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ORIGINAL INVESTIGATION

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Modulation of opioidergic system on mecamylamine-precipitated nicotine-withdrawal aversion in rats

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Abstract *Rationale:* Several lines of evidence indicate that central opioid systems may be involved in the behavioral effects of nicotine. We previously reported that mecamylamine-precipitated nicotine-withdrawal aversion can be evaluated using the conditioned place preference paradigm. *Objectives:* In the present study, modulation of opioidergic systems in mecamylamine-precipitated nicotine-withdrawal aversion was investigated. *Methods:* Male Sprague-Dawley rats were chronically treated s.c. with 10 mg/kg/day (–)-nicotine tartrate using an osmotic minipump. After nicotine treatment for 7 days, conditioning sessions were performed. In the morning, the rats were treated with mecamylamine (0.3–3.0 mg/kg, s.c.), hexamethonium (1.0–3.0 mg/kg, s.c.), naloxone (0.1–1.7 mg/kg), or saline (1.0 ml/kg, s.c.) in one compartment for 60 min. In the evening of the same day, rats were treated with the other treatments and confined to the other compartment for 60 min. Rats were treated with morphine (3.0 mg/kg, s.c.) or TAN-67 (56.0 mg/kg, s.c.) 30 min prior to mecamylamine injection in the conditioning session. On the next day of conditioning, tests were performed. *Results:* Mecamylamine, which is known to pass the blood–brain barrier, produced a dose-dependent place aversion. However, hexamethonium, which fails to penetrate the blood–brain barrier, failed to produce a place aversion. Mecamylamine-precipitated nicotine-withdrawal aversion was significantly attenuated by pretreatment with the μ-opioid receptor agonist morphine and the highly selective δ-opioid receptor agonist TAN-67, which was administered 30 min before mecamylamine injection in the conditioning session. Moreover, naloxone at doses (0.1–1.7 mg/kg) that alone failed to show a place aversion in non-treated rats, produced a dose-dependent place aversion in rats that had been chronically treated with nicotine. *Conclusions:* These results suggest that central opioid systems may be involved in nicotine-withdrawal aversion.

Key words Nicotine · Mecamylamine · Conditioned place preference paradigm · Place aversion · Central opioid system

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Introduction

Nicotine abuse has become widely accepted as the mechanism which supports chronic tobacco use (US Department of Health and Human Services 1988). It is well known that withdrawal from nicotine in chronic nicotine subjects produces an intense craving for nicotine (Shiffman and Jarvik 1976; Hughes et al. 1991). In humans, nicotine withdrawal produces withdrawal signs, which include depressed mood, difficulty falling asleep, awaking at night, irritability, frustration or anger, anxiety, difficulty concentrating, restlessness, and increased appetite (Hughes et al. 1991).

In animals, the termination of chronic nicotine treatment or challenge with the nicotinic receptor antagonist mecamylamine in nicotine-dependent models induces various withdrawal signs including behavioral deficits (Corrigall et al. 1989), enhanced acoustic startle response (Helton et al. 1993) and decreased reward response (Epping-Jordan et al. 1998). Moreover, rats that had been chronically treated with nicotine display several withdrawal signs after the termination of nicotine infusion or challenge with the nicotinic receptor antagonist mecamylamine (Malin et al. 1992, 1994; Hildebrand et al. 1997).

The conditioned place preference paradigm can be used to evaluate not only the rewarding effects but also the aversive effects of drugs (Mucha and Herz 1985; Funada et al. 1993). Naloxone-precipitated withdrawal

aversion has been observed in morphine-dependent rats, suggesting that place aversion may be a sign of morphine withdrawal. It has been proposed that the place conditioning procedure is very sensitive for investigating physical dependence on morphine (Mucha 1987). In addition to naloxone-precipitated withdrawal aversion, we previously demonstrated that mecamylamine-precipitated nicotine-withdrawal aversion can also be evaluated using the conditioned place preference paradigm, which may reflect physical dependence on nicotine (Suzuki et al. 1996a). Thus, we focused on mecamylamine-precipitated nicotine-withdrawal aversion as one of the signs of nicotine withdrawal.

It has been reported that the peripheral administration of hexamethonium, which passes the blood–brain barrier very poorly (Manson 1980), fails to reverse some nicotine effects mediated by the central nicotinic system, such as tail tremor (Gomita et al. 1988), locomotor activity (Clarke and Kumar 1983), conditioned place preference (Fudala et al. 1985), dopamine release in the nucleus accumbens (Benwell et al. 1995), and neuroendocrine changes (Matta et al. 1987). Considering these effects of hexamethonium, it may be worthwhile to investigate whether hexamethonium can precipitate nicotine-withdrawal aversion.

Several lines of evidence indicate that central opioid systems may be involved in the behavioral effects of nicotine. The opioid receptor antagonists naloxone and naltrexone reduce self-administration and conditioned place preference produced by nicotine (Opitz and Weischer 1988; Ise et al. 1996).

Recent studies have indicated that the physical signs of nicotine withdrawal after the termination of nicotine infusion or treatment with mecamylamine closely resemble signs of opioid withdrawal. Naloxone precipitates physical signs of nicotine withdrawal, and these withdrawal signs are inhibited by morphine in rats (Malin et al. 1993; Adams and Cicero 1998). Naloxone can also prevent the nicotine-induced inhibition of physical signs of nicotine withdrawal (Malin et al. 1996a). Therefore, the present study was designed to investigate the effects of the prototype μ-opioid receptor agonist morphine, the selective δ-opioid receptor agonist TAN-67 (Nagase et al. 1994; Suzuki et al. 1996b), and the classical opioid receptor antagonist naloxone on the expression of nicotine-withdrawal aversion.

Materials and methods

The present studies were carried out in accordance with the Guide for Care and Use of Laboratory Animals adopted by the Committee on Care and Use of Laboratory Animals of Hoshi University, which is accredited by the Ministry of Education, Science, Sports and Culture, Japan.

Animals

Male Sprague-Dawley rats (Tokyo Experimental Animals Ltd., Tokyo, Japan) weighing 250–300 g were housed in groups of four in a temperature-controlled (25±1°C) specific pathogen-free (SPF) room. The animals were maintained on a 12-h/12-h light/dark cycle (lights on 0800 hours to 2000 hours) with laboratory rat chow and tap water available ad libitum.

Apparatus

The apparatus consisted of a shuttlebox (30×60×30 cm: w×l×h), which was divided into two compartments of equal size. One compartment was white with a textured floor and the other was black with a smooth floor.

Procedure

Implantation of an osmotic minipump

On day 1, an osmotic minipump (Alzet 2001, Alza Corporation, Calif.) with a flow rate of 1.03 ml/h filled with (–)-nicotine tartrate in saline was implanted s.c. in rats that had been anesthetized with diethylether. The concentration of nicotine was adjusted for differences in body weight, but was approximately 121.4 mg/ml, resulting in continuous s.c. infusion of nicotine tartrate at a rate of 10 mg/kg/day, which is similar to that in a previous report (Suzuki et al. 1996a). Nicotine-naive rats received sham operations – they were subjected to the same anesthesia and surgical procedure as the implanted animals except for implantation of an osmotic minipump.

Place conditioning

Place conditioning was conducted according to the method of Suzuki et al. (1996a). In the morning (0900 hours) on day 7 of nicotine infusion, rats were injected s.c. with mecamylamine (0.3–3.0 mg/kg) or saline (1.0 ml/kg), and immediately confined to one compartment of the test apparatus for 60 min. In the evening (1900 hours) of the same day, rats were then treated with saline or mecamylamine, respectively, and confined to the other compartment for 60 min. The pairings of injection (mecamylamine or saline) and compartment (white or black) were counterbalanced across all of the subjects. The control rats in the sham-operated and nicotine-infused groups were injected with saline (1.0 ml/kg, s.c.) instead of mecamylamine in the conditioning session. After the saline injections, the rats were confined to one compartment in the morning and to the other compartment in the evening. Either the black or white place with a saline control was randomly regarded as a substitute for the drug-associated place before the start of the experiments.

Rats were treated with morphine (3.0 mg/kg, s.c.) or TAN-67 (56.0 mg/kg, s.c.) 30 min prior to mecamylamine injection in the conditioning session (on day 7 of nicotine infusion) only. Place conditioning was performed using mecamylamine, hexamethonium (1.0–3.0 mg/kg), and naloxone (0.1–1.7 mg/kg, s.c.).

Place conditioning tests

In the morning of day 8, tests of conditioning were performed as follows: the partition that separated the two compartments was raised to 12 cm above the floor, and a neutral platform was inserted along the seam separating the compartments. The time spent in each compartment during a 900-s session was measured automatically in a blind fashion by means of an infrared beam sensor (KN-80, Natsume Seisakusho, Tokyo, Japan). The position of the rat was defined by the position of its body. All sessions were conducted under conditions of dim illumination (40 lux) and masking white noise.

Drugs

The drugs used in the present study were (–)-nicotine hydrogen tartrate (Sigma Chemical Co., St. Louis, Mo.), mecamylamine hydrochloride (Sigma Chemical Co.), morphine hydrochloride (Sankyo Co., Tokyo, Japan), 2-methyl-4α-(3-hydroxyphenyl)-1,2,3,4,4α,5,12,12α-octahydro-quinolino[2,3,3,-g] isoquinoline (TAN-67), and naloxone hydrochloride (Research Biochemicals Inc., Wayland, Mass.). TAN-67 was synthesized by us. All drugs were dissolved in 0.9% NaCl and were injected in a volume of 1.0 ml/kg.

Data analysis

Conditioning scores represent the time spent in the drug-injected place minus the time spent in the saline-injected place and are expressed as the mean (s) ±SEM. Behavioral data were statistically evaluated using a one-way random factorial analysis of variance (ANOVA), and a two-way ANOVA which was used to determine the effects of treatment on mecamylamine-induced place conditioning. One-way ANOVA followed by a Dunnett's test was used to determine whether individual doses produced significant conditioning (*P<0.05, **P<0.01).

Results

The saline-treated control rats exhibited no preference for either compartment. The mean conditioning scores in non-treated and nicotine-treated rats were +42.9±57.3 s (n=8) and –14.4±54.2 s (n=8), respectively.

As shown in Fig. 1, upper panel A, mecamylamine (0.3, 1.0, and 3.0 mg/kg) did not produce either significant place preference or place aversion in non-treated rats. The mean conditioning scores associated with 0.3, 1.0, and 3.0 mg/kg mecamylamine were –34.5±55.8 s (n=8), –45.0±60.4 s (n=8), and –42.6±50.4 s (n=8), respectively. However, mecamylamine dose dependently ($F_{1,56}$=8.67, P<0.01) produced place aversion in rats that had been chronically treated with nicotine (Fig. 1, upper panel B). Low doses of mecamylamine (0.3 mg/kg and 1.0 mg/kg) induced slight place aversion, but this effect was not significant, with mean conditioning scores of –78.8±66.1 s (n=8) and –221.3±80.1 s (n=8), respectively. Significant place aversion was observed at 3.0 mg/kg mecamylamine, with a mean conditioning score of –287.8±72.5 s (n=8, P<0.05). There was a significant effect of dose ($F_{3,56}$=3.27, P<0.05) but not treatment × dose interaction ($F_{3,56}$=1.19, P>0.05). As shown in Fig. 1, lower panel A, hexamethonium (1.0 mg/kg and 3.0 mg/kg) did not produce either significant place preference or place aversion in non-treated rats. The mean conditioning scores associated with 1.0 mg/kg and 3.0 mg/kg hexamethonium were –44.8±97.4 s (n=8) and +33.1±83.3 s (n=8), respectively. Moreover, hexamethonium also produced neither significant place preference nor place aversion ($F_{1,42}$=0.19, P>0.05) in rats that had been chronically treated with nicotine (Fig. 1, lower panel B). The mean conditioning scores associated with 1.0 mg/kg and 3.0 mg/kg hexamethonium were –58.9±72.1 s (n=8) and –24.5±81.3 s (n=8), respectively. There was no significant effect of dose ($F_{2,42}$=0.64, P>0.05) or treatment × dose interaction ($F_{2,42}$=0.06, P>0.05).

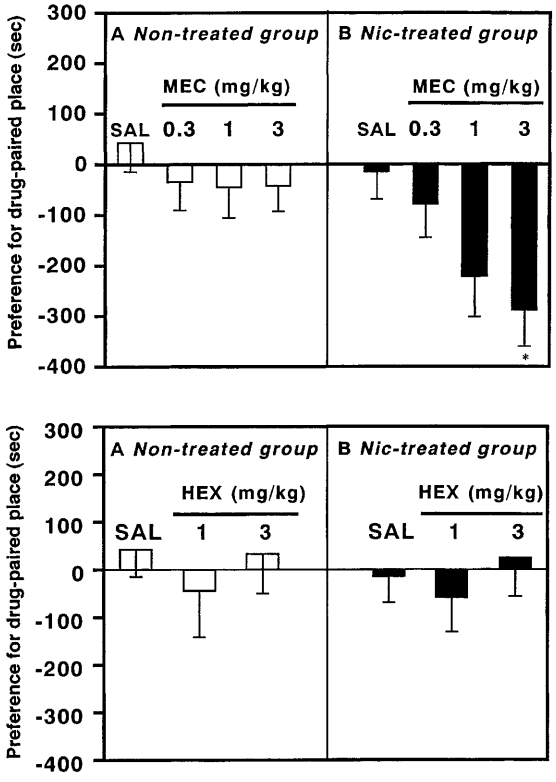

Fig. 1 *Upper panel:* place conditioning produced by mecamylamine (MEC, 0.3–3 mg/kg, s.c.) in non-treated (*A*) and nicotine (*Nic*)-treated (*B*) rats. *Lower panel:* place conditioning produced by hexamethonium (HEX, 1–3 mg/kg, s.c.) in non-treated (*A*) and nicotine-treated (*B*) rats. Each *column* represents the mean conditioning score with the SEM of eight rats. *P<0.05 versus saline-treated group in nicotine-treated rats

The effects of morphine (3.0 mg/kg) and TAN-67 (56.0 mg/kg) on mecamylamine (3.0 mg/kg)-induced place conditioning in non-treated rats are shown in Fig. 2A. The mean conditioning scores for the saline (1.0 ml/kg), morphine (3.0 mg/kg), and TAN-67 (56.0 mg/kg) pretreatment groups were –4.8±67.6 s (n=8), +50.5±57.1 s (n=8), and –40.3±90.5 s (n=8), respectively.

The effects of morphine (3.0 mg/kg) and TAN-67 (56.0 mg/kg) on mecamylamine (3.0 mg/kg)-induced place aversion in the nicotine-treated group are shown in Fig. 2B. Mecamylamine (3.0 mg/kg) produced place aversion in nicotine-treated rats that had been pretreated with saline (1 ml/kg). The mean conditioning score was –333.8±61.9 s (n=8). This place aversion was significantly attenuated by pretreatment with morphine ($F_{1,28}$=5.03, P<0.05). The mean conditioning score was –47.3±76.9 s (n=8, P<0.05). There was no significant effect of dose ($F_{1,28}$=2.81, P>0.05) but there was a significant effect of treatment × dose interaction ($F_{1,28}$=4.62, P<0.05). Moreover, TAN-67 also significantly attenuated the place aversion ($F_{1,28}$=4.39, P<0.05). The mean conditioning score was –20.9±73.0 s (n=8, P<0.01). There

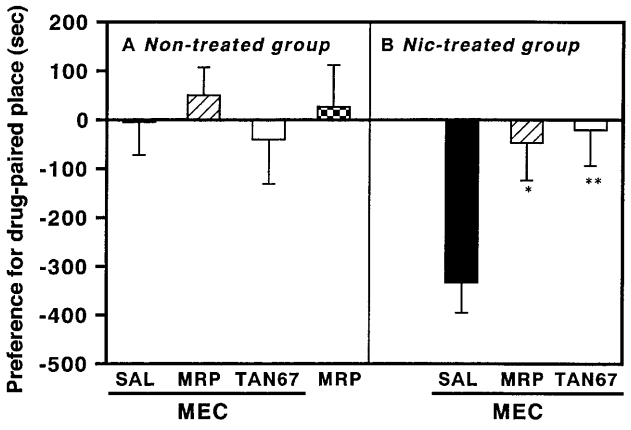

Fig. 2 Place conditioning produced by morphine (MRP) and mecamylamine (MEC) after pretreatment with morphine or TAN67 in non-treated (*A*) and nicotine (*Nic*)-treated (*B*) rats. Rats were injected with morphine (MRP, 3 mg/kg, s.c.) or TAN67 (56 mg/kg, s.c.) 30 min before treatment with mecamylamine (3 mg/kg, s.c.). Each *column* represents the mean conditioning score with the SEM of eight rats. **P*<0.05, ***P*<0.01 versus saline plus mecamylamine-injected group in nicotine-treated rats

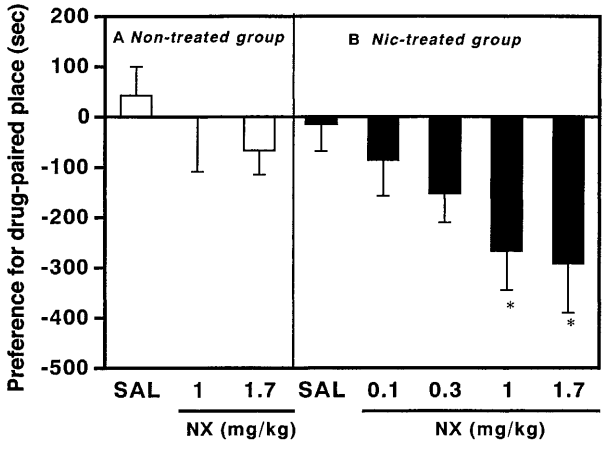

Fig. 3 Place conditioning produced by naloxone (NX, 0.1–1.7 mg/kg, s.c.) in non-treated (*A*) and nicotine (*Nic*)-treated (*B*) rats. Each *column* represents the mean conditioning score with the SEM of eight rats. **P*<0.05 versus saline-treated group in nicotine-treated rats

was no significant effect of dose ($F_{1,28}$=3.52, P>0.05) but there was a significant effect of treatment × dose interaction ($F_{1,28}$=5.55, P<0.05).

Morphine (3.0 mg/kg) alone induced neither significant place preference nor place aversion in non-treated rats. The mean conditioning score was +26.8±85.1 s (n=8, Fig. 2B).

As shown in Fig. 3A, naloxone (1.0–1.7 mg/kg) did not produce either significant place preference or place aversion in non-treated rats. The mean conditioning scores associated with 1.0 mg/kg and 1.7 mg/kg naloxone were –0.9±107.6 s (n=8) and –66.9±48 s (n=8), respectively. However, naloxone (0.1–1.7 mg/kg) dose-dependently produced ($F_{4,35}$=3.53, P<0.05) place aversion in rats that had been chronically treated with nicotine. Low doses of naloxone (0.1 mg/kg and 0.3 mg/kg) induced slight place aversion, but this effect was not significant, with mean conditioning scores of –86.1±71.2 s (n=8) and –152.8±57.7 s (n=8), respectively. Significant place aversion was observed at 1.0 mg/kg and 1.7 mg/kg naloxone, with mean conditioning scores of –267.6± 78.0 s (n=8, P<0.05) and –292.6±48.5 s (n=8, P<0.05), respectively.

Discussion

The present study showed that challenge with mecamylamine (3.0 mg/kg), but not hexamethonium, induced a significant place aversion in rats that had been chronically treated with nicotine. The data indicate that mecamylamine-precipitated nicotine withdrawal can be evaluated as an aversive effect. Additionally, central, but not peripheral, nicotinic receptors are mainly implicated in nicotine-withdrawal aversion. This contention can be supported by the finding that hexamethonium did not produce physical signs in rats that had been chronically treated with nicotine (Malin et al. 1997).

Recent studies support the idea that nicotine withdrawal may be related to reduction of the activity of endogenous opioid systems. Although acute and chronic nicotine treatment induce the release of endogenous opioid peptides and increase enkephalin mRNA levels in adrenal chromaffin cells (Eiden et al. 1984) and several brain regions (Hexum and Russett 1987; Houdi et al. 1991; Dhatt et al. 1995; Mathieu et al. 1996), the termination of chronic nicotine treatment results in a decrease of endorphin-like immunoreactivity in the mouse hypothalamus (Rosecrans et al. 1985) and preproenkephalin A mRNA levels in the striatum and hippocampus (Houdi et al. 1998).

It has been more directly demonstrated that naloxone and anti-opiate analogues precipitate physical signs of nicotine withdrawal (Malin et al. 1993, 1996b; Adams and Cicero 1998), and prevent the nicotine-induced inhibition of physical signs of nicotine withdrawal (Malin et al. 1996a). Furthermore, pretreatment with morphine attenuates naloxone-precipitated withdrawal in rats that have been chronically treated with nicotine (Malin et al. 1993). These results suggest the possibility that the inhibitory tone of endogenous μ- and δ-opioid systems contributes to the expression of nicotine-withdrawal aversion.

In this study, we found that mecamylamine-precipitated nicotine-withdrawal aversion can be attenuated by pretreatment with either μ- or δ-opioid receptor agonists. We also demonstrated that the opioid receptor antagonist naloxone itself produced nicotine-withdrawal aversion in rats that had been chronically treated with nicotine, confirming previous findings (Malin et al. 1993; Adams and Cicero 1998) on naloxone-precipitated nicotine withdrawal.

It is possible that the inhibition of mesolimbic dopaminergic systems related to the inhibition of endogenous

opioid systems contributes to the mecamylamine-precipitated aversive effect. For example, after treatment with naloxone or the selective δ-opioid receptor antagonist naltrindole, morphine-withdrawn rats show significant decreases in dopamine release in the nucleus accumbens, and exhibit conditioned place aversion (Spanagel et al. 1994; Funada et al. 1996). Therefore, it is likely that the inhibition of dopamine release in the nucleus accumbens, through inhibition of endogenous μ- and δ-opioid receptor opioid systems during nicotine withdrawal, may be an essential factor in the expression of nicotine-withdrawal aversion. This contention can be supported by the finding that dopamine release in the nucleus accumbens was reduced in rats, which produced mecamylamine-precipitated nicotine-withdrawal signs (Hildebrand et al. 1998). In support of this hypothesis, the reversal of dopamine levels in the nucleus accumbens by stimulation of μ- or δ-opioid receptors may result in the attenuation of mecamylamine-precipitated nicotine-withdrawal aversion.

The conditioned place aversion is thought to be the inhibition of the dopamine release in the nucleus accumbens (Schechter and Meechan 1994). In the present study, mecamylamine-precipitated nicotine-withdrawn rats revealed a place aversion, but not physical signs. The present data provide the evidence for different mechanisms of the place aversion and physical signs during the nicotine withdrawal. This contention was supported by the report on the dissociation of physical abstinence signs from changes in extracellular dopamine in the nucleus accumbens and in the frontal cortex of nicotine-dependent rats (Carboni et al. 2000).

In conclusion, the present results show that mecamylamine, but not hexamethonium, produces a significant place aversion in rats that have been chronically treated with nicotine, suggesting that central nicotinic receptors are involved in nicotine-withdrawal aversion. We have demonstrated here for the first time that mecamylamine-precipitated nicotine-withdrawal aversion was attenuated by pretreatment with the μ-opioid receptor agonist morphine and the highly selective δ-opioid receptor agonist TAN-67. Furthermore, naloxone precipitated withdrawal aversion in rats that had been chronically treated with nicotine. These results indicate that central opioid systems contribute to nicotine-withdrawal aversion in the rat.

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