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Roles of adenosine A_1 and A_{2A} receptors in the expression and development of methamphetamine-induced sensitization

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Abstract

We studied the effects of adenosine A_1 and A_{2A} receptor agonists on the expression and development of methamphetamine-induced sensitization in rats. When animals were treated with the adenosine A_1 receptor agonist, N^6-cyclohexyladenosine (CHA), along with methamphetamine every 3 days with a total of five administrations, the augmentation of hyperlocomotion by methamphetamine re-administration after 7-day withdrawal (methamphetamine challenge administration) was not inhibited. However, when the adenosine A_{2A} receptor agonist, 2-*p*-(2-carboxyethyl) phenethyl-amino-5′-*N*-ethylcarboxy-amide adenosine (CGS21680), was administered according to the same schedule, the augmentation was significantly inhibited. On the other hand, when CHA or CGS21680 was administered 30 min before methamphetamine challenge, both drugs dose-dependently inhibited the augmentation of hyperlocomotion. These results suggested that both adenosine A_1 and A_{2A} receptors play important roles in the expression of methamphetamine-induced sensitization, and that adenosine A_{2A} receptors do so in the development of this sensitization.

Keywords: Methamphetamine; Sensitization; Adenosine; Adenosine A_1 receptor; Adenosine A_{2A} receptor

1. Introduction

Many investigators have reported that repeated administration of psychomotor stimulants such as amphetamine, methamphetamine and cocaine induces a behavioral sensitization referred to as augmentation of locomotor activity and stereotyped behavior, even after their long-term withdrawal (Robinson and Camp, 1987; Kuribara, 1996). We have demonstrated that methamphetamine-induced sensitization causes the enhancement of striatal dopamine release, and that metabotropic glutamate receptors might be involved in this dopamine release (Arai et al., 1996).

Adenosine is known to play an important role in synaptic transmission in the central nervous system (Brundege and Dunwiddie, 1996, 1997). Adenosine A_1 receptors are distributed in various regions of the rat brain (Williams and Braunwalder, 1986), and their stimulation induces a decrease in cAMP level (Fredholm and Dunwiddie, 1988). On the other hand, adenosine A_{2A} receptors are distributed in the striatum, the accumbens, etc., and their stimulation induces an increase in the cAMP level (Jarvis and Williams, 1989; Schiffmann et al., 1991). Recently, adenosine was reported to affect synaptic plasticity in learning and memory (Alzheimer et al., 1991; Ohno and Watanabe, 1996; De Mendonca and Ribeiro, 1997; De Mendonca et al., 1997). Moreover, previous reports indicate that both receptors suppress dopamine transmission (Okada et al., 1996). An antagonistic adenosine A_1–dopamine D_1 and adenosine A_2–dopamine D_2 receptor interaction is known to exist (Ferré et al., 1991, 1994). Therefore, methamphetamine-induced sensitization may be influenced by adenosine-related drugs. In the present study, we investigated the effects of an adenosine A_1 receptor agonist, N^6-cyclohexyladenosine (CHA), and an adenosine A_{2A} receptor agonist, 2-*p*-(2-carboxyethyl) phenethylamino-5′-*N*-ethylcarboxy-amide adenosine (CGS21680), on the expression and development of methamphetamine-induced sensitization in rats.

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2. Materials and methods

2.1. Animals

The animals used in this experiment were male rats of the Wistar strain (Kyudo Experimental Animal, Saga, Japan), weighing between 230 and 250 g at the start of the experiment. The rats were housed in groups of four or five under constant temperature (23 ± 2°C) and a 12-h light/dark cycle (light period: 0700–1900 h). The rats were allowed free access to food and water throughout the experiments.

2.2. Drugs

The drugs used in the present study were methamphetamine (Dainippon Pharmaceuticals), N^6-cyclohexyladenosine (CHA, Research Biochemicals International) and 2-*p*-(2-carboxyethyl) phenethylamino-5′-*N*-ethylcarboxy-amide adenosine (CGS21680, Research Biochemicals International).

2.3. Experimental schedule

First, we studied the influence of CHA or CGS21680 treatment on the acute effects of methamphetamine. The home cages with rats were kept in the counter box for 60 min. After habituation, CHA or CGS21680 was intraperitoneally (i.p.) injected 30 min before saline or methamphetamine (1 mg/kg, i.p.). Then, locomotor activity was measured for 60 min.

To study methamphetamine-induced sensitization, rats were injected with methamphetamine or saline i.p. every 3 days with a total of five injections in their home cages. On the first day, the home cages were moved into the counter box, and kept there for 60 min. After the first administration of methamphetamine there, locomotor activity was measured for 60 min. The data were used to determine acute effects. The rats were returned to the housing room where the subsequent injections were given. After 5-day withdrawal, the cages were moved into the counter box. The rats were kept there for 60 min, and were given saline. Then, locomotor activity was measured for 60 min. The data were used as control (vehicle). The next day, the cages were moved into the counter box again. The rats were kept there for 60 min, and were challenged with methamphetamine (0.5 mg/kg, i.p.). Then, locomotor activity was measured for 60 min. To study the effects of CHA or CGS21680 on the development of methamphetamine-induced sensitization, each drug was injected i.p. 30 min before the intermittent treatment with methamphetamine. CHA or CGS21680 was also given intermittently without methamphetamine administration. After 6-day withdrawal, the rats were treated with methamphetamine (0.5 mg/kg, i.p.), and locomotor activity was measured to evaluate the influence of intermittent administration of each drug on the acute action of methamphetamine. Then, to study the effect of CHA or CGS21680 on the expression of sensitization, each drug was injected i.p. 30 min before methamphetamine challenge.

2.4. Locomotor activity measurement

Activity counts (number of horizontal and vertical movements such as locomotion and rearing) were determined using an area sensor (Omuron, F5B, Japan) as we described previously (Arai et al., 1996). All animals were injected in their home cages until methamphetamine challenge. Locomotor activity was recorded for 60 min after injection of methamphetamine and the record was printed out on an Intelligence Printer (Muromachi Kikai, Japan).

2.5. Data analysis

The data are expressed as means ± S.E.M. The significance of differences between groups was determined by one-way analysis of variance followed by Dunnet's test or Student's *t*-test for individual comparisons.

3. Results

Treatment with 0.005–0.05 mg/kg of CHA and 0.05–0.1 mg/kg CGS21680 did not affect locomotor activity in rats (data not shown). The hyperlocomotion induced by

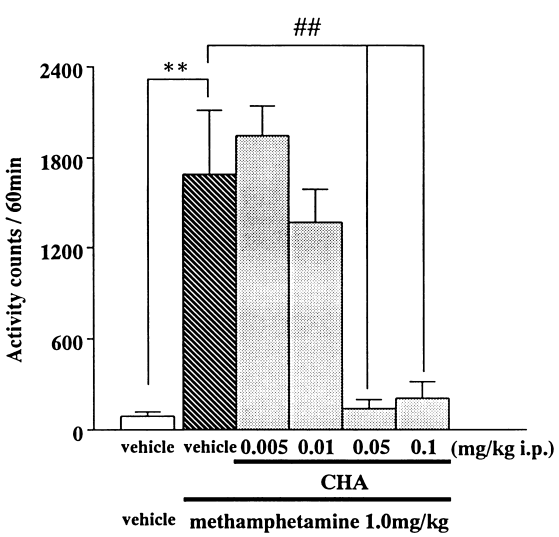

Fig. 1. Effect of N^6-cyclohexyladenosine (CHA) on acute action of methamphetamine. The data are shown as means ± S.E.M. The number of rats in each group was three to four. The data were analyzed by one-way analysis of variance followed by Dunnett's test or Student's *t*-test. $^{**}P < 0.01$, $^{\#\#}P < 0.01$.

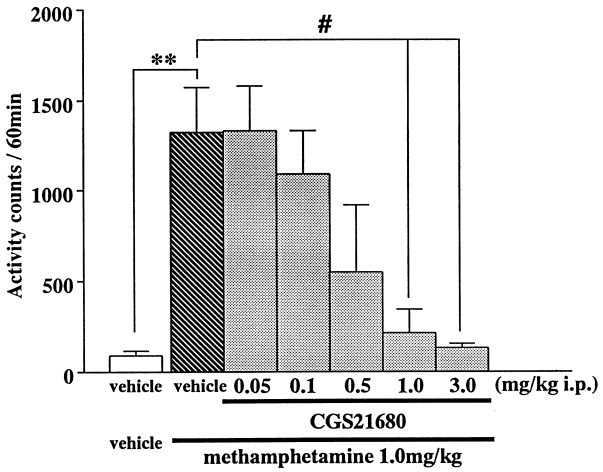

Fig. 2. Effect of 2-*p*-(2-carboxyethyl)phenethylamino-5′-*N*-ethyl-carboxy-amide (CGS21680) on acute action of methamphetamine. The data are shown as means ± S.E.M. The number of rats in each group was three to eight. The data were analyzed by one-way analysis of variance followed by Dunnett's test or Student's *t*-test. $^{**}P < 0.01$, $^{\#}P < 0.05$.

acute methamphetamine treatment (1.0 mg/kg) was significantly blocked by 0.05 and 0.1 mg/kg CHA ($P < 0.05$, Fig. 1). The hyperlocomotion was dose-dependently blocked by CGS21680 (Fig. 2). CGS21680 showed a significant inhibitory effect at 1.0 and 3.0 mg/kg ($P < 0.05$, Fig. 2).

When the animals were treated with CHA 30 min before methamphetamine challenge, the augmentation of hyperlocomotion was dose-dependently inhibited. At 0.01 mg/kg, CHA significantly inhibited this augmentation

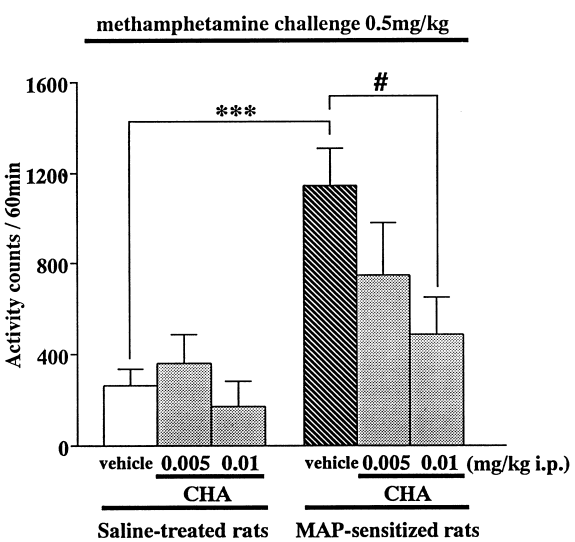

Fig. 3. Effect of CHA on the expression of methamphetamine-induced sensitization. CHA was given i.p. 30 min before methamphetamine challenge. The data are shown as means ± S.E.M. The number of rats in each group was four to eight. The data were analyzed by one-way analysis of variance followed by Dunnett's test or Student's *t*-test. $^{***}P < 0.001$, $^{\#}P < 0.05$.

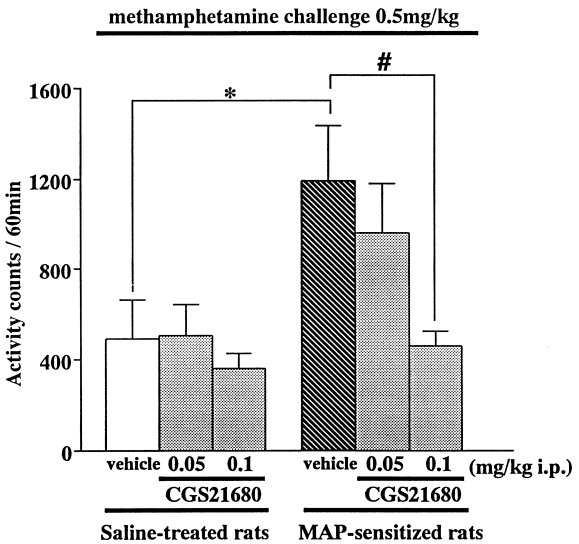

Fig. 4. Effect of CGS21680 on the expression of methamphetamine-induced sensitization. CGS21680 was given i.p. 30 min before methamphetamine challenge. The data are shown as means ± S.E.M. The number of rats examined was eight. The data were analyzed by one-way analysis of variance followed by Dunnett's test or Student's *t*-test. $^{*}P < 0.05$, $^{\#}P < 0.05$.

($P < 0.05$, Fig. 3). When CGS21680 was administered 30 min before methamphetamine challenge, the augmentation of hyperlocomotion was also dose-dependently inhibited. At 0.1 mg/kg, CGS21680 significantly inhibited this augmentation ($P < 0.05$, Fig. 4).

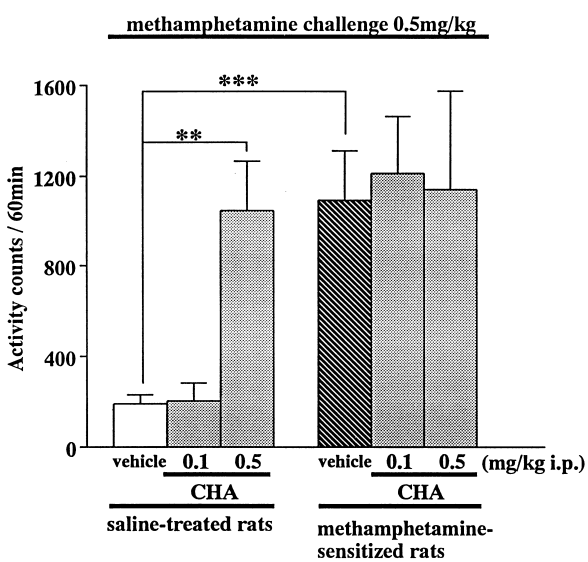

Fig. 5. Effect of CHA on the development of methamphetamine-induced sensitization. CHA was given i.p. 30 min before methamphetamine treatment or without methamphetamine treatment every 3 days with a total of five administrations. The data are shown as means ± S.E.M. The number of rats in each group was three to nine. The data were analyzed by one-way analysis of variance followed by Dunnett's test or Student's *t*-test. $^{**}P < 0.01$, $^{***}P < 0.001$.

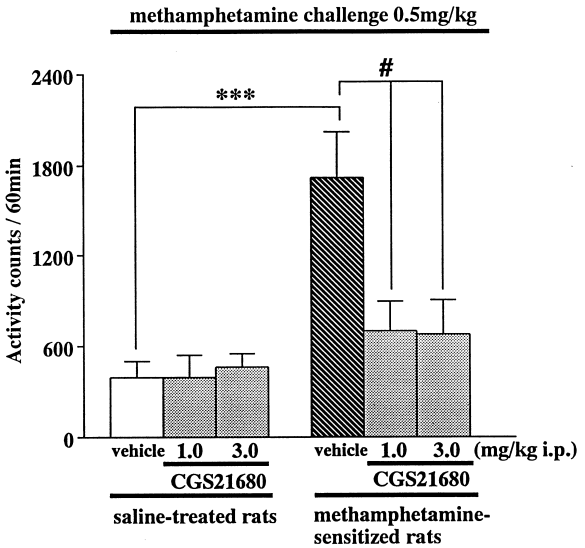

Fig. 6. Effect of CGS21680 on the development of MAP-induced sensitization. CGS21680 was given i.p. 30 min before methamphetamine treatment or without methamphetamine treatment every 3 days with a total of five administrations. The data are shown as means ± S.E.M. The number of rats in each group was 4–10. The data were analyzed by one-way analysis of variance followed by Dunnett's test or Student's *t*-test. $^{***}P < 0.001$, $^{\#}P < 0.05$.

The development of methamphetamine-induced sensitization was not inhibited by pretreatment with CHA (Fig. 5). Then, the intermittent treatment with CHA (0.5 mg/kg) significantly potentiated the acute effect of methamphetamine in saline-treated rats (Fig. 5). On the other hand, pretreatment with 1.0 and 3.0 mg/kg of CGS21680 along with intermittent methamphetamine administration significantly inhibited the augmentation of methamphetamine-induced hyperlocomotion ($P < 0.05$, Fig. 6). No special stereotyped behavior was observed during the experiment.

4. Discussion

We now studied the effects of adenosine A_1 and A_{2A} agonists on the action of methamphetamine. We first assessed the acute effects of adenosine A_1 and A_{2A} receptor agonists on the action of methamphetamine. Both CHA and CGS21680 dose-dependently blocked the acute motor activating effect of methamphetamine (Figs. 1 and 2). These results agree with some previous reports. As suggested in those reports, adenosine receptor agonists may suppress dopaminergic neurotransmission.

Different mechanisms are involved in the expression and in the development of sensitization (Wolf et al., 1995; Inoue et al., 1996; Karler et al., 1996). We, therefore, tried to clarify the effects of adenosine receptor agonists on the expression and on the development of the sensitization. Both CHA and CGS21680 have inhibitory effects on the expression of methamphetamine-induced sensitization. Adenosine A_1 receptors are widely distributed in the rat brain (Williams and Braunwalder, 1986). An antagonistic adenosine A_1–dopamine D_1 receptor interaction is known (Ferré et al., 1991, 1994). Ferré (1997) reported that adenosine A_1 receptors modulate the binding characteristics of dopamine D_1 receptors. Ballarin et al. (1995) reported that the dopamine release induced from the striatum in vitro by systemic administration of methamphetamine was not influenced by bath application of an adenosine A_1 receptor agonist. Moreover, in our preliminary microdialysis study, methamphetamine-induced dopamine release of the striatum was not inhibited by pretreatment with CHA. This suggests that CHA may block the expression of methamphetamine-induced sensitization by suppressing dopaminergic function postsynaptically.

On the other hand, adenosine A_{2A} receptors are mainly expressed in the striatum, the accumbens and the olfactory tubercle (Jarvis and Williams, 1989; Schiffmann et al., 1991). Antagonistic interactions between adenosine A_{2A} and dopamine D_2 receptors have been demonstrated in a number of studies (Ferré 1997; Ferré et al., 1991, 1996). Animals sensitized by psychomotor stimulants are more sensitive to apomorphine or to the selective dopamine D_2 receptor agonist, quinpirole (LY17155), than to the selective dopamine D_1 agonist, ±-1-phenyl-2,3,4,5-tetrahydrop-[^{1}H]-3-benzazepine-7,8-diol (SKF38393) (Schulz et al., 1981; Levy et al., 1988). On the other hand, it was also reported that stimulation of adenosine A_{2A} receptors has an inhibitory effect on the action of dopamine D_1 receptors (Morelli et al., 1994; Pinna et al., 1996). Therefore, we cannot eliminate a role of dopamine D_1 receptors in this inhibitory action of CGS21680.

Adenosine A_{2A} receptor agonists inhibit Fos expression induced by amphetamine injection in the striatum (Turgeon et al., 1996). Adenosine A_{2A} receptors are not expressed in the dopamine neuronal cell body. Therefore, CGS21680 may inhibit the post-synaptic pathway of dopaminergic function, and may block the expression of the sensitization. However, in our microdialysis study, CGS21680 inhibited the dopamine release induced by methamphetamine in the striatum of the sensitized rats. Presynaptic mechanisms may thus be involved in the effect of CGS21680.

The expression of sensitization is accompanied by supersensitivity of dopamine D_1 receptors in the accumbens (Higashi et al., 1989; Wolf et al., 1994). The following biosynthesis pathway has been reported (Rosenberg et al., 1994). cAMP produced by overactivation of adenylate cyclase is released via nucleoside transporters and is metabolized to adenosine. In cocaine- or morphine-dependent animals, the effect of adenosine is upregulated because cAMP is extracellularly metabolized by tonic activation of dopamine D_1 receptors in the ventral tegmental termini of γ-aminobutyric acid neurons projecting from the accum-

bens (Bonci and Williams, 1996). Taken together, these observations suggest that functions of adenosine in the accumbens might be activated in methamphetamine-sensitized rats. Therefore, pretreatment with CGS21680 might stimulate an activated adenosine function in the accumbens, and the expression of methamphetamine-induced sensitization may be then inhibited. We should try further experiments to clarify the precise mechanisms.

CGS21680 also blocked the development of the sensitization. Carlezon et al. (1995) reported that the dopamine D_2 receptor direct agonist, bromocriptine, induces sensitization. Thus, the development of methamphetamine-induced sensitization is inhibited by a dopamine D_2 receptor antagonist. Therefore, dopamine D_2 receptors may also play important roles in the development of sensitization. Thus, CGS21680 may inhibit responses of dopamine D_2 receptors and so block suppression of the development.

Intermittent treatment with CHA potentiated the motor-activating effect of methamphetamine. This result is quite interesting because CHA suppresses dopaminergic transmission. The possibility that intermittent treatment with CHA induces subsensitivity of adenosine A_1 receptors is under study.

5. Conclusion

In rats, both adenosine A_1 and A_{2A} receptors might play important roles in the expression, and A_{2A} receptors might be involved in methamphetamine-induced sensitization.

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