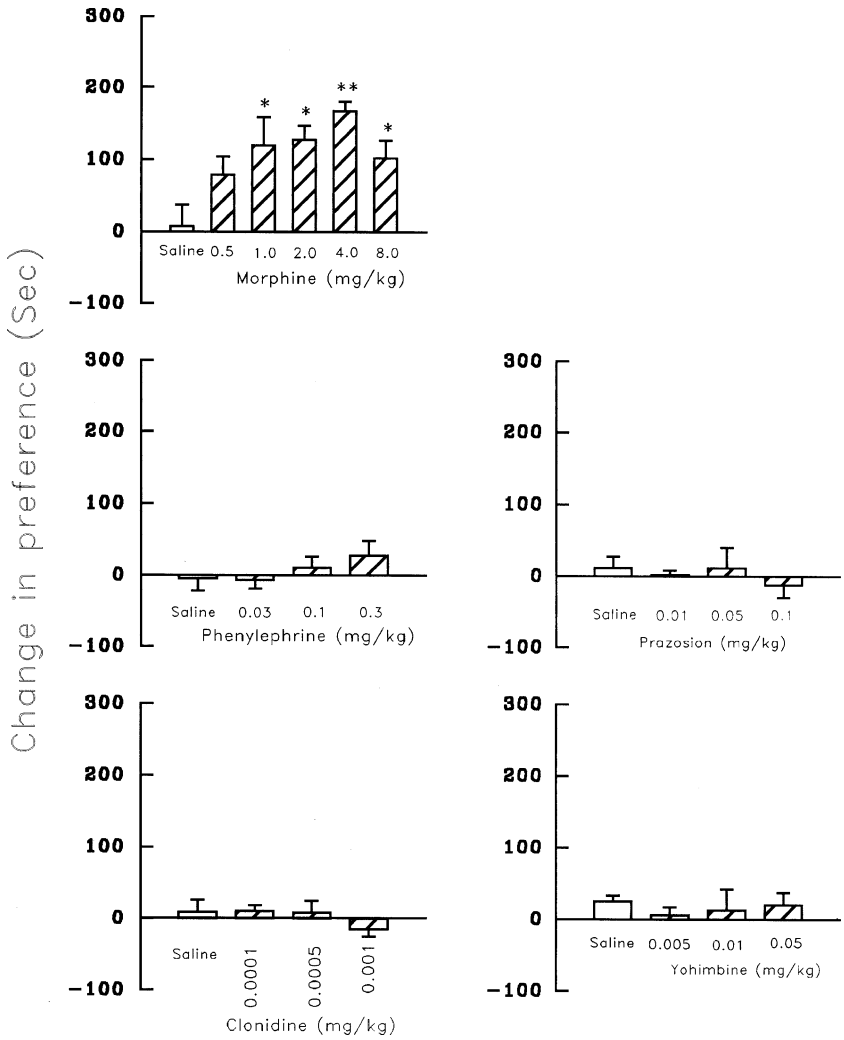

Fig. 1. Place conditioning induced by morphine and adrenoceptor agonists and antagonists. Animals received different doses of morphine (0.5, 1, 2, 4 and 8 mg/kg), phenylephrine (0.03, 0.1 and 0.3 mg/kg), prazosin (0.01, 0.05 and 0.1 mg/kg), clonidine (0.0001, 0.0005 and 0.001 mg/kg) and yohimbine (0.005, 0.01 and 0.05 mg/kg), and were tested on the sixth day in a drug-free state. Each point represents the mean ± S.E.M. of eight mice. * $P<.05$, * * $P<.01$ different from the saline control group.

before testing, on the test day. In a set of experiments, the adrenergic drugs were used alone in the conditioning phase, for evaluation of the motivational effects of the drugs. This part was identical to that described for morphine.

2.5. Drugs

The following drugs were used in these experiments: opioid receptor agonist, morphine sulfate (TEMAD, Iran); alpha-2 receptor agonist, clonidine hydrochloride; alpha-2 receptor antagonist, yohimbine hydrochloride; alpha-1 receptor agonist, phenylephrine hydrochloride and alpha-1 receptor antagonist, prazosin hydrochloride (Sigma, UK). The drugs were dissolved in saline (0.9%) and were injected intraperitoneally in a volume of 10 ml/kg. Morphine was injected subcutaneously in a volume of 10 ml/kg.

2.6. Data analysis

A change in preference, representing the time that the animal spent in the drug compartment in the test day minus the time that the animal spent in this compartment in the preconditioning day, was calculated and was expressed as mean ± S.E.M. Data were analyzed using one-way analysis of variance (ANOVA) following Student Newman–Keuls Multiple Comparisons Test. $P < .05$ was considered significant.

3. Results

3.1. Effects of morphine and alpha-adrenoceptor drugs on behavior in the CPP paradigm

The effects of morphine, phenylephrine, prazosin, clonidine and yohimbine have been shown in Fig. 1. Injection of different doses of morphine sulphate (1.0, 2.0, 4.0 and 8.0 mg/kg) to mice caused a significant increase in time spent in the drug-paired compartment compared to that spent in the saline-paired compartment [$F(4,35) = 5.5$, $P < .002$]. Subcutaneous injection of saline to the animals (saline control group) in the conditioning compartments did not produce any preference or aversion for either place. Based on these data, the dose of 4.0 mg/kg of morphine was selected for the rest of the experiments.

Injection of different doses of phenylepherine [0.03, 0.1 and 0.3 mg/kg; $F(3,29) = 1.2$, P=.34] or prazosin [0.01, 0.05 and 0.1 mg/kg; $F(3,27) = 1.02$, P=.23] to the animals did not alter the time spent in the drug-paired compartment compared to the saline-paired compartment. Similar results were obtained when clonidine [0.0001, 0.0005 and 0.001 mg/kg; $F(3,28) = 0.91$, P=.57] or yohimbine [0.005, 0.01 and 0.05 mg/kg; $F(3,28) = 0.85$, P=.7] was used for the investigation of motivational property of drugs in the animals.

3.2. Effects of alpha-1 adrenoceptor drugs on the expression of morphine-induced CPP

To determine the effects of alpha-1 adrenoceptors on the expression of morphine-induced CPP in mice, phenylepherine (an alpha-1 adrenoceptor agonist) and prazosin (an alpha-1 adrenoceptor antagonist) were administered 15 and 30 min (respectively) before the beginning of the test on the sixth day of the experiments. Administration of phenylepherine in doses of 0.03, 0.1 and 0.3 mg/kg decreased the expression of morphine-induced CPP [$F(3,28) = 11.34$, $P < .001$]. Prazosin (0.05 and 0.1 mg/kg) increased the expression of morphine-induced CPP [$F(3,26) = 6.54$, $P < .019$; Fig. 2].

3.3. Effects of alpha-2 adrenoceptor agents on the expression of morphine-induced CPP

To determine the effects of alpha-2 adrenoceptor drugs on the expression of morphine-induced CPP in mice, clonidine (an alpha-2 adrenoceptor agonist) and yohimbine (an alpha-2 adrenoceptor antagonist) were administered 15 and 30 min (respectively) before the beginning of the test on the sixth day of experiments. Administration of clonidine in 0.0005 and 0.001 mg/kg doses significantly decreased the expression of morphine-induced CPP [$F(3,28) = 12.4$, $P < .0008$], while administration of yohimbine (0.05 mg/kg), increased morphine-induced CPP [$F(3,29) = 2.88$, $P < .05$; Fig. 3].

3.4. Effects of alpha-1 adrenoceptor agents on the acquisition of morphine-induced CPP

Administration of different doses of phenylephrine, 15 min before morphine injection during the conditioning

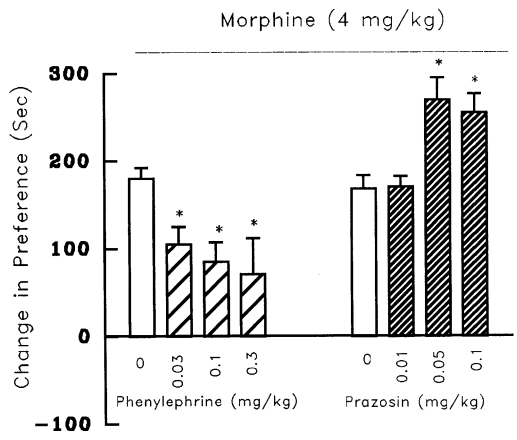

Fig. 2. Effects of phenylephrine and prazosin on the expression of morphine-induced CPP. Phenylephrine (0.03, 0.1 and 0.3 mg/kg) or prazosin (0.01, 0.05 and 0.1 mg/kg) was given on the test day 15 and 30 min (respectively) before the beginning of the test. Each point is the mean ± S.E.M. of eight mice. * $P < .05$ different from the saline control group.

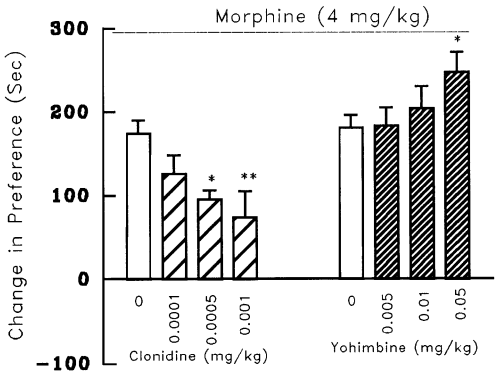

Fig. 3. Effects of clonidine and yohimbine on the expression of morphine-induced CPP. Clonidine (0.0001, 0.0005 and 0.001 mg/kg) or yohimbine (0.005, 0.01 and 0.05 mg/kg) was given on the test day 15 and 30 min (respectively) before the beginning of the test. Each point is the mean ± S.E.M. of eight mice. * $P<.05$ and * * $P<.01$ different from the saline control group.

phase altered morphine CPP [$F(3,29)=11.52$, $P<.0001$]. The lower dose (0.03 mg/kg) of the drug decreased, while the higher doses (0.1 and 0.3 mg/kg) increased morphine-induced CPP. Similar administration of prazosin (0.01, 0.05 and 0.1 mg/kg) 30 min before morphine injection during the conditioning phase, caused a significant decrease in morphine CPP [$F(3,29)=11$, $P<.0001$; Fig. 4].

3.5. Effects of alpha-2 adrenoceptor agents on the acquisition of morphine-induced CPP

Administration of clonidine (0.0001, 0.0005 and 0.001 mg/kg) 15 min before the beginning of morphine injection during the conditioning phase decreased morphine CPP [$F(3,29)=21$, $P<.0001$], while administration of yohimbine (0.05 mg/kg) 30 min before the beginning of morphine

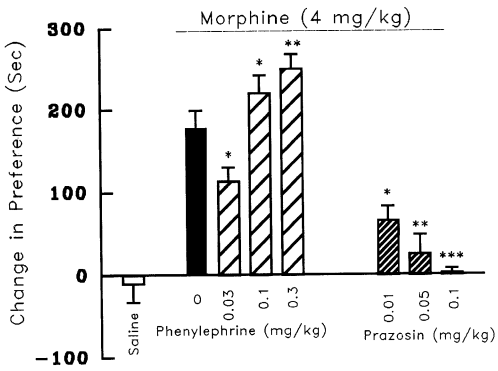

Fig. 4. Effects of phenylephrine and prazosin on the development (acquisition) of morphine-induced CPP. Phenylephrine (0.03, 0.1 and 0.3 mg/kg) or prazosin (0.01, 0.05 and 0.1 mg/kg) was given 15 and 30 min, respectively, before the beginning of morphine injection in the training days of the experiments. Each point is the mean ± S.E.M. of eight mice. * $P<.05$, * * $P<.01$ and * * * $P<.001$ different from the saline control group.

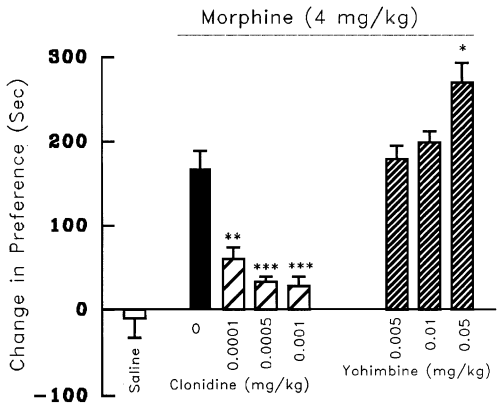

Fig. 5. Effects of clonidine and yohimbine on the development (acquisition) of morphine-induced CPP. Clonidine (0.0001, 0.0005 and 0.001 mg/kg) or yohimbine (0.005, 0.01 and 0.05 mg/kg) was given 15 and 30 min (respectively) before the beginning of morphine injection in the training days of the experiments. Each point is the mean ± S.E.M. of eight mice. * $P<.05$, * * $P<.01$ and * * * $P<.001$ different from the saline control group.

injection during the conditioning phase increased the morphine response [$F(3,29)=8.2$, $P<.0004$; Fig. 5].

4. Discussion

In the present study, morphine administration to female mice induced CPP in a dose-related manner. Because the method used is not state-dependent learning (see review, Tzschentke, 1998), all the animals were tested in drug-free state. These results are in agreement with those obtained by others in both male and female mice (see review, Tzschentke, 1998; Zarrindast et al., 2002, 2003). It is likely that dopamine mesocorticolimbic systems and μ-opioid receptors in these regions are the common substrates involved in this phenomenon (Koob, 1992; Mattes et al., 1996; Van Ree et al., 1999; McBride et al., 1999). However, there are also data indicating that nondopamine mechanism(s) may be involved in morphine reward (Kalivas and Stewart, 1991; Koob, 1992; Van Ree et al., 1999).

In the present study, phenylephrine (alpha-1 adrenoceptor agonist), clonidine (alpha-2 adrenoceptor agonist), prazosin (alpha-1 adrenoceptor antagonist) and yohimbine (alpha-2 adrenoceptor antagonist) did not produce CPP or CPA in female mice. These data are similar with results obtained previously that the alpha-adrenoceptor agents did not induce any response when used alone in male mice (Zarrindast et al., 2002). In contrast with the present data, it has been shown that clonidine induces CPA (Zarrindast et al., 2002; Hand et al., 1989) or CPP (Asin and Wirtshafter, 1985) and yohimbine induces CPA (File, 1986) in male mice. One explanation would be that the doses used in the present study are lower than that used in previous studies. This may be due to gender difference or the ability of the drugs to activate pre- or postsynaptic receptors which lead to the different responses.

Our data showed that phenylephrine and clonidine inhibit the expression of morphine-induced CPP. On the other hand, prazosin or yohimbine increased the time spent in the drug-paired compartment, i.e., increased in the expression of morphine-induced CPP in female mice. Thus, in agreement with the results obtained by others (Drouin et al., 2002; Zarrindast et al., 2002), it may be concluded that brain adrenoceptors have an essential role in the expression of morphine-induced CPP. However, our previous data indicated that clonidine, yohimbine and prazosin, but not phenylephrine, influence the expression of morphine-induced CPP in male mice (Zarrindast et al., 2002). The controversial responses obtained in the previous and present studies by phenylephrine, prezosin and yohimbine seem to be due to lower doses of the drugs used in the present study or mice gender. The present data showed that both agonists of alpha-1 and alpha-2 adrenoceptors have similar effects and thus, there is the possibility that activation of these receptors inhibit the expression of morphine CPP. In contrast, the data showed that the adrenoceptor antagonists enhanced the morphine response. These results indicate that there may be an adrenergic system which naturally has an inhibitory influence on the expression of morphine CPP. Moreover, the present data are not in agreement with the previous data showing that clonidine is ineffective in inhibiting the expression of conditioned opiate withdrawal (Schulteis et al., 1998) and discriminative-stimulus effects of morphine in rats (Hughes et al., 1996). The reason, which may explain the discrepancy, is that the paradigms that were used in those studies were completely different from ours. The conditioned opiate withdrawal represents the negative reinforcement properties of opiates (Schulteis et al., 1998), while the CPP paradigm is developed to investigate the positive reinforcement properties of natural rewards and abused drugs (Bozarth, 1987; Hoffman, 1989; Tzschentke, 1998). Because the adrenoceptor agonists and antagonists alter the morphine effect in our present study, one may conclude that brain adrenergic systems have an important role in the expression of conditioned reward induced by morphine.

Our data also indicated that both alpha-1 and alpha-2 receptor subtypes influence the acquisition of morphine CPP. Lower (0.03 mg/kg) and higher doses of phenylephrine (0.1 and 0.3 mg/kg) decreased or increased the acquisition of morphine CPP, respectively, while previous data indicated that phenylephrine did not change the acquisition of morphine CPP in male mice (Zarrindast et al., 2002). Because the response of the alpha adrenoceptors in females is different from the males (Turner et al., 1999), and because morphine produces different effects in male vs. female animals (Cicero et al., 2000), it may reflect the differences obtained in the present study. More studies may be required to clarify the biphasic results obtained by phenylephrine, because the drug may act on both alpha-1 and alpha-2 adrenoceptors. Blockade of alpha-1 adrenoceptors by prazosin decreased morphine CPP, which is similar to that obtained by us previously (2002) in male mice. Prazosin may also interact with alpha-2b receptors (Zarrindast et al., 2002) and therefore, the response of the drug may be due to the inhibition of alpha-2b receptors.

The response of the drugs in acquisition is opposite to that obtained in the expression. This may be due to different mechanisms involved in acquisition and expression of morphine CPP. Furthermore, clonidine decreased, while yohimbine increased the acquisition of morphine conditioning. This is in agreement with those obtained in male mice (Zarrindast et al., 2002; Tzschentke, 1998; Hand et al., 1989). The response obtained with clonidine and yohimbine in acquisition is similar to that obtained in the expression session for both drugs. There are reports that presynaptic alpha-2 receptor activity resulted in a reduction of adrenergic activity and postsynaptic alpha-2 receptors showed an adrenergic activity (Hoffman and Taylor, 2001); this may be the reason for the drugs which exerted the same response on the expression and acquisition of morphine CPP in the present study. However, a modulatory mechanism or gender differences may explain the results obtained. It must be considered that the results obtained with adrenergic agents in the acquisition phase are from animals which were in a morphine-free state in the test day. Therefore, for more interpretation of data, the effects of the drugs in animals which receive morphine in the test day may be needed.

Overall, in agreement with others (Drouin et al., 2002; Zarrindast et al., 2002), the present results may indicate involvement of alpha adrenoceptors in the expression and acquisition of morphine CPP in female mice.

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