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Interaction of Nicotine and N-cyanomethylmethamphetamine, a Main Pyrolysis Product of Smoking Methamphetamine Mixed with Tobacco, in Terms of the Sensitization to the Ambulatory Stimulant Effect in Mice

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Abstract: N-cyanomethylmethamphetamine (CMA) is a main pyrolysis product of smoking methamphetamine (MA) mixed with tobacco, and it has MA-like central stimulant effects, acceleration of ambulation and production of various types of stereotyped behavior, and induction of sensitization to these behavioral effects following repeated administration in mice and rats. The induction of behavioral sensitization to central stimulants has been considered to be intimately related to the development of the psychotoxic symptoms following repeated abuse of these drugs. Since CMA is inhaled simultaneously with nicotine, the aim of this study was to investigate the modifications by nicotine of induction and expression of sensitization to the ambulation-increasing effect of CMA in mice. During the 5 repeated co-administrations of CMA (3 mg/kg s.c.) with nicotine (0.03, 0.1, 0.3 and 1 mg/kg s.c.) at 3 day intervals, nicotine dose-dependently inhibited the progressive enhancement of CMA-induced ambulatory stimulation. However, such treatments did not modify the induction of sensitization to the ambulatory stimulant effect of MA (2 mg/kg s.c.). The MA-sensitized mice demonstrated significant cross-sensitization to CMA. In both the drug-naive and MA-sensitized mice, nicotine reduced the ambulatory stimulant effect of CMA. These results suggest that, although nicotine acts to reduce the ambulatory stimulant effect of CMA, nicotine does not protect the induction of behavioral sensitization to CMA and MA. The repeated 5 times experience of nicotine (1mg/kg s.c.) alone did not modify the sensitivity of mice to CMA or MA. These results also indicate that nicotine does not modify the psychotoxic liability of MA following repeated smoking MA mixed with tobacco, although nicotine may reduce the reward effect of MA.
(Reprint request should be sent to Hisashi Kuribara)

Key words: N-Cyanomethylmethamphetamine, Methamphetamine, Nicotine, Ambulatory activity, Behavioral sensitization, Psychotoxicity, Mice

Introduction

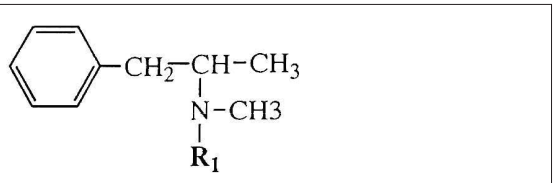
Methamphetamine (MA) abuse is the most serious drug abuse problem in Japan. The repeated abuse of MA has a high risk of induction of psychotoxic symptoms such as paranoid, hallucination, etc. (Robinson and Becker, 1986; Tadokoro and Kuribara, 1986). Mesolimbic dopaminergic systems (Van der Heuval and Pasterkamp, 2008) play significant roles not only in the reward effect of drugs, i.e., substance abuse liability (Ikemoto, 2007; Piercem and Kumaresan 2006; Berridge, 2007), but also in the behavioral and psychological activities, particularly, motivation (Matsumoto and Hikosaka, 2009), attention and learning and memory (Arias-Carrion and Poppel, 2007; Ikemoto, 2007). It is therefore important to assess the changes in the behavioral effect following the repeated administration of central stimulants including MA and related drugs.

Although MA has traditionally been administered intravenously, an inhalation of MA vapor, namely *ABURI*, or mixed with tobacco, namely *MOKU*, is increasing not only because to avoid infections and the trace of picking needle, but because of easier way for taking the drug (personal communication from Japanese Ministry of Police).

N-cyanomethylmethamphetamine (CMA) (Fig. 1) is a

main pyrolysis product of smoking MA mixed with tobacco (Sekine and Nakahara, 1987, 1990; Sekine et al., 1995). The behavioral examinations in mice and rats revealed that CMA had MA-like central stimulant effect at comparatively lower doses; acceleration of ambulatory activity (locomotion) with the peak effect at 1.5 hr after the subcutaneous (s.c.) administration, and induction of various types of stereotyped behavior at higher doses (Nakahara and Sekine, 1987). The potency of behavioral stimulant effect of CMA was estimated to be approximately 2/3 time as high as that of MA (Nakahara and Sekine, 1987; Kuribara et al., 1996a). Our previous experiments demonstrated that intermittent administrations of CMA at intervals of 3-4 days induced the behavioral sensitization to the ambulatory stimulant effect in mice (Kuribara et al., 1996a, b).

The central stimulant effect of amphetamines is caused by an acceleration of dopamine release from the presynaptic cytoplasmic pool at mesolimbic dopaminergic system (McMillen, 1873). Nicotine, an agonist of nicotinic acetylcholine receptors (Fuxe et al., 1986; Imperato et al., 1986; Marks et al., 1986), also accelerates dopamine release in the brain through stimulation of nicotinic acetylcholine receptors (Marks et al., 1986; Mereu et al., 1987; Rowell et al., 1987; Carr et al., 1989; Kita et al., 1990; Sershen et al., 1991; Jutkiewicz et al., 2008), and shows an ambulatory stimulant effect in rodents, particularly in rats (Clarke et al., 1988; Kita et al., 1990, 1992; Ann-Sophie et al., 2006). Such neurochemical and behavioral characteristics of nicotine are partially similar to those of amphetamines. However, some reports suggested an antagonistic effect of nicotine on the amphetamine-induced ambulatory stimulation (Stolerman et al., 1973; Stevens et al., 1995), stereotyped behaviors (Arnfred and Rundrup, 1968; Klawans et al., 1972), and impairment of auditory sensory gating (Stevens et al., 1995).



R_1	Compound name
$CH_2C{\equiv}N$	N-cyanomethylmethampheamine
H	Methamphetamine

Fig. 1. Chemical structures of N-cyanomethylmethamphetamine (CMA), a main pyrolysis product of smoking methamphetamine (MA) mixed with tobacco, and MA.

Since CMA is a main pyrolysis product of smoking MA mixed with tobacco and is inhaled simultaneously with nicotine, it is extremely important to evaluate the combined effect of CMA and nicotine in relation to the modification of the behavioral stimulant effects of CMA and MA.

The aims of this study were to assess the characteristics of modification by nicotine of the induction and expression of ambulatory sensitization to CMA and MA in mice. The following two experiments were conducted: 1) repeated co-administrations of CMA with nicotine, and then challenge administration of MA, and 2) co-administration of CMA with nicotine to the MA-sensitized mice.

Materials and Methods

Animals

Male mice of ddY strain (Japan Laboratory Animals, Tokyo) were used at the age of 6 weeks (weighing 25-30 g). These mice were housed in groups of 10 in Polycarbonate cages (20W × 25L × 10H cm). The conditions of breeding room of Institute of Experimental Animal Research, Gunma University School of Medicine were controlled to temperature of 23 ± 2℃, relative humidity of 55 ± 3%, and 14:10 hr light-dark cycle of lights on between 05:00-19:00 hr. They were allowed free access to a solid diet (MF: Oriental Yeast, Tokyo) and tap water except during the behavioral tests.

Apparatus

The ambulatory activity of 10 mice was individually and simultaneously recorded with a tilting-type ambulometer having 10 bucket-like activity cages of 20 cm in diameter and 15 cm in height (SMA-10: O'hara & Co., Tokyo). A horizontal movement (ambulation) for longer than 5 cm, but not any vertical movements or turning, of the mouse generated a slight tilt of the activity cage, and it was detected with one of 3 micro-switches attached to the activity cage.

Drugs

The drugs used were N-cyanomethylmethamphetamine hydrochloride (CMA: synthesized by Criminal Investigation Laboratories of Saitama Prefectural Police HQ, Saitama), methamphetamine hydrochloride (MA: Philopon; Dainippon-Sumitomo Pharm., Osaka) and nicotine free base (Nakarai Chemical., Tokyo). CMA, MA and nicotine were dissolved in physiological saline, and the concentration of each drug solution was adjusted so that the volume subcutaneously (s.c.) injected was always constant at 0.1 ml/10 g body weight of the mouse. According to the previous studies related to CMA (Kuribara et al., 1996a, b) and MA (Kuribara and Hirabayashi, 1985), the doses of CMA and MA were fixed to 3 mg/kg and 2 mg/kg, respectively, in the salt forms, which were considered to be almost equivalent doses for increasing the ambulatory activity, and optimal doses for induction of ambulatory sensitization without eliciting strong stereotyped behaviors throughout the 5 repeated administrations at 3-day intervals in the ddY strain mice.

Experimental schedules

Before each drug administration, mice were adapted to the activity cage for 10 min. Then the ambulation of each mouse was measured for 3 hr after each drug administration. All the behavioral tests were carried out between 09:00-16:00 hr.

Experiment 1. Repeated co-administrations of CMA with nicotine, and followed by the challenge administration of MA

Five groups of mice (10 each) were first treated with 5 repeated administrations of either CMA alone (nicotine dose=0) or CMA in combination with nicotine (0.03, 0.1, 0.3 or 1 mg/kg) at 3-day intervals. Three days after the 5th treatment, all the mice were challenged with MA alone. In addition, the administration of MA to the drug-naive mice (N=10) that were age-matched to the mice treated with the co-administrations of CMA with nicotine was also conducted.

Experiment 2. Combined administration of CMA with nicotine to the MA-sensitized mice

To induce the ambulatory sensitization to MA, 5 groups of mice (10 each) were first treated with 5 repeated administrations of MA at 3-day intervals in the same way as in experiment 1. Three days after the 5th treatment, these groups of mice were challenged with either CMA (nicotine dose=0), or combination of CMA with nicotine (0.03, 0.1, 0.3 or 1 mg/kg).

Experiment 3. Combined administration of nicotine and CMA or MA to the mice experienced 5 treatments with nicotine

Five groups of 10 mice each were given nicotine (1 mg/kg s.c.) or saline 5 times at intervals of 3 days, and their ambulatory activities were measured for 3 hr after each administration. Three days after the 5th treatment, the groups of mice were given either saline, CMA (3mg/kg s.c.), MA (2 mg/kg s.c.), nicotine + CMA or nicotine + MA.

Ethical consideration for experimental animals

All the experimental procedures mentioned above were carried out according to the "*Guiding Principles for the Care and Use of Laboratory Animals*" approved by The Japanese Pharmacological Society.

Statistical analysis

Mean 3-hr overall ambulatory activity counts after the drug administrations were first analyzed by one- or two-way analysis of variance. In cases of significant variance, post-hoc analyses were carried out by Bonferoni test. Values of p less than 0.05 were considered significant.

Results

1) Repeated co-administrations of CMA with nicotine, and then challenge with MA (Experiment 1)

As shown in Table 1, the repeated co-administrations of CMA with nicotine caused a progressive enhancement of the ambulatory stimulant effect, although nicotine reduced the effect of CMA in a dose-dependent manner. When the challenge administration of MA was conducted, there was no significant difference in the activity counts among groups of mice treated with CMA alone or combination of CMA with nicotine, and the activity counts were almost the same as that in the mice received 5 repeated administration of MA at 3 day-intervals.

2) Combined administration of CMA with nicotine to the MA-sensitized mice (Experiment 2)

Five repeated administrations of MA (2mg/kg s.c.) at 3-day intervals resulted in an ambulatory sensitization to MA in all groups of mice; the activity counts at the 1st and 5th administration being 1600-1800 and 4000-4200, respectively (data are not shown).

Table 2 shows mean 3-hr activity counts after the administration of CMA alone (nicotine dose=0) or CMA in combination with nicotine (0.03-1 mg/kg) to the MA-sensitized mice. For comparison, the activity counts after the combined administration of CMA with nicotine to the drug-naive mice, which are shown in Table 1 (the counts at the 1st administration), are also presented.

The MA-sensitized mice demonstrated a significant cross-sensitization to CMA. The ambulatory stimulant effect of CMA was reduced by nicotine in both the drug-naive and MA-sensitized mice. The activity counts following

Table 1. Mean 3-hr ambulatory activity counts ± SEMs after 5 repeated administrations of N-cyanomethylmethamphetamine (CMA: 3 mg/kg s.c.) alone and the combinations of CMA with nicotine (NCT: 0.03, 0.1, 0.3 and 1 mg/kg s.c.), and MA (2mg/kg s.c.) at 3-day intervals, and challenge administration of MA.

Drugs and doses	1st	2nd	3rd	4th	5th	MA-challenge
CMA only	1318 ± 188	1832 ± 265	3462 ± 499*	3829 ± 554*	3941 ± 601*	4505 ± 551#
CMA+NCT (0.03)	1301 ± 120	1752 ± 243	2992 ± 449*	3948 ± 562*	3880 ± 554*	4462 ± 604#
CMA+NCT (0.1)	1057 ± 169	1493 ± 214	2258 ± 309*,$	3503 ± 505*	3516 ± 527*	4517 ± 553#
CMA+NCT (0.3)	917 ± 108$	1206 ± 161$	2301 ± 355*,$	3046 ± 436*	3004 ± 446*	4491 ± 598#
CMA+NCT (1)	836 ± 125$	995 ± 139$	1592 ± 259*,$	2517 ± 359*,$	2494 ± 384*,$	4520 ± 528#
MA only	1806 ± 113	2607 ± 372*	4208 ± 429*	4495 ± 518*	4713 ± 496*	4520 ± 528#
MA to the drug-naive mice						1849 ± 207

CMA and NCT were administered simultaneously.

*: Significantly different from the count in the first administration within each group (p<0.05).

$: Significantly different from the count of CMA alone-treated group at the same administration number (p<0.05).

#: Significantly different from the count after the administration of MA to the drug-naive mice (p<0.05).

N=10 in each group.

Table 2. Mean 3-hr ambulatory activity counts ± SEMs after the administration of N-cyanomethylmethamphetamine (CMA: 3 mg/kg s.c.) alone, co-administration of CMA with nicotine (NCT: 0.03-1 mg/kg s.c.), or nicotine alone to the methamphetamine (MA)-sensitized mice.

	Drug naive	MA-sensitized
CMA alone	1318 ± 265	4096 ± 614
CMA + NCT (0.03)	1452 ± 243	3617 ± 523
CMA + NCT (0.1)	1493 ± 214	3108 ± 436
CMA + NCT (0.3)	917 ± 108*	2620 ± 403*
CMA + NCT (1)	836 ± 125*	2283 ± 312*

The sensitization to MA was induced by 5 repeated administrations of MA (2 mg/kg s.c.) at 3-day intervals, and the co-administrations of CMA with NCT, and NCT alone were carried out 3 days after the 5th pretreatment with MA.

*: Significantly different vs. the group administered CMA alone (p<0.05).

N=10 in each group.

the co-administration of CMA with nicotine 0.3-1 mg/kg in the drug-naive and CMA-sensitized mice were significantly lower than those following the administration of CMA alone.

3) Combined administration of nicotine and CMA or MA to the mice experienced 5 treatments with nicotine (Experiment 3)

The activity counts following nicotine or saline were very low; 110-130 counts/3 hr after nicotine, and 90-105 after saline (Data are not shown).

As shown in Table 3, the mice experienced 5 times treatment with nicotine (1mg/kg s.c.) did not change the sensitivity to CMA or MA. Furthermore, the combined administration of nicotine and CMA or MA did not demonstrate a marked change in the activity as compared to the saline-treated mice.

Discussion

In agreement with our previous studies (Kuribara et al., 1996a,b), the repeated administrations of CMA induced an ambulatory sensitization similar to the repeated administrations of MA (Kuribara and Hirabayashi, 1985). The central stimulant effect of MAP is caused by acceleration of dopamine release from the cytoplasmic pool (McMillen, 1983). It is generally considered that the nicotine-induced behavioral stimulation is caused by an acceleration of dopaminergic neurotransmission through stimulation of acetylcholine release in the brain (Fuxe et al., 1986; Imperato et al., 1986; Carr et al., 1989; Mereu et al., 1987; Rowell et al., 1987; Kita et al., 1990, 1992; Sershen et al., 1991). In rats, generally, amphetamine and nicotine interact to enhance their behavioral and neurochemical effects (Huston-Lyons et al., 1993; Anne-Sophie et al., 2006). In these respects, we first expected that nicotine might not only enhance the ambulatory stimulant effect of CMA but also accelerate the induction of behavioral sensitization to CMA.

However, it is notable that the ambulatory stimulant effect of CMA was significantly reduced by nicotine in the drug-naive mice (see the 1st administration shown in Table 1), the MA-sensitized mice (Table 2), and the nicotine-treated mice (Table 3), suggesting that nicotine acts to inhibit the ambulatory stimulant effect of CMA in mice. These results are in consistent with the inhibitory effects of nicotine on the amphetamine-induced locomotor stimulation (Stolerman et al., 1973), stereotyped behavior (Arnfred and Rundrup, 1968; Klawans et al., 1972), and impairment of auditory gating in rats (Stevens et al., 1995).

Some mechanisms can be considered to be involved in the antagonistic effect of nicotine on the behavioral stimulation caused by amphetamines including CMA. The first one is that the nicotine-induced dopamine release through a stimulation of the nicotinic acetylcholine receptors in the brain is responsible for the reduction of amphetamine-induced dopamine release (Sershen et al., 1991). The second one is a possibility that the anti-stress effect of nicotine (Benovitz et al., 1986) plays to inhibit the behavioral stimulant effect of amphetamines. It has been suggested that hypothalamic-pituitary adrenal axis is involved in the induction and expression of sensitization to amphetamines (Knich and Eisenberg, 1979; Rivet et al.. 1989; Cole et al., 1990a, b; Kalivas and Eisenberg, 1991). Anne-Sophie et al. (2006) suggested a role of serotonergic mechanism in the

Table 3. Mean 3-hr ambulatory activity counts ± SEMs after the administration of N-cyanomethylmethamp hetamine (CMA: 3 mg/kg s.c.), methamphetamine (2mg/kg s.c.), or co-administration of CMA or MA with nicotine (NCT: 1 mg/kg s.c.) to the mice pre-treated with NCT (1mg/kg s.c.).

Pretreatments	Challenge administrations				
	Saline	CMA	MA	NCT+CMA	NCT+MA
Saline	73 ± 15	1309 ± 163	1830 ± 142	872 ± 141*	1008 ± 127*
NCT	56 ± 11	1252 ± 140	1903 ± 179	901 ± 155*	1137 ± 152*

The pretreatment were carried out 5 times at 3-day intervals, and the challenge administrations were carried out 3 days after the 5th pretreatment.

*: Significantly different between groups of CMA/NCT+CMA and MA/NCT+MA (p<0.05).

N=10 in each group.

nicotine-induced locomotor-increasing effect in mice. Further study is required to elucidate the antagonistic effect of nicotine on the amphetamine-induced behavioral stimulation in mice.

The central stimulant effect of amphetamines is caused by an acceleration of dopamine release from the presynaptic cytoplasmic pool at mesolimbic brain system (McMillen, 1873). Mesolimbic dopaminergic systems in the brain (Van der Heuval and Pasterkamp, 2008) play significant roles in the substance abuse liability (Ikemoto, 2007; Piercem and Kumaresan 2006; Berridge, 2007). The behavioral sensitization to amphetamines and related compounds has been considered to be related not only to the risk of the psychotoxic symptoms, namely amphetamine psychosis, induced by the repeated abuse of amphetamines (Ellinwood and Kilbey, 1977; Kuribara and Hirabayashi, 1985; Robinson and Becker, 1986; Tadokoro and Kuribara, 1986), but also to the enhancement of the abuse liability (Wise and Bozarth, 1987).

The present study revealed that, although nicotine inhibited the acute ambulatory stimulant effect of CMA and MA, and the repeated treatment with nicotine did not change the sensitivity to the stimulant effect of CMA or MA, the ambulatory sensitization to MA was not modified by the repeated co-administration of CMA and nicotine. These results also suggest that nicotine does not change the process of the induction of the behavioral sensitization to MA. Taken together, it is highly probable that the repeated smoking MA mixed with tobacco (i.e., the combined abuse of CMA with nicotine) may not reduce the liability of MA abuse and MA-induced psychotoxic symptoms such as paranoid, hallucination, etc.

This result also indicates another problem of MA abuse mixed with tobacco. Thus, to maintain the reward effect of these drugs, the combined MA abuse mixed with tobacco may increase the MA dose, and accelerate the risk of the MA-induced psychotoxic symptoms.

Conclusion

Behavioral sensitization to central stimulants such as amphetamines has been considered to be intimately related to the induction of psychotoxic symptoms following repeated abuse. MA-like behavioral sensitization was also induced to CMA, a main pyrolysis product of smoking MA mixed with tobacco, when it was administration at interval of 3 days in mice. During the 5 repeated co-administration of CMA (3 mg/kg s.c.) with nicotine (0.03, 0.1, 0.3 and 1 mg/kg s.c.) at 3 day intervals, nicotine dose-dependently inhibited the progressive enhancement of CMA-induced ambulatory stimulation. However, such treatments did not modify the induction of sensitization to the ambulatory stimulant effect of CMA (3 mg/kg s.c.) and MA (2 mg/kg s.c.). The MA-sensitized mice demonstrated significant cross-sensitization to CMA. These results suggest that, although nicotine inhibited the ambulatory stimulant effect of CMA in both the drug-naive and MA-sensitized mice, nicotine does not protect the induction of behavioral sensitization to CMA or MA. These results also indicate that repeated smoking MA mixed with tobacco may not modify the process of the induction of psychotoxicity of MA.

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覚せい剤混入タバコの喫煙で生じるN-cyanomethylmethamphetamineとnicotineの相互作用
－マウスの移所運動促進効果に対する増感現象の修飾－

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抄録： N-cyanomethylmethamphetamine（CMA）はタバコに覚せい剤（methamphetamine：MA）を混入して喫煙した場合に生成する主要化合物である。すでに我々は、MAと類似した中枢刺激作用を示し、マウスやラットに運動促進効果や常同行動を誘発すること、さらに、CMAを反復投与すると、中枢刺激作用に対する増加現象が引き起こされることを報告した。本研究では、CMAはnicotineと繰り返し同時吸入されることを考慮して、マウスの移所運動を指標に、nicotineの併用によるCMAに対する増感現象の修飾を検討した。CMA（3 mg/kg s.c.）とnicotine（0.03, 0.1, 0.3および1 mg/kg s.c.）の併用を3日間隔で5回反復投与すると、移所運動促進効果はnicotineの用量に依存して軽減された。しかし、6回目にMA（2 mg/kg s.c.）を単独投与してみると、nicotineとCMAの併用前処置はMAに対する増感現象の誘発を修飾しなかった。MAに対して増感を形成したマウスはCMAに対しても交差増感を示したが、これらのマウスにおいてもnicotineによるCMAの移所運動促進効果の軽減が認められた。一方、nicotineのみの投与を5回経験したマウスは、CMAおよびMAのいずれに対しても感受性の変化を示さなかった。本実験結果は、nicotineはCMAやMAの移所運動促進効果に対して抑制的に働くが、覚せい剤およびその類似薬の反復乱用によって引き起こされる精神毒性に対する増感現象を軽減しないことを示唆している。
（別冊請求先：栗原　久）

キーワード：N-Cyanomethylmethamphetamine、Methamphetamine、Nicotine、移所運動、行動的増感現象、精神毒性、マウス