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ORIGINAL INVESTIGATION

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Scopolamine prevents augmentation of stereotypy induced by chronic methamphetamine treatment

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Abstract Cholinergic neurotransmission has been implicated in various forms of neural plasticity such as kindling and learning. We have previously shown that blockade of muscarinic cholinergic receptors prevents the development of locomotor sensitization to methamphetamine. The present study was conducted to examine whether scopolamine, a muscarinic cholinergic antagonist, would also block augmentation of stereotypy induced by chronic methamphetamine (MA) treatment. Rats treated with MA (2.5 mg/kg, SC) for 10 days indicated significantly enhanced stereotyped behavior when tested with MA (2.5 mg/kg) after a 7- to 8- day withdrawal. Pretreatment with scopolamine (3 mg/kg) prior to MA administration prevented the augmentation of stereotypy. Rats treated with scopolamine alone showed no difference in MA-induced stereotypy compared to those treated with saline. Scopolamine methylbromide, a derivative of scopolamine that does not easily cross the blood-brain barrier, had no effect on the augmentation of stereotypy. These results suggest that stimulation of central muscarinic cholinergic receptors plays a role in the development of sensitization to the stereotypy stimulating effect of methamphetamine.

Key words Methamphetamine · Behavioral sensitization · Scopolamine · Acetylcholine · Rat

Introduction

Repeated administration of amphetamine or methamphetamine (MA) results in an augmentation of its locomotor activating effects, a phenomenon known as behavioral sensitization (Robinson and Becker 1986; Kalivas and Stewart 1991). In humans, the chronic use of the drug elicits a progressive augmentation in paranoid symptoms that closely resemble schizophrenia (Robinson and Becker 1986; Kalivas and Stewart 1991). Therefore, understanding the neural mechanism of sensitization in rodents may provide insight into the pathogenesis of both amphetamine-induced psychosis and schizophrenia.

Behavioral sensitization has some common properties with other forms of neural plasticity such as kindling, learning and long-term potentiation (LTP). Each phenomenon is established and reinforced during repeated intermittent stimulation. In addition, it has been demonstrated that behavioral sensitization to amphetamine is blocked by *N*-methyl-D-aspartate (NMDA) antagonists (Karler et al. 1989; Wolf and Khansa 1991; Stewart and Druhan 1993; Ohmori et al. 1994) and protein synthesis inhibitors (Robinson 1991; Karler et al. 1993). NMDA antagonists have been shown to block or retard the development of kindling and learning as well as LTP (Dingledine et al. 1990; McEntee and Crook 1993; Malenka and Nicoll 1993). Protein synthesis inhibitors have also been reported to inhibit learning and LTP (Barondes 1970; Quinton and Kramarcy 1977; Otani et al. 1992). These phenomenological and pharmacological similarities led us to examine whether behavioral sensitization would be blocked by scopolamine, an antagonist of the muscarinic cholinergic receptor, known to inhibit kindling, learning as well as LTP (Westerberg and Corcoran 1987; Elrod and Buccafusco 1988; Hirotsu et al. 1989; Tanaka et al. 1989).

We have previously reported that the cholinergic antagonist completely prevented the development of MA-induced locomotor sensitization (Ohmori et al. 1995a). In the present study, we examined whether scopolamine would also block augmentation of stereotypy induced by chronic methamphetamine treatment. Since locomotor activity and stereotypy are generally thought to be mediated by the activity of the nucleus accumbens and striatum, respectively (Randrup and

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Munkvad 1970; Kelly and Iversen 1975), the effect of antagonism of muscarinic receptors on the development of sensitization to the two types of behavior should be examined separately.

Materials and methods

Subjects

Male Wistar-King rats (Hokkaido University Animal Facility), weighing 200–250 g at the start of the experiment, were housed individually in a plastic cage 30 × 25 × 18 cm with a wire mesh top and with bedding of sawdust. The animal house was under controlled conditions of light (from 6:30 a.m. to 6:30 p.m.), temperature (24°C) and humidity (50%). They were allowed free access to standard laboratory diet and tap water. Animals were handled daily for at least 4 days before the start of the study. This study was conducted in accord with a guide for the care and use of laboratory animals regulated by Hokkaido University School of Medicine, and NIH guidelines on animal care.

Experiment 1 measured acute effects of scopolamine on stereotyped behavior induced by a single injection of MA. One group of rats received a single injection of MA (2.5 mg/kg, $n = 6$). Another group received MA (2.5 mg/kg) 5 min after scopolamine administration (3 mg/kg, $n = 6$). Behavior was visually analyzed as described below.

Experiment 2 examined effects of scopolamine on augmentation of stereotypy induced by chronic MA treatment.Rats were randomly assigned to one of the following four groups ($n = 12$ per group), as summarized in Table 1. The first group was treated with MA (2.5 mg/kg). The second group received scopolamine (3 mg/kg). The third group received MA (2.5 mg/kg) 5 min after the injection of scopolamine (3 mg/kg). The fourth group received saline (1 ml/kg). Drugs were injected daily from day 1 to day 10 in their home cages. On day 17 or 18, MA (2.5 mg/kg) was injected to all four groups (MA, scopolamine, scopolamine +MA, and saline groups). Behavior was analyzed by visual observation as well as using an apparatus as described below.

Experiment 3 measured acute effects of scopolamine methylbromide (scopolamine MB) on stereotyped behavior induced by a single injection of MA. One group of rats received a single injection of MA (2.5 mg/kg, $n = 6$). Another group received MA (2.5 mg/kg) 5 min after scopolamine MB administration (3.11 mg/kg, weight expressed to equal scopolamine free base in 3.0 mg/kg scopolamine hydrobromide, $n = 6$). Behavior was visually analyzed as described below.

Experiment 4 examined effects of scopolamine MB on augmentation of stereotypy induced by chronic MA treatment. Rats were randomly assigned to one of the following three groups ($n = 8$ per group), as summarized in Table 1. The first group was treated with MA (2.5 mg/kg). The second group received MA (2.5 mg/kg) 5 min after the injection of scopolamine MB (3.11 mg/kg). The third group received saline (1 ml/kg). Drugs were injected daily from day 1 to day 10 in their home cages. On day 17 or 18, MA (2.5 mg/kg) was injected to all three groups (MA, scopolamine MB +MA, and saline groups). Behavior was analyzed by visual observation as well as using an apparatus as described below.

Motor activity measurement

The home cage of the rat was moved to an observation room and placed under the sensor. Measurement of motor activity was started after 2 h habituation using an apparatus with an infrared sensor as previously described (Ohmori et al. 1994). In brief, horizontal movements of the rat were digitized and fed into a computer every 10 min. Locomotion predominantly contributed to the count, but repeated rearing and other nonspecific body movements could also contribute to the count when these movements had substantial horizontal components.

Visual observation

Visual observation of the behavior was conducted as previously described (Ohmori et al. 1995b), using the rating scale devised by Dougherty and Ellinwood (1983) with minor modifications. Each animal was assigned a rating score of 1–9 according to the scale every 10 min for 150 min after MA injection. Ratings were made by two observers, one of whom was unaware of the treatment conditions. In most cases, two observers gave the same score. In case of inconsistency, consensus was reached by quick review of the behavior. Definition of each score was as follows. 1: Lying Down, Eyes Closed. 2: Lying Down, Eyes Open. 3: Normal Grooming or Chewing 4: Sniffing or Rearing Intermittently. 5: Increased Locomotion, Jerky Movements. 6: Nearly Continuous Sniffing, Gnawing, or Licking, Normal Level of Locomotor Activity, but Repetitive. 7: Nearly Continuous Sniffing, Gnawing, or Licking with Hyperactive, Repetitive Exploration of Cage. 8: Rapid, Intense, Continuous Head and/or Foreleg Activity in the Same Place. 9: Backing Up, Jumping, Seizures, Abnormally Maintained Postures, Dyskinetic Movements. If two behavioral scores were observed in an observational period, both behavioral scores were recorded and the mean score was used for statistical analysis.

Drugs

Methamphetamine hydrochloride (Dainippon Pharmaceuticals, Japan), scopolamine hydrobromide (Sigma, St Louis, USA) and scopolamine methylbromide (Sigma, St Louis, USA) were dissolved in saline. All doses refer to salts. All injections were given subcutaneously in the morning.

Table 1 Summary of different groups in experiment 2 and 4

Groups	Treatment (from day 1 to 10)	Test (day 17 or 18)
Experiment 2		
I. MA	Methamphetamine (2.5 mg/kg)	Methamphetamine (2.5 mg/kg)
II. Scopolamine	Scopolamine (3 mg/kg)	
III. Scopolamune + MA	Scopolamine (3 mg/kg+ methamphetamine (2.5 mg/kg)	
IV. Saline	Saline (1 ml/kg)	
Experiment 4		
I. MA	Methamphetamine (2.5 mg/kg)	Methamphetamine (2.5 mg/kg)
II. Scopolamine MB + MA	Scopolamine MB (2.5 mg/kg) + methamphetamine (2.5 mg/kg)	
III. Saline	Saline (1 ml/kg)	

Statistics

Behavioral scores were analyzed by Kruskal-Wallis test at each time (defined as $P < 0.05$). When there was a statistically significant difference, Mann-Whitney *U*-test was used to determine which group differed from others. When a comparison was made between two groups, Mann-Whitney *U*-test was conducted at each time. Cumulated motor activity was analyzed by a one-way analysis of variance (ANOVA) followed by post-hoc Duncan new multiple range test (defined as $P < 0.05$)

Results

Figure 1 shows the results of experiment 1. Mann-Whitney *U*-tests revealed that rats received both scopolamine and MA showed greater behavioral scores than those received MA alone at 10, from 40 to 100, and from 120 to 140 min.

The results of experiment 2 are shown in Figs. 2 and 3. Figure 2 illustrates behavioral scores induced by readministration of MA on day 17 or 18 in the MA, scopolamine, scopolamine +MA, and saline groups. Kruskal-Wallis tests indicated a significant difference from 20 min to 90 min. Mann-Whitney *U*-tests revealed that MA-treated rats showed significantly greater scores than the other three groups (saline, scopolamine, and scopolamine +MA). Figure 3 illustrates the motor activity induced by readministration of MA on day 17 or 18. The histogram represents cumulated motor activity from 0 to 80 min. One-way ANOVA followed by Duncan new multiple range tests revealed that the cumulated motor activity was significantly reduced in the MA group compared to the other three groups.

Experiment 3 revealed that pretreatment with scopolamine MB resulted in no difference in behavioral scores induced by a single injection of MA (Mann-Whitney U tests, data not shown).

Behavioral scores in experiment 4 are illustrated in Fig. 4. Kruskal-Wallis tests indicated a significant difference from 30 to 90 and at 130 min. Mann-Whitney *U*-tests revealed that rats treated with MA alone as well as those treated with both scopolamine MB and MA showed significantly greater scores compared to those treated with saline. Motor activity was cumulated from 0 to 80 min. The mean (± SEM) cumulated counts were

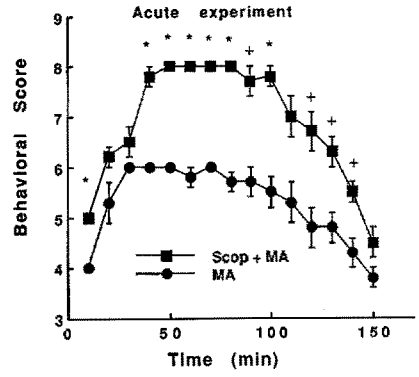


Fig. 1 Rats were administered with either methamphetamine (*MA*) alone or scopolamine (*Scop*) and MA. Scopolamine was injected 5 min prior to MA injection. MA was administered at 0 min. Each point represents the mean ± SEM for six rats per group. The Scop + MA group showed significant enhancement in the motor activity compared to the MA group ($^{*}P < 0.01$, $^{\dagger}P < 0.05$)

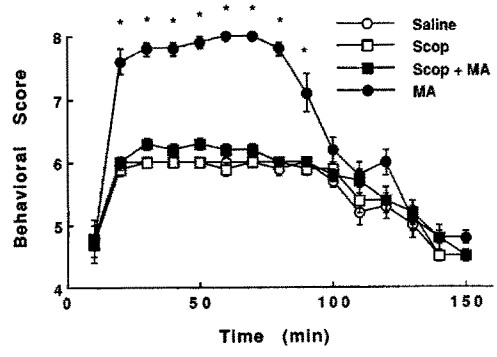
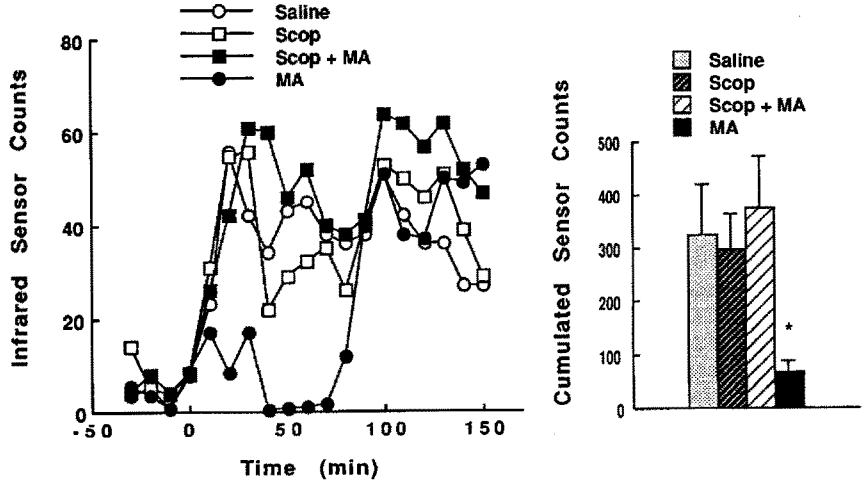


Fig. 2 Rats were treated with saline, methamphetamine (*MA*), scopolamine (*Scop*), and scopolamine + MA from day 1 to day 10. They were challenged with MA (2.5 mg/kg, SC) at time 0 on day 17 or 18, and MA-induced behavior was rated for 150 min. Each point represents the mean±SEM for 12 rats per group. The MA group showed significant enhancement in the behavioral score compared to the saline, Scop, and Scop +MA groups ($^{*}P < 0.05$)

Fig. 3 Motor activity measured on day 17 or 18 at the same time with the rating of MA-induced behavior in rats treated with saline, methamphetamine (*MA*), scopolamine (*Scop*), and scopolamine +MA. Each point represents the mean for 12 rats per group. The histogram represents cumulated motor activity of each group from 0 to 80 min (mean ± SEM). The MA group showed significantly reduced motor activity compared to the other three groups ($^{*}P < 0.01$)



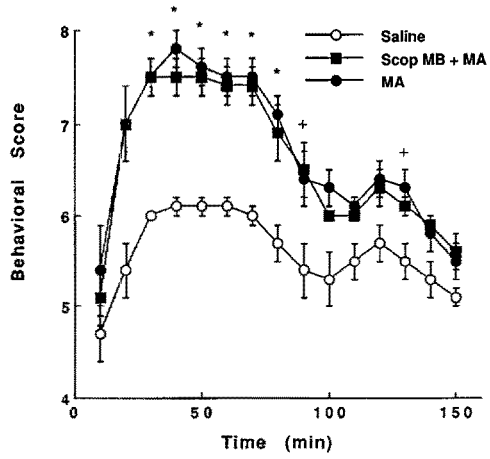


Fig. 4 Rats were treated with saline, methamphetamine (*MA*), and scopolamine methylbromide (*Scop MB*) +MA from day 1 to day 10. They were challenged with MA (2.5 mg/kg, SC) at time 0 on day 17 or 18, and MA-induced behavior was rated for 150 min. Each point represents the mean ± SEM for eight rats per group. The MA group as well as the Scop MB + MA group showed significant enhancement in the behavioral score compared to the Saline group (* $P < 0.01$, + $P < 0.05$)

174 ± 45, 68 ± 14, and 399 ± 90 in the MA, scopolamine MB + MA and saline groups, respectively. One-way ANOVA followed by Duncan multiple range test revealed that the cumulated motor activity was significantly reduced in the MA group as well as the scopolamine MB + MA group compared to the saline group. There was no significant difference in the cumulated activity between the scopolamine MB + MA and MA groups.

Discussion

Rats treated with MA for 10 days showed significantly enhanced behavioral scores and significantly reduced motor activity compared to those treated with saline. Rats pretreated with scopolamine prior to MA administration showed no difference in either behavioral scores or motor activity from saline treated rats. These results suggest that scopolamine prevented augmentation of stereotypy induced by chronic MA treatment. This finding is in line with our previous study which showed the muscarinic antagonist blocks enhancement in locomotion induced by chronic treatment with a low dose of MA (Ohmori et al. 1995a). The finding that scopolamine methylbromide, a muscarinic antagonist which does not easily cross the blood-brain barrier, had no effect on MA-induced augmentation in stereotyped behavior indicates that antagonism of the central muscarinic receptors was relevant to the inhibitory effect of scopolamine. These results suggest an important role of the central cholinergic transmission in the development of behavioral sensitization.

In the present experiments, stereotyped behavior was assessed not by only visual observation but also using an apparatus with an infrared sensor. Although the latter method primarily measured locomotion, the measurement was able to provide objective information on the degree of stereotypy. When a rat showed continuous stereotypy (sniffing and licking) in the same place without any locomotion, the sensor count indicated zero or almost zero, whereas the count increased to measurable levels when an animal showed intermittent stereotypy with a certain degree of locomotion. Thus, assessment of stereotypy became more reliable by using the two different measurements.

The exact mechanism by which scopolamine blocked sensitization is unknown. It is well documented that amphetamine-induced behavior is enhanced when the stimulant is coadministered with anticholinergic drugs (Arnfred and Randrup 1968; Naylor and Costall 1971; Costall and Naylor 1972). In agreement with these previous studies, we observed that pretreatment with scopolamine acutely enhanced MA-induced stereotyped behavior. However, even though animals pretreated with the muscarinic antagonist exhibited enhanced stereotypy during the treatment period, they showed no behavioral sensitization when tested 7–8 days after the treatment. Any residual or withdrawal effects of scopolamine cannot account for its blockade of the development of behavioral sensitization, since treatment with scopolamine alone for 10 days produced no effects on MA-induced behavior when tested 7–8 days after the treatment. Inconsistent with our findings, Yui and Miura (1994) recently reported that repeated administration of MA (4.0 mg/kg) plus scopolamine (0.5 mg/kg) resulted in slightly but significantly more apparent behavioral sensitization compared to MA alone. Their study used a greater dose of MA and a smaller dose of scopolamine compared to ours. Therefore, a relatively large dose of scopolamine seems to be necessary to block behavioral sensitization. It may be that blockade of muscarinic receptors outlasts the behavioral effects of MA to prevent the development of behavioral sensitization.

It is unlikely that behavioral sensitization was blocked through interference with the development of conditioning of the effect of MA to a specific environment where the drug was given. The rats were repeatedly treated with MA and/or scopolamine, and tested with MA, in their home cages. Therefore, it is assumed that conditioning variables were minimized in the present experiment. Alternatively, recent studies have suggested that the extent of locomotor sensitization reflects the amount of locomotion elicited during the repeated treatment (Willner et al. 1992; Einat and Szechtman 1993; Ohmori et al. 1995b). However, as discussed above, the rats showed significantly greater stereotypy when treated with both scopolamine and MA compared to when treated with MA alone. Therefore, it is also unlikely that scopolamine blocked behavioral sensitization by suppressing the stereotypy increasing effect of MA during the chronic treatment.

One possibility is that scopolamine prevented the development of behavioral sensitization by blocking the cholinergic stimulation in the hippocampus and/or the cortex. The hippocampal cholinergic pathway, originating from the medial septum and diagonal band of Broca and projecting to the hippocampus, is of crucial importance for certain aspects of hippocampal function such as learning and memory (Hepler et al. 1985; Nilsson et al. 1987). The cortical acetylcholine projection from the nucleus basalis magnocellularis also appears to be related to arousal and cognitive function (Riekkinen et al. 1990, 1991). Both pathways have been known to have functional links with dopaminergic activity (Lindvall 1975; Casamenti et al. 1986). Specifically, recent in vivo microdialysis studies have shown that systemic administration of amphetamine increases acetylcholine release in the hippocampus as well as the cortex, by increasing dopaminergic transmission (Day and Fibiger 1992; Nilsson et al. 1992; Imperato et al. 1993). Therefore, it is possible that MA-induced stimulation of muscarinic cholinergic receptors in the hippocampus and/or the cortex might be relevant to behavioral sensitization and that scopolamine blocks this process.

In summary, the present study indicates that scopolamine, a muscarinic cholinergic receptor antagonist, prevents sensitization to the stereotypy stimulating effect of MA. This finding, together with our previous finding that the antagonist blocks sensitization to the locomotion stimulating effect of MA, suggests an important role for central cholinergic transmission in the development of behavioral sensitization. As mentioned in the Introduction, glutamatergic systems and protein synthesis, both of which are thought to be involved in a variety of phenomena associated with neural plasticity such as kindling, learning and LTP, have been shown to be implicated in the development of behavioral sensitization (Karler et al. 1989; Robinson 1991; Wolf and Khansa 1991; Karler et al. 1993; Stewart and Druhan 1993; Ohmori et al. 1994). The present findings, taken together with the role of cholinergic systems in kindling, learning and LTP, may support a notion that behavioral sensitization to stimulants drugs shares a common property with other forms of neural plasticity.

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