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Cross-tolerance between morphine- and nicotine-induced conditioned place preference in mice

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Abstract

The acquisition of morphine and nicotine conditioned place preference (CPP) and cross-tolerance between the response of two drugs was studied in mice. A biased CPP paradigm was used to study the effect of the agents. Morphine (5 mg/kg) and nicotine (1 mg/kg) induced CPP. Naloxone (0.5, 1 and 2 mg/kg), but not mecamylamine (0.025, 0.05 and 0.1 mg/kg), induced conditioned place aversion (CPA). Both antagonists reversed CPP induced by morphine and nicotine. Administration of one daily dose of morphine (12.5, 25 or 50 mg/kg) for 3 days or nicotine (0.5, 1 or 2 mg/kg) three times a day for 12 days, in order to develop tolerance to the drugs, reduced the conditioning induced by morphine (5 mg/kg) or nicotine (1 mg/kg). CPA-induced by naloxone was reduced in animals, which were rendered tolerant to morphine (50 mg/kg) or nicotine (2 mg/kg). Mecamylamine, however, which did not induce any response in the nontolerant mice, elicited CPP in the tolerant animals. It is concluded that there may be a cross-tolerance between morphine- and nicotine-induced CPP.

Keywords: Morphine; Nicotine; Naloxone; Mecamylamine; Tolerance; Conditioned place preference

1. Introduction

Although human smoking behavior is a complex process with psychological and pharmacological components, nicotine appears to be the primary substance involved in this behavior. Nicotine exhibits several pharmacological actions in the central and peripheral nervous systems, and releases a number of neurotransmitters. The drug has effects on many neurochemical systems; it particularly increases dopaminergic and cholinergic activities (Watkins et al., 2000). There is evidence suggesting that nicotine activates the dopamine system and that such an activating effect underlies the reinforcing and stimulant effects of this drug (Watkins et al., 2000). Nicotine receptor stimulation activates enkephalin release and biosynthesis in discrete brain nuclei and adrenal chromaffin cells (Houdi et al., 1991). The drug also is involved in activating the opioid system(s) (Ismail and el-Guebaly, 1998). These findings may have some bearing on the observation that opiate addicts and cigarette smokers display parallel emotional profiles during abstinence from their habits (Gossop et al., 1990). We have shown previously that nicotine could attenuate jumping induced by the opioid receptor antagonist naloxone in morphine-dependent mice (Zarrindast and Farzin, 1996). Chronic administration of opioids (Bhargava, 1994) and nicotine (Pauly et al., 1992; Zarrindast et al., 1999, 2001) for long periods may result in the development of tolerance to their pharmacological actions. We also have shown that there is a cross-tolerance between morphine and nicotine antinociception (Zarrindast et al., 1999) and hypotheremia (Zarrindast et al., 2001) in mice.

Drugs of abuse, such as morphine and nicotine, share several behavioral and rewarding properties (Koob, 1992; Koob and Le Moal, 2001). These drugs produce a reinforcing effect, which, according to some hypotheses, may be due to their common property of facilitating dopaminergic transmissions (Di Chiara, 2000). The conditioned place preference (CPP) paradigm has been widely used as a model for studying

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the reinforcing effects of drugs with dependence liability (Tzschentke, 1998).

Tolerance develops to some of the behavioral effects of nicotine (Marks et al., 1983) and also to antinociception induced by morphine and nicotine (Zarrindast et al., 1999). Furthermore, both morphine (Carr and white, 1983; Olmstead and Franklin, 1997) and nicotine (Calcagnetti and Schechter, 1994) induce CPP. The present study investigated tolerance to morphine- and nicotine-induced CPP. In a set of experiments, the effects of the opioid receptor antagonist naloxone and the nicotinic receptor antagonist mecamylamine on morphine and nicotine CPP were examined.

2. Materials and methods

2.1. Animals

Female NMRI mice (20–25 g) were used. The animals (Pasteur Institute, Tehran, Iran) were housed 10 per cage in an animal room that was lit for 12 h/day (lights on at 7:00 a.m.) in a temperature-controlled environment (23 ± 1 °C). Food and water were available continuously. Each animal was used only once, and attention was paid to the ethical guidelines for investigations of experimental pain in conscious animals. The experimental protocol was approved by the Ethical Committee of Baghyatollah University (78/105; 1 March 2000).

2.2. Drugs

The following drugs were used: morphine sulphate (Temad, Iran), naloxone hydrochloride (Sina-Daru, Iran), nicotine base and mecamylamine (Sigma, UK). The control groups received saline. All drugs were dissolved in normal saline (0.9%) and administered intraperitoneally except morphine, which was injected subcutaneously.

2.3. Development of tolerance to morphine or nicotine

Tolerance to morphine was achieved on the method based on our previous work (Rezayat et al., 1994). The mice were randomly treated subcutaneously with morphine (12.5, 25 and 50 mg/kg) or saline (0.9%; 10 ml/kg) once daily (8:00 a.m.), for a period of 3 days. Tolerance to nicotine was obtained using the method of Pauly et al. (1992). The animals were treated intraperitoneally with nicotine (0.5, 1.0 and 2.0 mg/kg) three injections per day (8:00 a.m., 1:00 p.m. and 6:00 p.m.) for a period of 12 days. Each animal was used only once.

2.4. Apparatus

The place preference apparatus based on the design of Kivastik et al. (1996) was made of wood and consisted of two square-base compartments (15 × 15 × 15). One was painted white and the other black. There is a texture on the floor area of the black compartment. Compartments were separated by a guillotine door and covered with a transparent Plexiglas ceiling.

2.5. CPP paradigm

The CPP paradigm took place on 5 consecutive days, using a biased procedure. Because all of the animals preferred the black compartment, they were conditioned to the white compartment. CPP training began after tolerance was achieved. Injections and CPP testing were performed in the same room.

2.5.1. Preconditioning

On day 1, each mouse was placed separately into the apparatus for 10 min, with free access to the two compartments.

2.5.2. Conditioning

This phase consisted of a 3-day schedule of double conditioning sessions. The first day involved a morning session (9:00–11:00 h), in which animals received a single subcutaneous dose of morphine sulfate or intraperitoneal dose of nicotine, and were placed immediately in the white compartment for 30 min. This compartment had been isolated from the other using a removable partition. In the evening session (15:00–17:00 h), the animals received a single subcutaneous injection of saline, and were placed for 30 min in the black compartment. On the second day of conditioning, the animals received the saline injections in the morning session and the drug administration in the evening session. The third day of conditioning had the same schedule as the first day.

2.5.3. Postconditioning

On the 5th day of the schedule, as in the preconditioning phase, the partition was raised and the mice were placed in the apparatus (between the white and black compartments) and allowed again to freely explore the two compartments. The time spent in the white (drug-paired side) or black (saline-paired side) compartment was recorded for each mouse for 10 min as follows:

1. CPP = time spent in the drug-paired side > time spent in the saline-paired side
2. conditioned place aversion (CPA) = time spent in the drug-paired side < time spent in the saline-paired side

2.6. Drug treatment

In order to test the effects of morphine and nicotine on the acquisition of CPP, drugs were injected immediately before each conditioning session. The tests were carried out 24 h after the last conditioning session without any preceding injection. In order to evaluate the effects of naloxone (0.5, 1 and 2 mg/kg ip) and mecamylamine (0.025, 0.05 and

0.1 mg/kg ip) on the acquisition of CPP, these drugs were injected 5, 5 and 30 min, respectively, before treatment with either morphine or nicotine. The drugs were injected in the same room in which the CPP was measured.

2.7. Statistical analysis

Conditioning scores represent the time spent in the drug-paired compartment minus the time spent in the saline-paired compartment, and are expressed as the mean ± S.E.M. (Susuki, 1995). One- or two-way analysis of variance (ANOVA), followed by Tukey HSD test for multiple post-hoc comparisons, was used to evaluate the significance of the drug effects. A value of $P < .05$ was considered significant.

3. Results

3.1. Dose–response effects of place conditioning produced by morphine and nicotine

The place conditioning produced by morphine is shown in Fig. 1. One-way ANOVA shows a significant difference between the response of subcutaneous administration of different doses of morphine (1.0, 2.5, 5 and 10 mg/kg) or nicotine (0.5, 0.75, 1.0 and 2.0 mg/kg ip) with that of the control [$F(8,63) = 6.0$, $P < .0001$]. The doses of 5 mg/kg of morphine and 1.0 mg/kg of nicotine induced significant CPP relative to saline.

3.2. Effects of naloxone on the acquisition of CPP per se and in the presence of morphine or nicotine

Fig. 2 shows the effect of the opioid receptor antagonist naloxone on the CPP induced by morphine and naloxone. In this experiment, animals were treated with different doses of naloxone (0.5, 1.0 and 2.0 mg/kg ip) in order to evaluate the effect of the antagonist on the acquisition of CPP. Naloxone (1.0 mg/kg) caused a significant decrease in the time spent in the drug-paired side compared to the time spent in the saline-paired side (CPA).

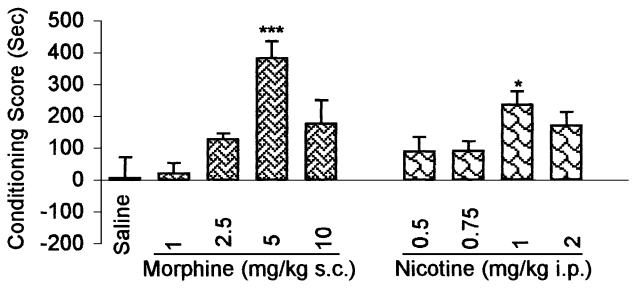

Fig. 1. Effect of morphine (1.0, 2.5, 5 and 10 mg/kg sc) or nicotine (0.5, 0.75, 1.0 and 2.0 mg/kg ip) on place conditioning. Ordinate: mean difference (s) between times spent in the drug- and saline-paired sides of the test box. Each point represents the mean ± S.E.M. of eight mice. $^{*}P < .05$, $^{***}P < .001$ different from saline control group.

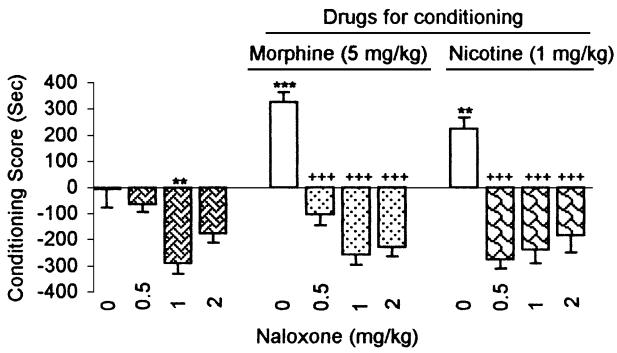

Fig. 2. Effects of naloxone on the acquisition of CPP per se and in the presence of morphine or nicotine. Different doses of naloxone (0.5, 1.0 and 2.0 mg/kg ip) were injected immediately before each conditioning session or 5 min before morphine (5 mg/kg) or nicotine (1 mg/kg). Animals were tested 24 h after the last conditioning session. Each point represents the mean ± S.E.M. of eight mice. $^{**}P < .01$, $^{***}P < .001$ different from saline control group. $^{+++}P < .001$ different from respective morphine or nicotine control group.

Also, two-way ANOVA revealed that naloxone significantly decreased CPP induced by morphine [within group comparison, treatment: $F(1,56) = 5.0$, $P < .05$; dose: $F(3,56) = 39.5$, $P < .001$; interaction: $F(3,56) = 8.9$, $P < .001$] and nicotine [within group comparison, treatment: $F(1,56) = 0.4$, $P > .05$; dose: $F(3,56) = 22.4$, $P < .001$; interaction: $F(3,56) = 6.4$, $P < .01$]. The results indicate that, even the lower dose of naloxone (0.5 mg/kg), which did not produce much aver sion by itself, still reversed the preference shown for morphine and nicotine.

3.3. Effects of mecamylamine on the acquisition of CPP per se and in the presence of morphine or nicotine

Fig. 3 indicates the effect of the nicotine receptor antagonist mecamylamine on the CPP induced by morphine

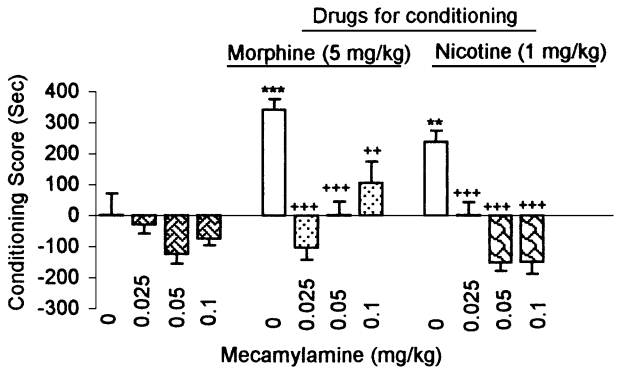

Fig. 3. Effects of mecamylamine on the acquisition of CPP per se and in the presence of morphine or nicotine. Different doses of mecamylamine (0.025, 0.05 and 0.1 mg/kg ip) were injected immediately before each conditioning session or 30 min before morphine (5 mg/kg) or nicotine (1 mg/kg). Animals were tested 24 h after the last conditioning session. Each point represents the mean ± S.E.M. of eight mice. $^{**}P < .01$, $^{***}P < .001$ different from saline control group. $^{++}P < .01$, $^{+++}P < .001$ different from the respective morphine or nicotine control groups.

and nicotine. Administration of mecamylamine (0.025, 0.05 and 0.1 mg/kg ip) in conditioning sessions by itself did not show any response. Pretreatment with the drug 30 min before each conditioning session significantly decreased CPP induced by morphine [within group comparison, treatment: $F(1,56)=17.3$, $P<.001$; dose: $F(3,56)=14.3$, $P<.001$; interaction: $F(3,56)=6.0$, $P<.001$] and nicotine [within group comparison, treatment: $F(1,56)=1.2$, $P>.05$; dose: $F(3,56)=20.6$, $P<.001$; interaction: $F(3,56)=4.7$, $P<.01$]. The data show that mecamylamine is able to reverse morphine- and nicotine-induced CPP.

3.4. CPP response induced by morphine or nicotine in morphine-tolerant mice

Fig. 4 shows the effect of tolerance to morphine on the CPP induced by morphine or nicotine in mice. Animals were treated with morphine (12.5, 25 and 50 mg/kg sc) once daily for 3 days in order to induce tolerance to morphine. CPP was induced by morphine (5 mg/kg sc) or nicotine (1 mg/kg ip) from days 4 to 7. CPP response in tolerant animals was measured on test day 8 (24 h after the last conditioning session). Data indicate that repeated administration of morphine before conditioning blocked the acquisition of CPP induced by morphine [one-way ANOVA; $F(3,27)=20.2$, $P<.0001$] or nicotine [one-way ANOVA; $F(3,28)=10.9$, $P<.0001$]. The results show that tolerance to morphine reduced morphine- and nicotine-induced CPP.

3.5. CPP effect induced by morphine or nicotine in nicotine-tolerant animals

Fig. 5 shows the tolerance to nicotine on the CPP induced by morphine or nicotine in mice. Animals were injected with nicotine (0.5, 1.0 and 2.0 mg/kg ip) three times a day for a period of 12 days, in order to induce tolerance, and then CPP training was carried out on days 13–16. The CPP response to

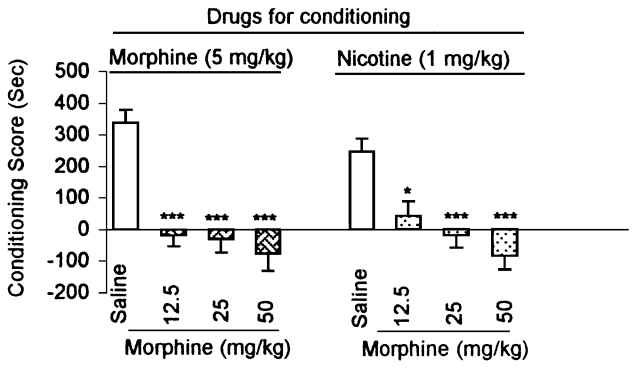

Fig. 4. CPP response of morphine or nicotine in morphine-tolerant mice. Animals were treated with morphine (12.5, 25 and 50 mg/kg sc, once daily for 3 days) in order to induce tolerance, and CPP induced by morphine (5 mg/kg sc) or nicotine (1 mg/kg ip) was measured on the test day, 24 h after the last conditioning session. Each point represents the mean ± S.E.M. of eight mice. * $P<.05$, * * * $P<.001$ different from saline control group.

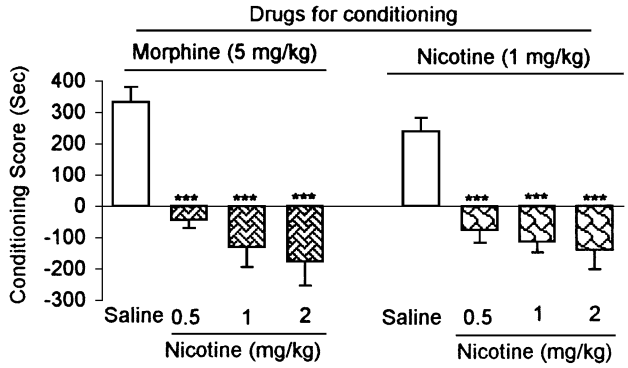

Fig. 5. CPP response of morphine or nicotine in nicotine-tolerant mice. Animals were treated with nicotine (0.5, 1.0 and 2.0 mg/kg ip) three times a day for a period of 12 days in order to induce tolerance, and CPP induced by morphine (5 mg/kg sc) or nicotine (1 mg/kg ip) was measured on the test day, 24 h after the last conditioning session. Each point represents the mean ± S.E.M. of eight mice. * * * $P<.001$ different from saline control group.

morphine (5 mg/kg sc) or nicotine (1 mg/kg ip) was tested on test day 17. Data show that repeated administration of nicotine before conditioning blocked the acquisition of CPP induced by morphine [one-way ANOVA; $F(3,28)=16.1$, $P<.0001$] or nicotine [one-way ANOVA; $F(3,27)=15.5$, $P<.0001$]. The data indicate that tolerance to nicotine reduced morphine- and nicotine-induced CPP.

3.6. Effects of tolerance to morphine or nicotine on naloxone-induced CPA

Fig. 6 shows the effect of tolerance to morphine or nicotine on the CPA induced by naloxone. Mice were tolerant to a dose of morphine (50 mg/kg sc) or nicotine (2.0 mg/kg ip) as described before, and then naloxone-induced CPA was elicited as described in Section 2. The response of different doses of naloxone (0.5, 1.0 and 2.0 mg/kg ip) was tested 24 after the last naloxone administration. Results show that CPA induced by naloxone was decreased by repeated administra-

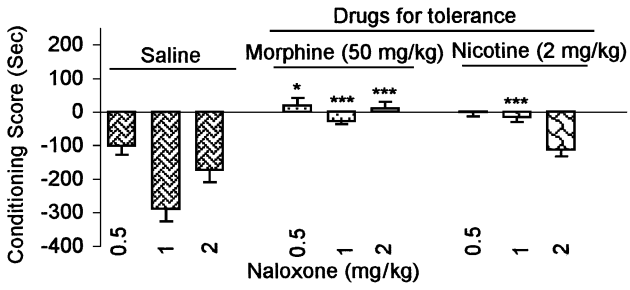

Fig. 6. Effects of tolerance to morphine or nicotine on naloxone-induced CPA. Mice were injected with morphine (50 mg/kg sc, once daily for 3 days) or nicotine (2.0 mg/kg ip, three times a day for a period of 12 days) in order to induce tolerance, and the CPA response to different doses of naloxone (0.5, 1.0 and 2.0 mg/kg ip) were tested 24 after the last administration of naloxone. Each point represents the mean ± S.E.M. of eight mice. * $P<.05$, * * * $P<.001$ different from respective saline control group.

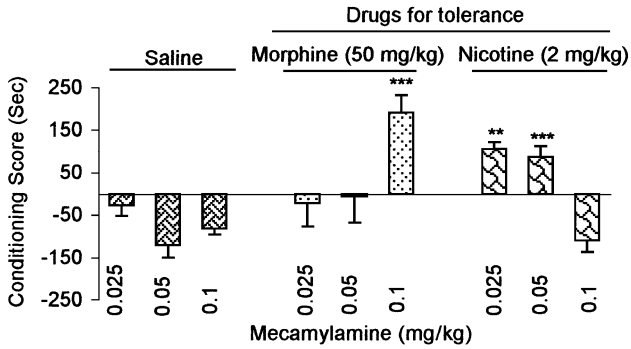

Fig. 7. Effects of tolerance to morphine or nicotine on the mecamylamine-induced response. Mice were injected with morphine (50 mg/kg sc, once daily for 3 days) or nicotine (2.0 mg/kg ip, three times a day for a period of 12 days) in order to induce tolerance, and the response to different doses of mecamylamine (0.025, 0.05 and 0.1 mg/kg ip) were tested 24 after the last administration of mecamylamine. Each point represents the mean ± S.E.M. of eight mice. $^{**}P<.01$, $^{***}P<.001$ different from respective saline control group.

tion of morphine [within group comparison, treatment: $F(1,42)=70.3$, $P<.001$; dose: $F(2,42)=12.2$, $P<.001$; interaction: $F(2,42)=4.7$, $P<.05$] or nicotine [within group comparison, treatment: $F(1,42)=44.6$, $P<.001$; dose: $F(2,42)=9.2$, $P<.001$; interaction: $F(2,42)=9.2$, $P<.001$]. The data show that tolerance to morphine or nicotine reduced naloxone-induced CPA.

3.7. Effects of tolerance to morphine or nicotine on the mecamylamine-induced response

Fig. 7 shows the effect of mecamylamine in tolerance to morphine or nicotine in mice. Animals were rendered tolerant to morphine (50 mg/kg sc) or to nicotine (2.0 mg/kg ip), and then conditioning was achieved as before and the response to different doses of mecamylamine (0.025, 0.05 and 0.1 mg/kg ip) was measured 24 after the last mecamylamine administration. The results show that the doses of mecamylamine, which did not show any response in non-tolerant mice, induced CPP in the animals, which were made tolerant to morphine [within group comparison, treatment: $F(1,42)=12.9$, $P<.01$; dose: $F(2,42)=4.0$, $P<.05$; interaction: $F(2,42)=6.1$, $P<.01$] or nicotine [within group comparison, treatment: $F(1,42)=29.9$, $P<.001$; dose: $F(2,42)=13.4$, $P<.001$; interaction: $F(2,42)=12.0$, $P<.001$]. The results show that mecamylamine induced CPP in animals which were tolerant to morphine or nicotine.

4. Discussion

Most drugs of abuse evoke dopamine release in the terminal fields of ventral tegmental area dopamine neurons (Di Chiara and Imperato, 1988; Koob, 1992). The role of dopamine in the behavioral actions of nicotine, in relation to addiction, has been demonstrated previously (Di Chiara, 2000). Opioid mechanisms in the behavioral effects (Corrigall et al., 1988; Pomerleau, 1998) and opioid peptides in the reinforcing effects (Watkins et al., 2000) of nicotine also have been indicated. Furthermore, the CPP paradigm has been widely used as a model for studying both the reinforcing properties of drugs of abuse and drug craving (Tzschentke, 1998).

In the present study, the CPP induced by morphine or nicotine was tested to determine tolerance to their place conditioning responses and cross-tolerance between the responses of these two drugs.

The present data are in accordance with previous studies indicating that morphine (Olmstead and Franklin, 1997; Rodriguez De Fonseca et al., 1995) and nicotine (Shoaib et al., 1994) induce CPP. In agreement with others (see Tzschentke, 1998), the administration of naloxone by itself induced CPA, but mecamylamine (intraperitoneally) did not show any effect on place conditioning or place aversion. Pretreatment of animals with the lower dose of naloxone during conditioning sessions significantly decreased CPP induced by morphine or nicotine. The data obtained indicate that opioid receptor mechanisms may be involved in both morphine- and nicotine-induced CPP. Similar results for morphine CPP have been shown by Koob (1992). Since mecamylamine, which is a central nicotinic receptor antagonist (Martin et al., 1989), also reduced the place conditioning effect of both nicotine and morphine, this may point to a possible central nicotinic component in the CPP induced by nicotine or morphine. Intracellular recording experiments have shown that nicotine depolarizes ventral tegmental area dopamine neurons due to stimulation of nicotinic receptors (Calabresi et al., 1989) and local infusion of nicotine into the ventral tegmental area has been shown to increase dopamine release in the nucleus accumbens (Nisell et al., 1994). This may indicate that the response of the drug is elicited by an increase in dopaminergic function. However, blockade of morphine CPP by mecamylamine and nicotine CPP by naloxone may show that an interaction between nicotinic receptors and opioid systems may be involved in controlling the release of dopamine and the induction of CPP.

Drug tolerance can be defined as a reduction of response to a challenging dose following repeated administration of that drug. The present data showed that morphine CPP was reduced by repeated administration. Tolerance to the effects of morphine, including hypothermia (Bhargava, 1994) and antinociception (Zarrindast et al., 1999), have been demonstrated before. Several mechanisms have been proposed to mediate morphine tolerance. The μ-opioid (Sanchez-Blazquez et al., 1996; Wang et al., 1994) and δ-opioid receptors (Kest et al., 1996) have been implicated in the development of tolerance and dependence to morphine. Several studies also have demonstrated that tolerance develops to the effects of nicotine on antinociception (Zarrindast et al., 1999) and body temperature (Zarrindast et al., 2001). In agreement with these data, the present results showed that nicotine CPP

could be reduced in animals that repeatedly received nicotine. The aim of the present study was to evaluate the ability of morphine or nicotine to alter the development of tolerance to CPP induced by either drug.

The present data also showed that the CPP induced by morphine and nicotine were reduced in nicotine- and morphine-tolerant mice respectively. In the present study, repeated doses of morphine induced tolerance to the place conditioning effect of both morphine and nicotine. The data may show a cross-tolerance between the effects of the two drugs. An interaction between nicotine receptors and the opioid systems has been observed in relation to the release of endogenous opioid peptides including enkephalins (Eiden et al., 1984; Davenport et al., 1990; Houdi et al., 1991) and beta-endorphin (Rosecrans et al., 1985). There is evidence indicating that nicotine attenuates naloxone-induced jumping (Zarrindast and Farzin, 1996). Cross-tolerance between antinociception (Zarrindast et al., 1999) and hypothermia (Zarrindast et al., 2001) induced by morphine and nicotine also has been shown. These findings may indicate a common pathway or similar mechanism(s) involved in the development of tolerance to morphine or nicotine CPP.

Our present data showed that tolerance to either morphine or nicotine even decreased naloxone-induced CPA. Mecamylamine, which had no effect in naïve animals, induced CPP in morphine- or nicotine-tolerant animals. In summary, the results suggest an extensive interaction between opioid and nicotinic cholinergic mechanisms in mediating rewarding or aversive consequences of drug administration.

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