DOES NICOTINE MODIFY THE PSYCHOTOXIC EFFECT OF METHAMPHETAMINE? ASSESSMENT IN TERMS OF LOCOMOTOR SENSITIZATION IN MICE

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ABSTRACT — In this study, effects of nicotine on locomotor sensitization to methamphetamine in mice were investigated to assess whether nicotine modified induction and expression of psychotoxic action of methamphetamine.

Although nicotine (0.03-1 mg/kg s.c.) had no effect at first administration, 5-time nicotine administrations at 3-day intervals progressively developed a significant locomotor stimulant effect, and caused an enhanced sensitivity (cross-sensitization) to methamphetamine (2 mg/kg s.c.). Five-time administrations of methamphetamine (2 mg/kg) at 3-day intervals produced not only a locomotor sensitization to methamphetamine itself, but also a cross-sensitization to nicotine (0.1-1 mg/kg). Nicotine (0.03-1 mg/kg) did not affect the locomotor stimulant effect of methamphetamine (2 mg/kg) in the drug-naïve mice. However, nicotine acted dose-dependently to reduce the progressive enhancement of the locomotor stimulant effect of methamphetamine during 5-time repeated administrations. Mice treated with coadministration of methamphetamine with nicotine (1 mg/kg) showed less sensitization to methamphetamine than mice treated with methamphetamine alone. In addition, nicotine (1 mg/kg) inhibited the locomotor stimulant effect of methamphetamine in mice sensitized to methamphetamine.

These results suggest that methamphetamine and nicotine produce a symmetrical cross-sensitization, although nicotine may act to inhibit the induction and expression of locomotor sensitization to methamphetamine in mice.

KEY WORDS: Methamphetamine, Nicotine, Locomotion, Combined administration,
Behavioral sensitization

INTRODUCTION

A repeated administration of amphetamines easily induces a sensitization to their behavioral stimulant effects, in particular locomotor stimulant and stereotypy-producing effects in rodents (e.g., Ellinwood and Kilbey, 1977; Demellweek and Goudie, 1983). It has been considered that the induction and maintenance of the behavioral sensitization to amphetamines is intimately related to the development of psychopathological and psychotoxic symptoms (amphetamine-psychosis) following the repeated abuse of these drugs

(Robinson and Becker, 1986; Tadokoro and Kuribara, 1986).

Methamphetamine abuse has been one of the most serious drug abuse problems in Japan, and it has been generally administered through the intravenous route. Recently, however, to avoid infections and the trace of pricking needles, inhalation of methamphetamine alone or methamphetamine mixed with tobacco has been progressively increasing (personal information from Japanese Ministry of Police). It is therefore important to assess the combined effect of methamphetamine and nicotine.

Nicotine, a typical agonist of nicotinic acetylcholine

receptors (Marks *et al.*, 1986a), stimulates release of dopamine in the brain (Imperato *et al.*, 1986; Rowell *et al.*, 1987; Kita *et al.*, 1990), and increases locomotion in rats (Clarke *et al.*, 1988; Kita *et al.*, 1990,1992). Some reports have demonstrated that an intermittent administration of nicotine changes dopaminergic neurotransmission (Carr *et al.*, 1989; Fuxe *et al.*, 1986; Sershen *et al.*, 1991), and causes a sensitization to the locomotor stimulant effect of nicotine in rats (Kita *et al.*, 1990,1992; Shoaib and Stolerman, 1992). Such neurochemical and behavioral characteristics following repeated administrations of nicotine are partially similar to the features of amphetamines (Robinson and Becker, 1986). However, other reports also revealed that nicotine reduced locomotor stimulation (Stolerman *et al.*, 1973; Stevens *et al.*, 1995) and impairment of auditory sensory gating (Stevens *et al.*, 1995) induced by amphetamine, suggesting an antagonistic interaction between nicotine and amphetamines.

The aims of this study were to assess whether nicotine modified the induction and expression of locomotor sensitization to methamphetamine in mice. The following four experiments were conducted: 1) Five-time repeated administrations of nicotine, and then challenge administration of methamphetamine; 2) Five-time repeated administrations of methamphetamine, and then challenge administration of nicotine; 3) Five-time repeated coadministrations of methamphetamine with nicotine, and then challenge administration of methamphetamine; and finally 4) Coadministration of methamphetamine with nicotine to mice sensitized to the locomotor stimulant effect of methamphetamine.

MATERIALS AND METHODS

Animals

Male mice of the ddY strain (Japan Laboratory Animals, Tokyo) were used at the age of 6 weeks and weight of 25-28 g. These mice were housed in groups of 10 in polycarbonate cages (25L × 15W × 10H cm) in a controlled room (temperature; 23 ± 2 °C, relative humidity; 55 ± 3 %, and a 12:12 hr light/dark schedule; lights on between 06:00 and 18:00 hr). They were freely given a solid diet (MF: Oriental Yeast, Tokyo) and tap water except during behavioral testing.

Apparatus

The apparatus for measurement of locomotion of mice was a tilting-type "ambulometer" with 10 bucket-like activity cages of 20 cm diameter and 15 cm height (SMA-10: O'hara & C $\acute{o}$., Tokyo). Each slight tilt

of the activity cage generated by the locomotion of a mouse was detected with one of 3 microswitches attached to the activity cage.

Drugs

The drugs used were methamphetamine HCl (Dainippon Pharm., Osaka) and nicotine (free base) (Nakarai Chem., Tokyo). Methamphetamine and nicotine were dissolved in physiological saline, and the concentration of each drug solution was adjusted so that each volume injected was always constant at 0.1 ml/10 g body weight of the mouse. The dose of methamphetamine was fixed to 2 mg/kg (expressed in the salt form), which was an optimum dose for increasing the locomotion in the ddY mice without eliciting a marked stereotypy during the repeated administrations (Hirabayashi and Alam, 1981; Kuribara and Uchihashi, 1994). The drugs were administered subcutaneously (s.c.) to the back of the mouse.

Administration schedules

Before each drug administration mentioned below, mice were adapted to the activity cage for 30 min. The locomotor activity of mice was measured for 3 hr after each drug administration. All the behavioral experiments were carried out between 09:00-16:00 hr.

1. Repeated administration of nicotine, and then challenge administration of methamphetamine

Five groups of mice (10 each) were given 5-time administrations of either saline (nicotine dose=0) or nicotine (0.03, 0.1, 0.3 or 1 mg/kg) at 3-day intervals. Three days after the fifth administration, all the mice were challenge-administered with methamphetamine.

2. Repeated administration of methamphetamine, and then challenge administration of nicotine

Two sets of 5 groups of mice (10 each) were treated with 5-time administrations of either saline or methamphetamine at 3-day intervals. Three days after the fifth treatment, 5 groups of mice in each set were challenge-administered with either saline (nicotine dose=0) or nicotine (0.03, 0.1, 0.3 or 1 mg/kg).

3. Repeated coadministration of methamphetamine with nicotine, and then challenge administration of methamphetamine

Five groups of mice (10 each) were given 5-time administrations of either methamphetamine alone (nicotine dose=0) or a combination of methamphetamine with nicotine (0.03, 0.1, 0.3 or 1 mg/kg) at 3-day intervals. Three days after the fifth administration, all

the mice were challenge-administered with methamphetamine.

4. Coadministration of methamphetamine with nicotine to methamphetamine-sensitized mice

Five groups of mice (10 each) were first treated with 5-time administrations of methamphetamine at 3-day intervals to induce methamphetamine sensitization. Three days after the fifth administration, these groups of mice were subsequently given either methamphetamine alone, or coadministration of methamphetamine with nicotine (0.03, 0.1, 0.3 or 1 mg/kg).

Statistical analyses

Mean 3-hr overall locomotor activity counts after the drug administration were first analyzed by analysis of variance. In cases of significant variance, post-hoc analyses were carried out by Dunnett's test (Dunnett, 1955). Values of *P* less than 0.05 were considered significant.

RESULTS

Repeated administration of nicotine, and then challenge administration of methamphetamine

Fig. 1 represents mean 3-hr overall activity counts following the 5-time administrations of saline, and nicotine (0.03, 0.1, 0.3 and 1 mg/kg) at 3-day intervals. Saline and nicotine (0.03 mg/kg) did not cause any sig-

nificant change in the activity count throughout the 5-time administrations. Although nicotine (0.1-1 mg/kg) had no effect on the locomotor activity at the first administration (i.e., the drug-naïve mice), the repeated administrations of the same doses of nicotine resulted in progressive enhancement in the locomotor stimulant effect.

Fig. 1. Mean 3-hr overall locomotor activity counts with SEMs after 5 repeated s.c. administrations of saline (nicotine dose=0), and nicotine (NICO: 0.03-1 mg/kg) at 3-day intervals. *: Significant difference vs. the first administration within each group ($P < 0.05$). \$: Significant difference vs. the saline-treated group ($P < 0.05$). $N=10$ in each group.

Fig. 2. Mean 3-hr overall locomotor activity counts with SEMs after the challenge administration of methamphetamine (2 mg/kg s.c.) to the groups of mice treated with the 5 repeated administrations of saline (nicotine dose=0), or nicotine (0.03, 0.1, 0.3 or 1 mg/kg s.c.) at 3-day intervals. The challenge administration of methamphetamine was carried out 3 days after the fifth nicotine treatment. *: Significant difference vs. the saline-treated control group ($P < 0.05$). $N=10$ in each group.

As shown in Fig. 2, the mice treated with 0.3 and 1 mg/kg nicotine, but not 0.03 and 0.1 mg/kg, showed a significantly higher activity count than the saline-treated control mice following the challenge administration of methamphetamine (2 mg/kg).

Repeated administration of methamphetamine, and then challenge administration of nicotine

Five-time administrations of methamphetamine (2 mg/kg), but not saline, induced a progressive enhancement of the locomotor stimulant effect. The mean 3-hr activity counts at the 1st and 5th administration were 102 and 40 counts, respectively, for the saline-treated group, and 2,185 and 5,041 counts, respectively, for the methamphetamine-treated group.

Fig. 3 shows mean 3-hr overall activity counts following the challenge administration of saline (nicotine dose=0) or nicotine (0.03-1 mg/kg) to the groups of mice treated with saline (control; methamphetamine non-sensitized mice) or methamphetamine (2 mg/kg) (methamphetamine-sensitized mice). The methamphetamine-sensitized groups showed significantly higher activity counts than the control groups following the challenge administration of both saline (nicotine dose=0) and nicotine (0.1-1 mg/kg). Furthermore, among the methamphetamine-sensitized groups, the activity count following the challenge administration of nicotine (1 mg/kg) was significantly higher than that

Fig. 4. Mean 3-hr overall locomotor activity counts with SEMs after 5 repeated s.c. administrations of methamphetamine (MAP: 2 mg/kg s.c.) alone and the combinations of methamphetamine with nicotine (NICO: 0.03, 0.1, 0.3 and 1 mg/kg) at 3-day intervals. In each administration, mixtures of two drugs were administered. *: Significant difference vs. the first administration within each group ($P < 0.05$). \$: Significant difference vs. the methamphetamine alone-treated group ($P < 0.05$). $N = 10$ in each group.

Fig. 3. Mean 3-hr overall locomotor activity counts with SEMs after the challenge administration of nicotine (0: saline, 0.03-1 mg/kg s.c.) to the mice treated with saline or methamphetamine (2 mg/kg s.c.) 5 times at 3 day intervals. The challenge administration of nicotine was carried out 3 days after the fifth saline or methamphetamine treatment. *: Significant difference vs. the count in the mice treated with saline and subsequently the same dose of nicotine ($P < 0.05$). \$: Significant difference vs. the group of mice treated with methamphetamine and subsequently challenge-administered with saline ($P < 0.05$). $N = 10$ in each group.

following the challenge administration of saline.

Repeated coadministration of methamphetamine with nicotine, and then challenge administration of methamphetamine

Fig. 4 represents mean 3-hr overall activity counts following the 5-time administrations of methamphetamine (2 mg/kg) alone, and the combinations of methamphetamine with nicotine (0.03-1 mg/kg). Similar to the results in Experiment 2, the 5-time administrations of methamphetamine (2 mg/kg) produced the locomotor sensitization. Although nicotine did not significantly change the locomotor stimulant effect of methamphetamine at the first administration (i.e., the drug-naïve mice), it dose-dependently inhibited the progressive enhancement of the locomotor stimulation caused by the repeated administration of methamphetamine.

Fig. 5 shows mean 3-hr overall activity counts following the challenge administration of methamphetamine (2 mg/kg) to the mice treated with methamphetamine alone or the combination of methamphetamine with nicotine, and to the drug-naïve mice. The mice having experience of the coadministration of methamphetamine with nicotine (1 mg/kg) exhibited a signifi-

Fig. 5. Mean 3-hr overall locomotor activity counts with SEMs after the challenge administration of methamphetamine (2 mg/kg s.c.) to the mice treated with the 5 repeated administrations of methamphetamine (2 mg/kg s.c.) alone (nicotine dose=0), and the combination of methamphetamine with nicotine (0.03, 0.01, 0.03 or 1 mg/kg s.c.) at 3-day intervals. The challenge administration of methamphetamine was carried out 3 days after the fifth treatment. *: Significant difference vs. the control group treated with methamphetamine alone ($P < 0.05$). $N = 10$ in each group.

cantly lower activity count than the mice treated with methamphetamine alone.

Coadministration of methamphetamine with nicotine to methamphetamine-sensitized mice

The mean 3-hr overall activity counts of 5 groups at the fifth administration of methamphetamine (2 mg/kg) were approximately 4,950 to 5,400 counts, and there was no significant difference in the counts among groups.

Fig. 6 shows mean 3-hr overall activity counts following the administration of methamphetamine (2 mg/kg) alone (nicotine dose=0) or methamphetamine in combination with nicotine (0.03-1 mg/kg) to

Fig. 6. Mean 3-hr overall locomotor activity counts with SEMs after the s.c. administration of methamphetamine (2 mg/kg) alone (nicotine dose=0) or coadministration of methamphetamine with nicotine (0.03-1 mg/kg s.c.) to the methamphetamine-sensitized mice. The methamphetamine-sensitization was induced by 5-time repeated administrations of methamphetamine (2 mg/kg s.c.) at 3-day intervals, and the coadministrations were subsequently carried out 3 days after the fifth methamphetamine treatment. For comparison, the activity counts following the coadministration of methamphetamine with nicotine to the drug-naïve mice (duplicate of the data presented in Fig. 1) are also shown. *: Significant difference vs. the administration of methamphetamine alone ($P < 0.05$). $N = 10$ in each group.

Legend:
 [Stippled bar] : The activity counts of the drug-naïve mice.
 [Cross-hatched bar] : The activity counts of the methamphetamine-sensitized mice.

the methamphetamine-sensitized mice. For the comparison, the data in the drug-naïve mice, which are the duplicate of the data presented in Fig. 1 (the first administration), are also shown. Nicotine reduced the locomotor stimulant effect of methamphetamine in the methamphetamine-sensitized mice, but not in the drug-naïve mice.

DISCUSSION

Many reports have revealed that nicotine increases dopamine overflow in nucleus accumbens and stimulates dopaminergic neurotransmission (Imperato *et al.*, 1986; Rowell *et al.*, 1987; Sershen *et al.*, 1991). However, in the present experiment, nicotine caused no significant increase in locomotion in the drug-naïve mice. This result is in contrast to the nicotine-induced locomotor stimulation in rats (e.g., Clarke *et al.*, 1988; Kita *et al.*, 1990). Marks *et al.* (1986b) and Freeman *et al.* (1987) suggested that the locomotor stimulant effect of nicotine may be masked in mice because of their comparatively higher level of baseline locomotor activity. It is also suggested that the anti-stress effect of nicotine is involved in the non-significant increase in locomotion in the drug-naïve mice (Benovitz, 1986).

However, similar to the results in rats (Kita *et al.*, 1990, 1992; Shoaib and Stolerman, 1992), repeated administrations of nicotine to mice produced sensitization to the locomotor stimulant effect. It has also been reported that repeated (intermittent) administrations of nicotine induced an enhanced dopamine overflow in the nucleus accumbens (Benwell, 1990; Benwell and Balfour, 1992), and increased dopaminergic neurotransmission (Fuxe *et al.*, 1986; Carr *et al.*, 1989). Furthermore, Benwell (1990) demonstrated that 5 daily treatments with 0.4 mg/kg nicotine resulted in an increased basal level of extracellular dopamine and a decreased level of homovanilic acid, the metabolite of dopamine, in the rat nucleus accumbens. Such changes in the dopaminergic neurotransmission induced by the repeated administrations of nicotine may also support the present result that repeated treatments with nicotine (0.3 and 1 mg/kg) induced a cross-sensitization to methamphetamine, the psychostimulant having an indirect agonistic action on the dopamine receptors (McMillen, 1983).

Consistent with our previous report (Kuribara and Uchihashi, 1994), 5-time administrations of methamphetamine at 3-day intervals produced sensitization to its locomotor stimulant effect, and the mean 3-hr overall activity count at the fifth methamphetamine admin-

istration was around the 5,000 count in each group of mice. The methamphetamine-sensitized mice demonstrated a significant increase in locomotor activity following the challenge administration of nicotine. This result indicates the induction of cross-sensitization from methamphetamine to nicotine. It has been suggested that the psychopharmacological properties of nicotine are different from those of psychostimulants, such as amphetamines and cocaine (Balfour, 1990; Stolerman, 1990). However, the behavioral characteristics of nicotine (i.e., the induction of the behavioral sensitization to nicotine itself and the symmetrical cross-sensitization between nicotine and methamphetamine) strongly suggest that nicotine has psychopharmacological properties that are partially similar to those of psychostimulants.

It is notable that the induction of sensitization to methamphetamine was reduced in the mice that had been treated with methamphetamine in combination with nicotine (1 mg/kg) in the repeated administration phase. Furthermore, nicotine (1 mg/kg) reduced the locomotor stimulant effect of methamphetamine in the methamphetamine-sensitized mice, but not in the drug-naïve mice. These results suggest that nicotine, at comparatively higher doses, can inhibit both the induction and expression of the sensitization to the locomotor stimulant effect of methamphetamine in mice. Stolerman *et al.* (1973) and Stevens *et al.* (1995) also reported that nicotine inhibited the amphetamine-induced locomotion stimulation and the impairment of the auditory gating in rats.

Two candidates of mechanism are considered to be involved in such protective effects of nicotine on the methamphetamine sensitization. The first one is that the nicotine-induced release of dopamine (Imperato *et al.*, 1986; Rowell *et al.*, 1987; Sershen *et al.*, 1991) may be responsible for the blockade of methamphetamine-induced release of dopamine (McMillen, 1983). The second one is the anti-stress effect of nicotine. It has been reported that the hypothalamic pituitary adrenal axis is responsible for the induction and expression of amphetamine sensitization (Knich and Eisenberg, 1979; Rivet *et al.*, 1989; Cole *et al.*, 1990a, 1990b; Kalivas and Stewart, 1991). The anti-stress effect of nicotine (Benovitz, 1986) may act to inhibit the induction and expression of the behavioral sensitization to amphetamines. However, further experiments are required to determine which is the main mechanism for the antagonistic interaction of nicotine with methamphetamine.

It has been considered that the behavioral sensi-

zation to amphetamines is related not only to the abuse liability (Kalivas *et al.*, 1993; Robinson and Becker, 1993) but also to the development of the psychopathological and psychotoxic symptoms, namely amphetamine psychosis, following the repeated abuse (Ellinwood and Kilbey, 1977; Robinson and Becker, 1986; Tadokoro and Kuribara, 1986). The present results suggest a possibility that, when methamphetamine is abused simultaneously with nicotine (e.g., cigarette smoking mixed with methamphetamine), nicotine may reduce the central stimulant (and/or reinforcing) effect of methamphetamine, and protect the development of amphetamine psychosis. However, it is also probable from the present result, a symmetrical cross-sensitization between methamphetamine and nicotine at the higher doses, that heavy nicotine use (smoking) may increase risks of the abuse of amphetamines and the development of amphetamine psychosis following repeated abuse of amphetamines.

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