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The effects of nitric oxide on the acquisition and expression of nicotine-induced conditioned place preference in mice

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This article is dedicated to the memory of Dr. Mansour Falahi, who died in March 2001 shortly before completing the dissertation studies described here and after a year-long struggle against cancer. Throughout, Mansoor evinced a degree of courage and dedication that we can only describe as heroic. His premature death is a loss to pharmacology as well as to those knew him.

Abstract

In the present study, the possible role of nitric oxide on the conditioned place preference (CPP) induced by nicotine in mice was investigated. Intraperitoneal (i.p.) injections of nicotine (1 mg/kg) and the nitric oxide (NO) precursor, L-arginine (200 and 500 mg/kg), produced significant place preference. However, injection of mecamylamine (0.05 and 0.1 mg/kg; i.p.) or the NO synthase (NOS) inhibitor, L-Nitro-amino-methyl-ester, L-NAME (5–20 mg/kg; i.p.), had no effect. Ineffective doses of nicotine in combination with ineffective doses of L-arginine produced significant place preference.

Administration of L-arginine (50, 100 and 150 mg/kg; i.p.) on the test day reduced the expression of nicotine-induced place preference. Nicotine injection (0.25, 0.5 and 0.75 mg/kg) on the test day reduced the expression of place preference induced by L-arginine, while both mecamylamine (0.05 and 0.1 mg/kg) and L-NAME (5, 10 and 20 mg/kg) inhibited the acquisition of place preference induced by nicotine (1 mg/kg) and L-arginine (200 mg/kg). Moreover, neither of the antagonists reduced the expression of nicotine- or L-arginine-induced place preference. It is suggested that nitric oxide may play an important role in nicotine-induced place preference.

Keywords: Nitric oxide; Nicotine; Conditioned place preference; (Mouse); L-arginine; L-NAME

1. Introduction

It is now widely accepted that a majority of habitual tobacco smokers become dependent upon the nicotine present in tobacco smoke, and that this accounts for the problems many smokers experience when they try to quit the habit (Benowitz, 1988, 1996). Evidence suggests that nicotine has neurochemical as well as behavioral properties common to other psychostimulants (Di Chiara, 2000). Considerable evidence suggests that the behavioral and reinforcing effects of nicotine may be mediated by central dopaminergic systems, especially the mesolimbic system from the ventral tegmental area to the nucleus accumbens (Wise, 1998). Glutamatergic neurotransmission might also

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be a critical neurochemical determinant of nicotine dependence (Balfour et al., 2000; Vleeming et al., 2002). Furthermore, pharmacological studies suggested that glutamate releases nitric oxide (NO) through activation of *N*-methyl-D-aspartate (NMDA) receptors (Fedele and Raiteri, 1999). NO is a gas produced by many mammalian cells and is synthesized from L-arginine by NO synthase (NOS) (Bredt and Snyder, 1992). According to the results of previous studies, NO may be implicated in the action of nicotine; for instance, inhibitors of NOS can prevent nicotine tolerance (Uzbay and Oglesby, 2001; Malin et al., 1998) and attenuate the development and expression of the nicotine abstinence syndrome (Malin et al., 1998; Adams and Cicero, 1998). Moreover, it has been shown that nicotine increases NOS activity and thus NO production in various sites in the central nervous system (Pogun et al., 2000; Tonnessen et al., 2000).

There are also data which indicate that NO may play a role in nicotine dependence. For example, inhibition of NOS by 7-nitro-indazole inhibits the development of place preference induced by nicotine (Martin and Itzhak, 2000), nicotine-induced behavioral sensitization in the rat (Shim et al., 2002), and antagonist-precipitated withdrawal in nicotine-dependent rats (Adams and Cicero, 1998).

It seems that this major and widespread interaction between nicotine and NO supports the idea that the rewarding properties of nicotine may be due to an interaction between nicotinic and NO systems. Based on these data, the present study focuses on changes in NO levels and the effect on the development and expression of nicotine-induced place preference in mice.

2. Materials and methods

2.1. Animals

Male albino Swiss-Webster mice (20–25 g, Razi Institute, Tehran, Iran) were used throughout the study (10 mice for each experiment). Animals were housed in groups of five per cage under a 12/12-h light cycle (07:00–19:00), with food and water available ad libitum. The animals were randomly allocated to different experimental groups.

2.2. Drugs

Nicotine base, mecamylamine, N^G-nitro-L-arginine methyl-ester (L-NAME) and L-arginine (Sigma, CA, USA) were dissolved in saline (0.9%) and intraperitoneally (i.p.) administered in volumes of 10 ml/kg. Nicotine solutions were prepared in saline with the pH adjusted to 7.2±0.1. All drugs were administered according to salt weight except for nicotine, which was administered according to base weight.

2.3. Apparatus

The apparatus, which has been previously described (Sahraei et al., 2002; Carr and White, 1983), consisted of two (A and B) large adjacent compartments (45×45×30 cm) as well as a communicating tunnel (23×15×30 cm) attached to one side. The conditioning compartments (A and B) were painted white and black. Access to the tunnel could be blocked by a removable partition. In the particular experimental set-up used in the present study, the animals did not show an unconditioned preference for either of the compartments (white side=364±51 s, black side=330±35 s), which supported our unbiased method. In addition, the drug and control compartments were randomly assigned for each animal in a counterbalanced way. All experiments were conducted in accordance with standard ethical guidelines and were approved by the local ethics committee (The Baghyatallah University of Medical Committee on the Use and Care of Animals, 125; June 23, 2001).

2.4. Experimental procedure

2.4.1. Measurement of conditioned place preference

Conditioned place preference (CPP) consisted of three phases: pre-conditioning, conditioning and post-conditioning.

2.4.1.1. Pre-conditioning. On day 1 (pre-exposure), each mouse was placed separately into the apparatus for 10 min, with free access to all compartments (A, B and C).

2.4.1.2. Conditioning. This phase consisted of a 6-day schedule of conditioning sessions. In this phase, animals received three trials (i.e. days 2, 4 and 6) in which they experienced the effects of the drugs while confined to one compartment for 30 min. On the other days (i.e. days 3, 5 and 7), they received a normal saline injection and were confined to the other compartment. Access to the communicating tunnel was blocked on these days.

2.4.1.3. Post-conditioning phase. On the 8th day (the preference test day), the communicating tunnel was opened, and the mice could access all compartments. The mean time that each mouse spent in each compartment during a 15-min period was determined as the preference criteria. No injection was given in the acquisition tests.

2.5. Experimental procedure

2.5.1. Experiment 1: dose–response effects of place conditioning produced by the drugs

In this experiment, different doses of nicotine (0.25, 0.5, 0.75, 1 and 2 mg/kg; i.p.), mecamylamine (0.05 and 0.1 mg/kg; i.p.), L-arginine (50, 100, 150, 200 and 500 mg/kg; i.p.) and L-NAME (5, 10 and 20 mg/kg; i.p.) were tested for producing place preference. Four separate groups of animals

received saline (10 ml/kg; i.p.) in two compartments (A and B) in order to confirm that the injection and conditioning schedules did not affect the time spent in the compartments. These groups were used as control (Fig. 1).

2.5.2. Experiment 2: effects of L-arginine in combination with nicotine on the acquisition of conditioned place preference

In order to show the possible interaction of nicotine with NO on the acquisition of place preference, the first group of animals received either saline (10 ml/kg; i.p.) or different doses of L-arginine (50, 100 and 150 mg/kg) immediately before the administration of an ineffective dose of nicotine (0.5 mg/kg; i.p.) during conditioning sessions and were tested on the 8th day of the schedule with no preceding injection (Fig. 2A).

Similarly, a second group of animals received either saline (10 ml/kg; i.p.) or different doses of nicotine (0.25, 0.5 and 0.75 mg/kg) immediately before the administration of an ineffective dose of L-arginine (50 mg/kg; i.p.) during conditioning sessions and were tested on the 8th day of the schedule with no preceding injection (Fig. 2B).

2.5.3. Experiment 3: effects of mecamylamine and L-NAME on the acquisition of conditioned place preference induced by nicotine or L-arginine

To test the antagonistic influence of nicotine receptor antagonist or NOS inhibition on the acquisition of place

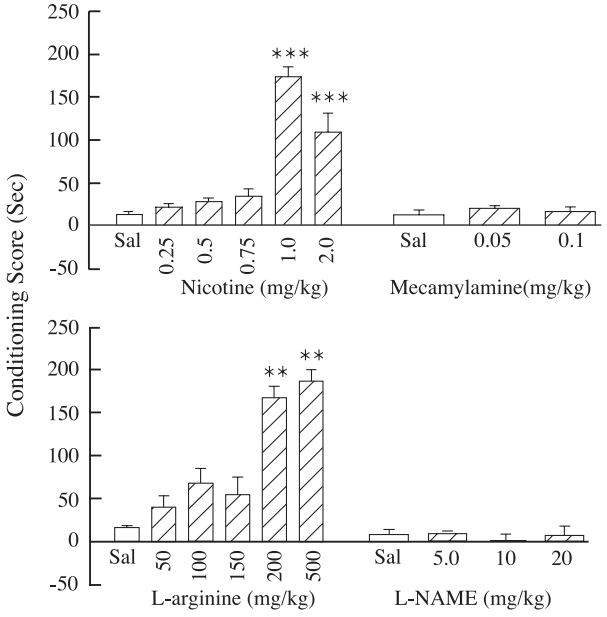

Fig. 1. Effects of nicotine, mecamylamine, L-arginine and L-NAME on conditioned place preference (CPP). Animals received saline (10 ml/kg) or different doses of nicotine (0.25–2 mg/kg), mecamylamine (0.05 and 0.1 mg/kg), L-arginine (50–500 mg/kg) and L-NAME (5–20 mg/kg) during a 3-day schedule of conditioning. Conditioning score is defined as the time spent in the drug-paired place minus that spent in the saline-paired place. Each point is the mean±S.E.M. for 10 mice. $^{**}P<0.01$, $^{***}P<0.001$ different from respective saline control group.

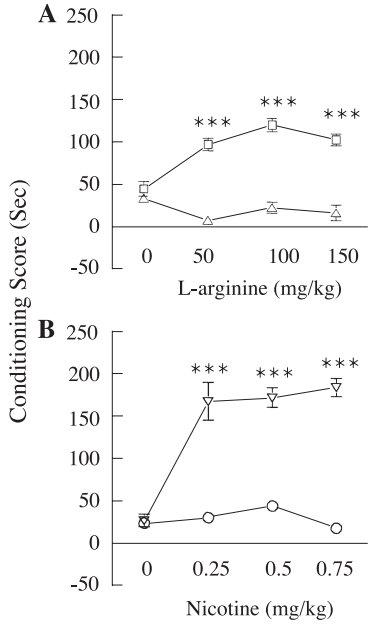

Fig. 2. Effects of a combination of nicotine with L-arginine on the acquisition of conditioned place preference. (A) Indicates the effects of different doses of L-arginine (50, 100 and 150 mg/kg) in the presence (□) or the absence (△) of an ineffective dose of nicotine (0.5 mg/kg). (B) Shows the effects of different doses of nicotine (0.25, 0.5 and 0.75 mg/kg) in the presence (▽) or the absence (○) of an ineffective dose of L-arginine (50 mg/kg). Conditioning score is defined as in Fig. 1. Each point is the mean±S.E.M. for 10 mice. $^{***}P<0.001$ different from respective saline control group.

preference induced by nicotine or L-arginine, one group of animals received either saline (10 ml/kg), mecamylamine (0.05 and 0.1 mg/kg; i.p.) or L-NAME (5, 10 and 20 mg/kg; i.p.) and 20 min later were injected with nicotine (1 mg/kg; i.p.; Fig. 3A). A second group of animals received either saline (10 ml/kg), L-NAME (5, 10 and 20 mg/kg; i.p.) or mecamylamine (0.05 and 0.1 mg/kg; i.p.) and 20 min later were injected with L-arginine (200 mg/kg; Fig. 3B) during the conditioning sessions.

2.5.4. Experiment 4: effects of L-arginine on the expression of nicotine-induced conditioned place preference

In order to examine the possible influence of NO on the expression of nicotine-induced place preference, all the animals were conditioned with nicotine (1 mg/kg; i.p.) and tested 24 h later. They received either saline (10 ml/kg; i.p.) as control or different doses of L-arginine (50, 100 and 150 mg/kg; i.p.) immediately before the test session (Fig. 4A).

2.5.5. Experiment 5: effects of nicotine on the expression of L-arginine-induced conditioned place preference

To test the possible influence of nicotine on the expression of L-arginine-induced place preference, all animals were conditioned with L-arginine (200 mg/kg; i.p.) and tested 24 h later. They received either saline (10 ml/kg; i.p.) as control or different doses of nicotine (0.25,

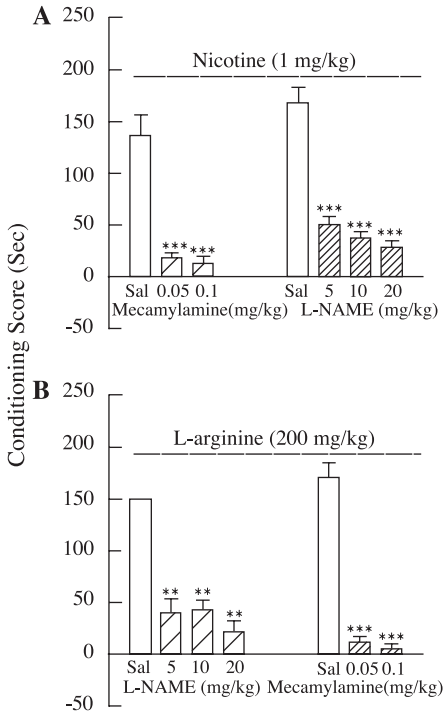

Fig. 3. Effects of mecamylamine and L-NAME on the acquisition of place preference induced by nicotine or L-arginine. A group of animals received a dose of nicotine (1 mg/kg) during a 3-day schedule of conditioning, in the presence of saline (10 ml/kg) and different doses of either mecamylamine (0.05 and 0.1 mg/kg) or L-NAME (5, 10 and 20 mg/kg) (A). Another group of animals received a dose of L-arginine (200 mg/kg) during a 3-day schedule of conditioning, in the presence of saline (10 ml/kg) and different doses of either L-NAME (5, 10 and 20 mg/kg) or mecamylamine (0.05 and 0.1 mg/kg) (B). Conditioning score is defined as in Fig. 1. Each point is the mean±S.E.M. for 10 mice. $^{**}P<0.01$, $^{***}P<0.001$ different from respective saline control group.

0.5 and 0.75 mg/kg; i.p.) immediately before the test session (Fig. 4B).

2.5.6. Experiment 6: effects of mecamylamine and L-NAME on the expression of conditioned place preference induced by nicotine or L-arginine

To examine the antagonistic effects of mecamylamine or L-NAME on the expression of place preference induced by the drugs, the animals were conditioned with nicotine (1 mg/kg; Fig. 5A) or L-arginine (200 mg/kg; i.p.; Fig. 5B) and tested 24 h after the last conditioning session. They received either saline (10 ml/kg), mecamylamine (0.05 and 0.1 mg/kg) or L-NAME (5, 10 and 20 mg/kg) 20 min before the test session.

2.6. Statistical analysis

The conditioning scores representing the time spent in the drug-paired place minus the time spent in the saline-paired place are presented as the means±S.E.M. for 10 animals (Zarrindast et al., 2003). In order to test the hypothesis, one-way and two-way analyses of variance (ANOVA) followed by Tukey test were performed to assess specific group comparisons. Differences with $P<0.05$ were considered statistically significant.

3. Results

3.1. Effects of nicotine, mecamylamine, L-arginine and L-NAME on behavior in the conditioned place paradigm

Fig. 1 indicates that injection of different doses of nicotine (0.25, 0.5, 0.75, 1.0 and 2.0 mg/kg; i.p.) [$F(5,54)=33.9$, $P<0.0001$], and L-arginine (50, 100, 150, 200 and 500 mg/kg, i.p.) [$F(5,54)=21.63$, $P<0.0001$], but not mecamylamine (0.05 and 0.1 mg/kg, i.p.) [$F(2, 27)=0.27$, $P>0.05$] or L-NAME (5, 10 and 20 mg/kg, i.p.) [$F(3,36)=0.58$, $P>0.05$], into mice caused a significant increase in the time spent in the drug-paired compartment, compared to that spent in the saline-paired compartment. Injection of saline into the animals (saline control group) in the conditioning compartments did not produce any preference or aversion for either place. Further analysis showed that doses of 1 and 2 mg/kg of nicotine and 200 and 500 mg/kg of L-arginine produced place preference.

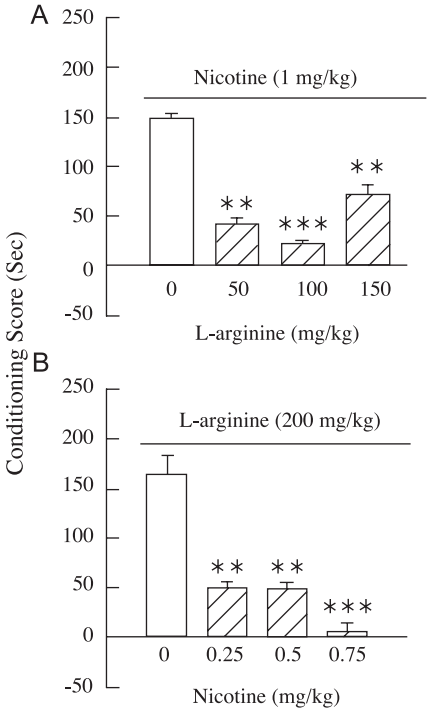

Fig. 4. Effects of nicotine on the expression of L-arginine-induced place preference. A group of animals received a dose of nicotine (1 mg/kg) during a 3-day schedule of conditioning. The effect of different doses of L-arginine (50–150 mg/kg) on the expression of nicotine-induced conditioning was tested on day 4 (test day) (A). Another group of animals received a dose of L-arginine (200 mg/kg) during a 3-day schedule of conditioning. The effect of different doses of nicotine (0.25, 0.5 and 0.75 mg/kg) on the expression of L-arginine-induced conditioning was tested on day 4 (test day) (B). Conditioning score is defined as in Fig. 1. Each point is the mean±S.E.M. for 10 mice. $^{**}P<0.01$, $^{***}P<0.001$ different from respective saline control group.

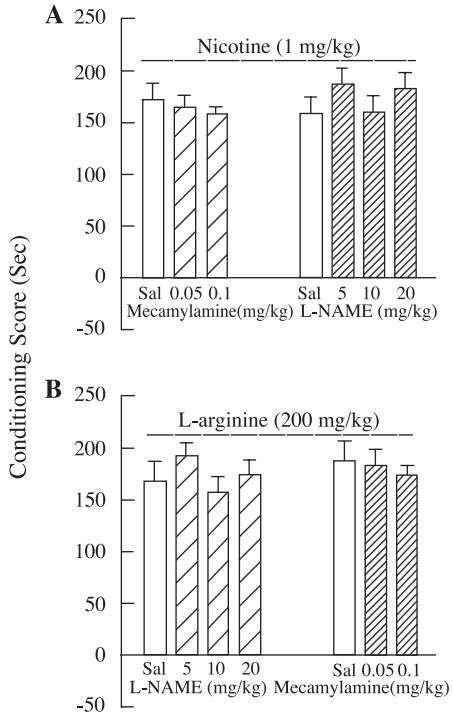

Fig. 5. Effects of mecamylamine and L-NAME on the expression of nicotine- or L-arginine-induced place preference. A group of animals received a dose of nicotine (1 mg/kg) during a 3-day schedule of conditioning. The effect of different doses of mecamylamine (0.05 and 0.1 mg/kg) or L-NAME (5, 10 and 20 mg/kg) on the expression of nicotine-induced conditioning was tested on day 4 (test day) (A). Another group of animals received a dose of L-arginine (200 mg/kg) during a 3-day schedule of conditioning. The effect of different doses of L-NAME (5, 10 and 20 mg/kg) or mecamylamine (0.05 and 0.1 mg/kg) on the expression of L-arginine-induced conditioning was tested on day 4 (test day) (B). Conditioning score is defined as in Fig. 1. Each point is the mean±S.E.M. for 10 mice.

3.2. Effects of L-arginine in combination with nicotine on the acquisition of conditioned place preference

Fig. 2A shows the effect of different doses of L-arginine (50, 100 and 150 mg/kg, i.p.) in combination with an ineffective dose of nicotine (0.5 mg/kg, i.p.) on the induction of place preference. Two-way ANOVA indicated an interaction between L-arginine with nicotine [$F(1,72)=18.8$, $P<0.0001$]. Further analysis indicated that the combination of the drugs induced place preference, while none of the drugs alone induced place preference.

Fig. 2B shows the effect of different doses of nicotine (0.25, 0.5 and 0.75 mg/kg, i.p.) in combination with an ineffective dose of L-arginine (50 mg/kg, i.p.) on the induction of place preference. Two-way ANOVA indicated an interaction between nicotine with L-arginine [$F(1,72)=25.1$, $P<0.0001$]. Further analysis indicated that the combination of the drugs induced conditioned place preference, while none of the drugs alone induced place preference.

3.3. Effects of mecamylamine and L-NAME on conditioned place preference induced by nicotine or L-arginine

Fig. 3A indicated that the place preference induced by nicotine (1 mg/kg) was reduced by either mecamylamine (0.05 and 0.1 mg/kg) [$F(2,27)=32.3$, $P<0.0001$], or L-NAME (5, 10 and 20 mg/kg) [$F(3,36)=49.4$, $P<0.0001$].

Fig. 3B showed that the place preference induced by L-arginine (200 mg/kg) was reduced by both L-NAME (5, 10 and 20 mg/kg) [$F(3,36)=23.8$, $P<0.0001$] and mecamylamine (0.05 and 0.01 mg/kg) [$F(2,27)=120.0$, $P<0.0001$].

3.4. Effect of L-arginine on the expression of nicotine-induced place preference

In the animals which were conditioned with nicotine (1 mg/kg; i.p.), one-way ANOVA indicated that the administration of different doses of L-arginine (50, 100 and 150 mg/kg; i.p.) immediately before the test session reduced the expression of nicotine-induced place preference [$F(3,36)=67$, $P<0.0001$] (Fig. 4A).

3.5. Effect of nicotine on the expression of L-arginine-induced place preference

In the animals which were conditioned with L-arginine (200 mg/kg), one-way ANOVA indicated that the administration of different doses of nicotine (0.25, 0.5 and 0.75 mg/kg) immediately before the test session reduced the expression of L-arginine-induced place preference [$F(3,36)=14.6$, $P<0.0001$] (Fig. 4B).

3.6. Effects of mecamylamine and L-NAME on the expression of conditioned place preference induced by nicotine or L-arginine

In the animals which were conditioned with nicotine (1 mg/kg), one-way ANOVA indicated that the administration of different doses of mecamylamine (0.05 and 0.1 mg/kg) [$F(2,27)=0.4$, $P>0.05$] or L-NAME (5, 10 and 20 mg/kg) [$F(3,36)=0.9$, $P>0.05$] immediately before the test session did not alter the expression of nicotine-induced place preference (Fig. 5A).

In the animals which were conditioned with L-arginine (200 mg/kg), one-way ANOVA indicated that the administration of different doses of L-NAME (5, 10 and 20 mg/kg) [$F(3,36)=0.9$, $P>0.05$] or mecamylamine (0.05 and 0.1 mg/kg) [$F(2,27)=0.24$, $P>0.05$] immediately before the test session did not alter the expression of L-arginine-induced place preference (Fig. 5B).

4. Discussion

In accordance with our previous studies (Zarrindast et al., 2003), the present study shows that nicotine administration

increases the time spent by mice in the drug-paired side, i.e. it induces place preference, while intraperitoneal injections of the nicotine receptor antagonist, mecamylamine, by itself did not induce any response. Several lines of evidence have demonstrated that nicotine exerts its positive reinforcing effect via activation of nicotinic acetylcholine receptors located in the nucleus accumbens and ventral tegmental area (Brioni et al., 1997; Marks et al., 1992; McGehee and Role, 1995). The inability of mecamylamine to induce motivational effects may indicate that the central physiological cholinergic system does not have a positive reinforcing effect.

In another part of the study, injection of the NO precursor, L-arginine (Moncada and Higgs, 1993), also induced conditioned place preference. The effect of L-arginine was abolished by pretreatment with the NOS inhibitor, L-NAME (Prast and Philippu, 2001). These results may show that NO is involved in conditioning paradigm or reward mechanisms. These results are consistent with those of our previous study, which showed that self-administered L-arginine in rats was also inhibited by L-NAME (Sahraei et al., 2004). Administration of L-NAME did not influence CPP on its own, which may be consistent with our previous study, showing that L-NAME cannot produce self-administration in rats (Sahraei et al., 2004). The results suggest that inhibition of physiological NO has no influence on reward effects in mice.

NOS immunoreactivity has been detected in the ventral tegmental area (Rodrigo et al., 1994), and over 30% of NOS is seen in vesicle-filled axons and axon terminals in the shell of the nucleus accumbens (Gracy and Pickel, 1997). Since these two sites are the main regions of the reward system (Koob and Le Moal, 2001), the increase in NO levels induced by L-arginine in the nucleus accumbens may account for the place preference induced by L-arginine.

The present results indicate that the combination of ineffective doses of nicotine and L-arginine during conditioning induces place preference, which may show that these drugs elicit the response through a similar mechanism(s). This hypothesis may be supported by the data showing that mecamylamine or L-NAME was able to reduce the place preference response induced by both nicotine and L-arginine. Our results agree with the report showing that the NOS inhibitor, 7-nitroindazole, blocks nicotine-induced place preference (Martin and Itzhak, 2000). Nicotine is thought to cross the blood–brain barrier, to cause NO release and NO synthesis (Krukoff, 1998, 1999). The possibility exists that part of the nicotine effect is mediated through an increase in the NO levels.

Our present data show that pre-test administration of L-arginine can attenuate the expression of place preference induced by nicotine. Similarly, nicotine can also decrease L-arginine-induced place preference. However, pre-test administration of both mecamylamine and L-NAME did not alter the expression of nicotine- or L-arginine-induced place preference. In conclusion, NO induces conditioned place preference and may be involved in the acquisition and expression of nicotine-induced place preference.

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