Psychopharmacology (2002): 160:122–131
DOI 10.1007/s00213-001-0958-1

ORIGINAL INVESTIGATION

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Effect of MS-153 on the development of behavioral sensitization to locomotion- and ataxia-inducing effects of phencyclidine

Received: 18 January 2001 / Accepted: 6 October 2001 / Published online: 10 January 2002

Abstract *Rationale:* Repeated administration of phencyclidine (PCP) produces behavioral sensitization to PCP. Although the precise mechanism is unknown, glutamatergic neurotransmission seems to play an important role in the development of sensitization. *Objectives:* The present study examined whether a novel compound, MS-153 ((*R*)-(–)-5-methyl-1-nicotinyl-2-pyrazoline), which has an ability to enhance glutamate uptake and inhibit glutamate release, would block the development of behavioral sensitization to PCP. *Methods:* For studying effects of MS-153, locomotor activity was measured by an infrared sensor and ataxia was measured by a rating scale. *Results:* MS-153 (10 and 100 mg/kg) enhanced locomotion and ataxia induced by a single injection of PCP (7.5 mg/kg). Repeated administration of PCP (20 mg/kg, once in every day, for 5 days) developed sensitization to locomotion- and ataxia-inducing effects of PCP (7.5 mg/kg). MS-153 given 60 min and 120 min later of every PCP treatment blocked the development of behavioral sensitization to both locomotion- and ataxia-inducing effects of PCP. Co-administration of MS-153 with repeated saline treatment did not produce hypersensitivity to PCP. *Conclusions:* These results suggest that the attenuation of glutamatergic neural transmission enhances acute effects of PCP, in contrast, blocks the behavioral sensitization developed by repeated PCP treatment. Therefore, glutamatergic neural transmission plays an important role in the development of behavioral sensitization to PCP.

Keywords Phencyclidine · Behavioral sensitization · Locomotion · Ataxia · Glutamate

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Introduction

Phencyclidine (PCP) induces a psychotomimetic state that closely resembles schizophrenia. Acute injection of PCP to normal volunteers induces autism, catatonia, and thought disorder, although it only weakly induces delusion and hallucination (Davies and Beech 1960; Bakker and Amini 1961). Acute PCP administration also exacerbates psychotic symptoms in chronic as well as acute schizophrenic subjects (Luby et al. 1959; Javitt and Zukin 1991). On the other hand, chronic PCP abuse induces not only so-called "positive symptoms" such as delusion and hallucination but also disorganization of thought and "negative symptoms" such as apathy, flattened affect, and social withdrawal (Javitt and Zukin 1991). As amphetamine (AMPH) does not induce core schizophrenic thought disorder or "negative symptoms" (Sayed and Garrison 1983), PCP-psychosis is a more comprehensive model of schizophrenia than AMPH-psychosis.

Although acute abuse of PCP produces short-lived schizophreniform symptoms, chronic abuse of this psychostimulant induces not only the long-lived psychotic symptoms (Luisada 1978; Cosgrove and Newel 1991) but also "flashback" of the psychosis after long-term withdrawal from PCP (Fauman and Fauman 1978). Therefore, it is possible that chronic abuse of PCP develops plastic changes in neurons and the circuits in which they participate, leading to hypersensitivity to re-use of the psychostimulant and non-specific stressful events. Furthermore, although acute abuse of PCP does not decrease prefrontal cortical metabolism (Piercy and Ray 1988), chronic abuse produces hypometabolism in this region (Wu et al. 1989), which is known to be implicated in the pathogenesis of schizophrenia (Ingvar and Franzen 1974). Therefore, these findings suggest the importance of studying behavioral and neurochemical changes induced by chronic PCP administration for clarifying the pathogenesis of schizophrenia.

Animals receiving repeated PCP injections are reported to develop behavioral sensitization for locomotor ac-

tivity (Nabeshima et al. 1987; Wolf and Khansa 1991; Xu and Domino 1994; Johnson et al. 1998) or stereotyped behaviors such as sniffing and rearing (Greenberg and Segal 1986; Nabeshima et al. 1987; Xu and Domino 1994). However, the precise mechanism of the sensitization is unknown. Taking into account the role of glutamatergic neural transmission in the development of behavioral sensitization to amphetamines or cocaine (Kalivas et al. 1993; Wolf 1998), we postulated that PCP-induced changes in glutamatergic neural transmission would be closely related to PCP-sensitization. To examine this hypothesis, the present study first aimed to confirm that five injections of PCP (20 mg/kg) induce behavioral sensitization to both the locomotion- and ataxia-inducing effects of PCP (7.5 mg/kg). We then examined the effect of MS-153, which has the ability to enhance glutamate uptake and inhibit glutamate release (Kosuge et al. 1995; Umemura et al. 1996; Shimada et al. 1997), on the development of behavioral sensitization.

Acute injection of PCP to animals induces not only locomotion but also stereotyped behaviors such as sniffing, rearing, and repetitive head movement (Johnson and Jones 1990). PCP-induced locomotion and stereotypy are closely related to mechanism in the nucleus accumbens (NAC) (McCullough and Salamone 1992; Steinpreis and Salamone 1992) and striatum (ST) (Nabeshima et al. 1983a, 1983b), respectively. Considering apparent differences in the neurochemical substrates of locomotion and stereotypy, we examined these two types of behaviors separately. Therefore the present study focused on the PCP-induced locomotion. Since increases in degree of ataxia are known to reduce locomotion (Sturgeon et al. 1979), we examined not only locomotion but also ataxia, and employed 7.5 mg/kg PCP, which minimally produces ataxia and induces locomotion effectively (Sturgeon et al. 1979).

Materials and methods

Animals

Male Sprague-Dawley rats (SLC, Inc., Japan) weighing 250–290 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.

Drugs

Phencyclidine hydrochloride (synthesized in the laboratory of Hokkaido University) and MS-153 (gift from Institute of Biological Science, Mitsui Pharmaceuticals, Inc., Japan) were dissolved in saline. The dose of PCP refers to salt and that of MS-153 refers to itself. All injections were given intraperitoneally.

Experimental procedures

Experiment 1 measured acute effects of MS-153 on locomotion and ataxia induced by a single injection of PCP (7.5 mg/kg). Rats were administered saline or MS-153 (1, 10, and 100 mg/kg) at 0 min, and administered saline or PCP (7.5 mg/kg) at 20 min. Behavior was analyzed as described below. The number of animals for each group was six to seven.

Experiment 2 examined the effects of MS-153 on the augmentation of locomotion or ataxia induced by repeated PCP treatment. Rats were randomly assigned to one of the following four groups. The first group received saline (1 ml/kg) 60 min and 120 min after the saline (1 ml/kg) injection. The second group received MS-153 (10 mg/kg) 60 min and 120 min after the saline (1 ml/kg) injection. The third group received saline (1 ml/kg) 60 min and 120 min after the PCP (20 mg/kg) injection. The fourth group received MS-153 (10 mg/kg) 60 min and 120 min after the PCP (20 mg/kg) injection. Administration of PCP leads to increase in glutamate level in the medial prefrontal cortex or nucleus accumbens for at least 60 min (Adams and Moghaddam 1998; Moghaddam and Adams 1998). Considering a very short half-life of MS-153, we administered MS-153 60 min and 120 min after PCP treatment to block effectively this increase in glutamate level. These treatments were repeated for 5 consecutive days in home cages. PCP (7.5 mg/kg) was administered in activity chambers to all the four groups 4 days after the 5-day treatment. Behavior was analyzed as described below. The number of animals for each group was six to eight.

Measurement of locomotion

The home cages of the rats were moved to an observation room and the rats were placed individually into activity chambers where locomotion was automatically monitored. Measurement of motor activity was begun after at least 120 min habituation, and was continued for 140 min after the first injection in experiment 1, or 120 min in experiment 2 after the challenge administration. We measured locomotor activity, using an apparatus with an infrared sensor, as previously described (Ohmori et al. 1994). Horizontal movements of the rats were digitized and fed into a computer every 10 min.

Rating of ataxia or stereotypy

Visual observation of ataxia was conducted using the rating scale devised by Sturgeon et al. (1979). Each animal was assigned a rating score of 0–5 according to the scale every 10 min. Ratings were made by two observers, one of whom was unaware of the treatment conditions. In most cases, two observers gave the same score. Interscore reliability of two observers calculated using data from the present experiment was very high (more than 0.9). In case of inconsistency, consensus was reached by a quick review of the behavior. Definition of each score of ataxia was as follows: 0, inactive or in-place, coordinated movement; 1, unusual, awkward of jerky movements, loss of balance during rearing, occasional falling on side; 2, awkward-jerky movements, moderate rate of falling on side while rearing or moving about; 3, frequent falling on back or side while moving, partial impairment of antigravity reflexes; 4, cannot move beyond a restricted area, antigravity reflexes greatly impaired, may support weigh on haunches or abdomen; 5, unable to move except for twitching/convulsive movements, occasional rolling on side or raising head. Definition of each score of stereotypy was as follows: 0, inactive or in-place activity of a nonrepetitive nature; 1, locomotor activity, sniffing, and grooming more frequent than observed for control; 2, gagging, weaving, nondirected movements, occasional reciprocal forepaw treading (RFT), higher frequency of rearing or sniffing than in 1; 3, moderate rate and intermittent turning, backpeddling, praying, RFT, nondirected movements, sniffing, weaving, gagging; 4, rapid rate and continuous turning, backpeddling, praying, sniffing, weaving, gag-

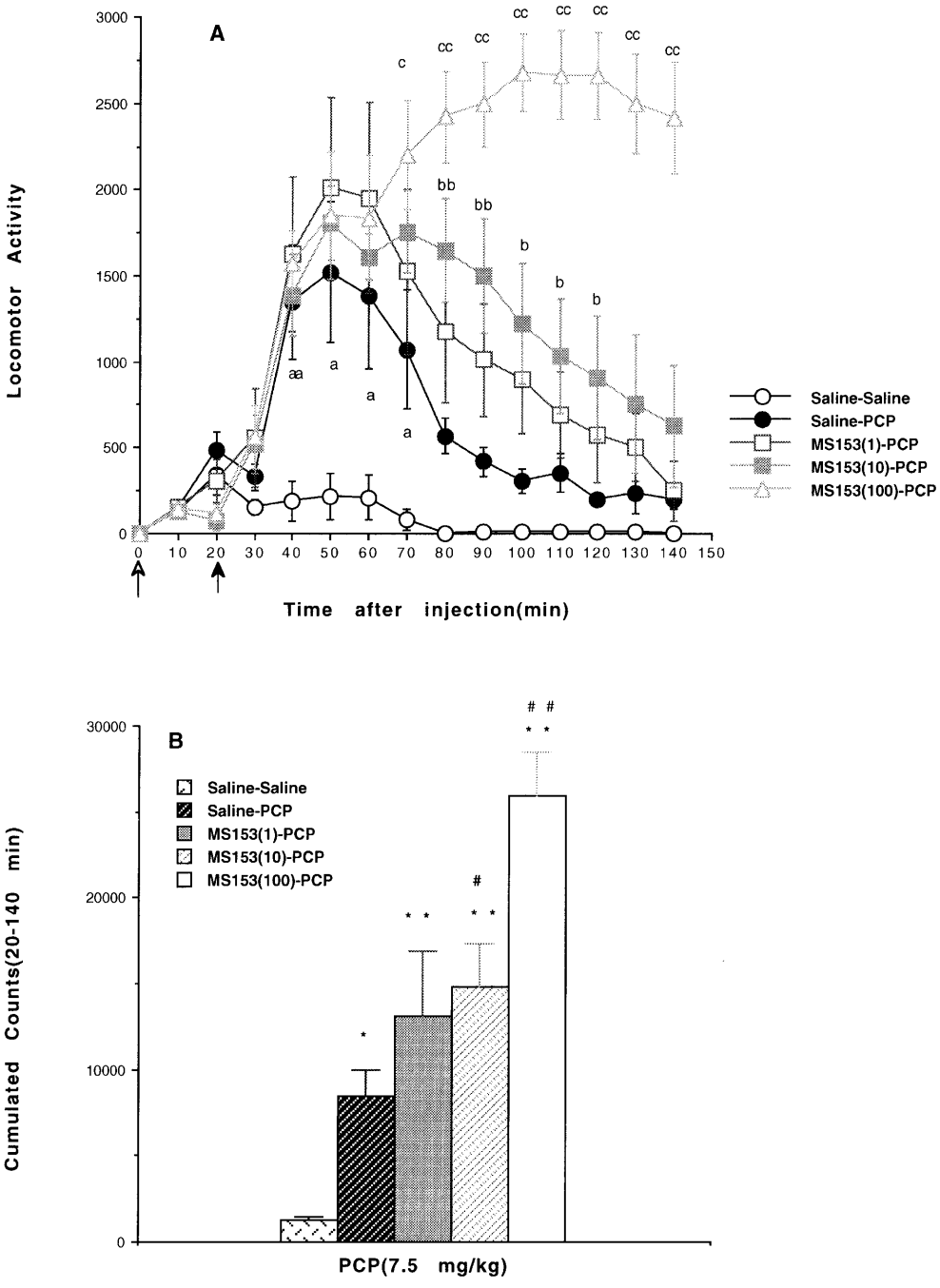

Fig. 1 Effects of MS-153 on locomotion (**A**) and cumulated counts of locomotion (**B**) induced by a single administration of PCP. Locomotion (**A**) was enhanced in MS153 (10)-PCP group and MS153 (100)-PCP group compared with Saline-PCP group. $^{a}P<0.05$, $^{aa}P<0.01$: Saline-Saline group versus Saline-PCP group, $^{b}P<0.05$, $^{bb}P<0.01$: MS153 (10)-PCP group versus Saline-PCP group, $^{c}P<0.05$, $^{cc}P<0.01$: MS153 (100)-PCP group versus Saline-PCP group. Cumulated counts of locomotion (**B**) were enhanced in MS153 (10)-PCP group and MS153 (100)-PCP group compared with Saline-PCP group. $*P<0.05$, $**P<0.01$ versus Saline-Saline group, $\#P<0.05$: Saline-PCP group versus MS153 (10)-PCP group, $\#\#P<0.01$: Saline-PCP group versus MS153 (100)-PCP group. The number of animals for each group was six to seven

ging; 5, dyskinetic extension and flexion of limbs, head and neck, gagging and weaving. If two behavioral scores were observed in an observation period, both behavioral scores were recorded and the mean score was used for statistical analysis.

Statistics

Data from locomotor activity in experiments 1 and 2 were analyzed by a repeated two-way ANOVA using the treatment-group as the between subject variable and time as the repeated-measures variable (defined as $P<0.05$). Then a post-hoc Duncan new multiple range test was used to determine which group significantly differed from the others (defined as $P<0.05$). Cumulated counts of locomotion were analyzed by a one-way ANOVA followed by the post-hoc Duncan test to determine which group differed from others (defined as $P<0.05$). Non-parametric data from ataxia or stereotypy were analyzed by Kruskal-Wallis test at each time to determine when a significant difference was observed (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 (defined as $p<0.05$). Cumulated scores of ataxia were analyzed by a one-way ANOVA followed by the post-hoc Duncan test (defined as $P<0.05$).

Results

Effect of MS-153 on locomotor activity

Figure 1 shows locomotion (A) and cumulated counts of locomotion (20–140 min) (B) induced by a single injec-

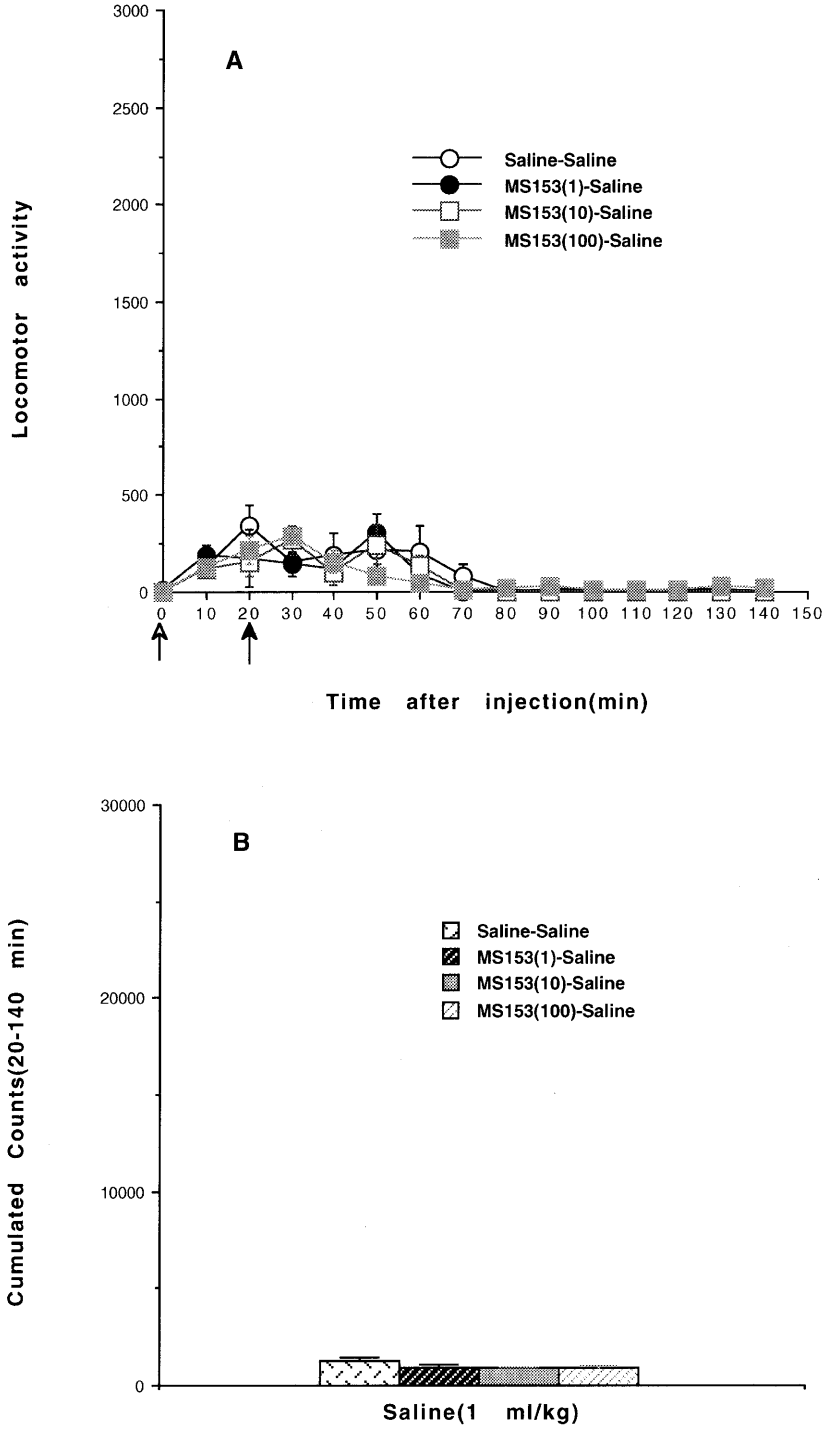

Fig. 2 Effects of MS-153 on locomotion (**A**) and cumulated counts of locomotion (**B**) after saline injection. There was no difference of locomotion (**A**) or cumulated counts of locomotion (**B**) among the four groups. The number of animals for each group was six to seven

tion of either saline or PCP (7.5 mg/kg) 20 min after the pretreatment of saline or MS-153 (1, 10, or 100 mg/kg). A repeated two-way ANOVA indicated significant effects for interaction between the group and time for locomotion [$F(48,312)=6.58$, $P<0.01$], an effect for group [$F(4,26)=14.78$, $P<0.01$], and an effect for time [$F(12,312)=18.34$, $P<0.01$]. The post-hoc Duncan test revealed that locomotion of Saline-PCP group, MS153 (1)-PCP group, MS153 (10)-PCP group, or MS153 (100)-PCP group was higher than that of Saline-Saline group at 40–70 min, 40–110 min, 40–130 min, and 40–140 min, respectively. Furthermore, the post-hoc test revealed that locomotion was enhanced in MS153 (10)-PCP group and MS153 (100)-PCP group compared with Saline-PCP group at 80–120 min and 70–140 min, respectively.

One-way ANOVA followed by the post-hoc test revealed that cumulated counts of locomotion (20–140 min) of Saline-PCP group, MS153 (1)-PCP group, MS153 (10)-PCP group, or MS153 (100)-PCP group were higher than those of Saline-Saline group. Furthermore, one-way

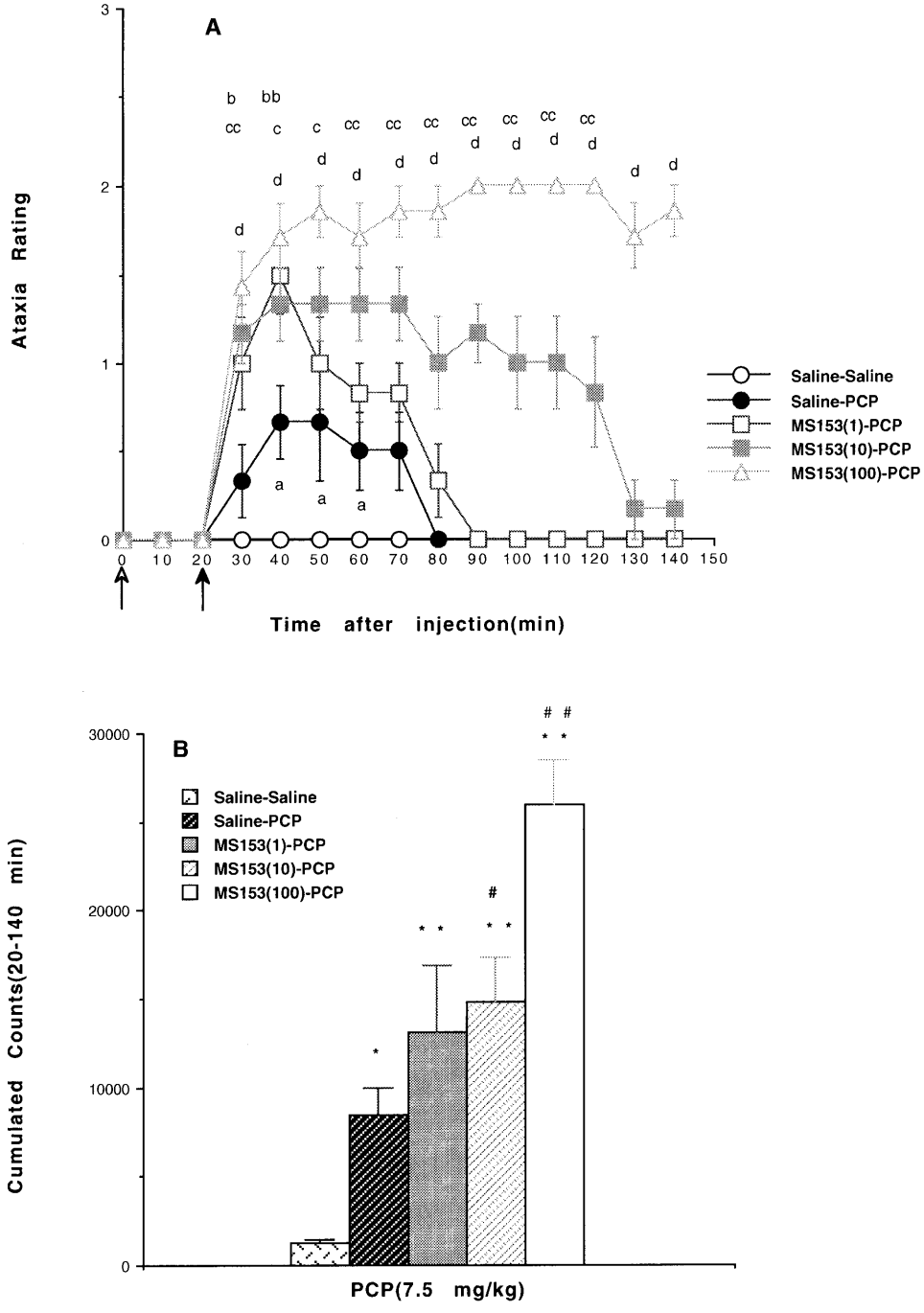

Fig. 3 Effects of MS-153 on ataxia (**A**) and cumulated ratings of ataxia (**B**) induced by a single administration of PCP. Ataxia (**A**) was enhanced in MS153 (1)-PCP group, MS153 (10)-PCP group, and MS153 (100)-PCP group compared with Saline-PCP group. $^{a}P<0.05$: Saline-Saline group versus Saline-PCP group, $^{b}P<0.05$, $^{bb}P<0.01$: Saline-PCP versus MS153 (1)-PCP group, $^{c}P<0.05$, $^{cc}P<0.01$: Saline-PCP versus MS153 (10)-PCP group, $^{d}P<0.01$: Saline-PCP versus MS153 (100)-PCP group. Cumulated ratings of ataxia (**B**) were enhanced in MS153 (10)-PCP group and MS153 (100)-PCP group compared with Saline-PCP group. $^{**}P<0.01$ versus Saline-Saline group, $\#\#P<0.01$ Saline-PCP group versus MS153 (10 or 100)-PCP group. The number of animals for each group was six to seven

ANOVA followed by the post-hoc test revealed that cumulated counts of locomotion (20–140 min) were enhanced in MS153 (10)-PCP group and MS153 (100)-PCP group compared with Saline-PCP group.

Figure 2 shows locomotion (A) and cumulated counts of locomotion (20–140 min) (B) induced by a single injection of saline 20 min after the pretreatment of saline or MS-153 (1, 10, or 100 mg/kg). There was no difference of locomotion or cumulated counts among the four groups, i.e. Saline-Saline, MS153 (1)-Saline, MS153 (10)-Saline, and MS153 (100)-Saline groups.

Effect of MS-153 on ataxia

Figure 3 shows ataxia (A) and cumulated ratings of ataxia (20–140 min) (B) induced by a single injection of either saline or PCP (7.5 mg/kg) 20 min after the pretreatment of saline or MS-153 (1, 10, or 100 mg/kg). Kruskal-Wallis tests revealed a significant difference among the five groups from 20 to 140 min. Mann-Whitney *U*-test revealed that ataxia of Saline-PCP group, MS153 (1)-PCP, MS153 (10)-PCP, or MS153 (100)-PCP group was higher than that of Saline-Saline group at 40, 50, 70 min, 30–70 min, 30–120 min, and 30–140 min,

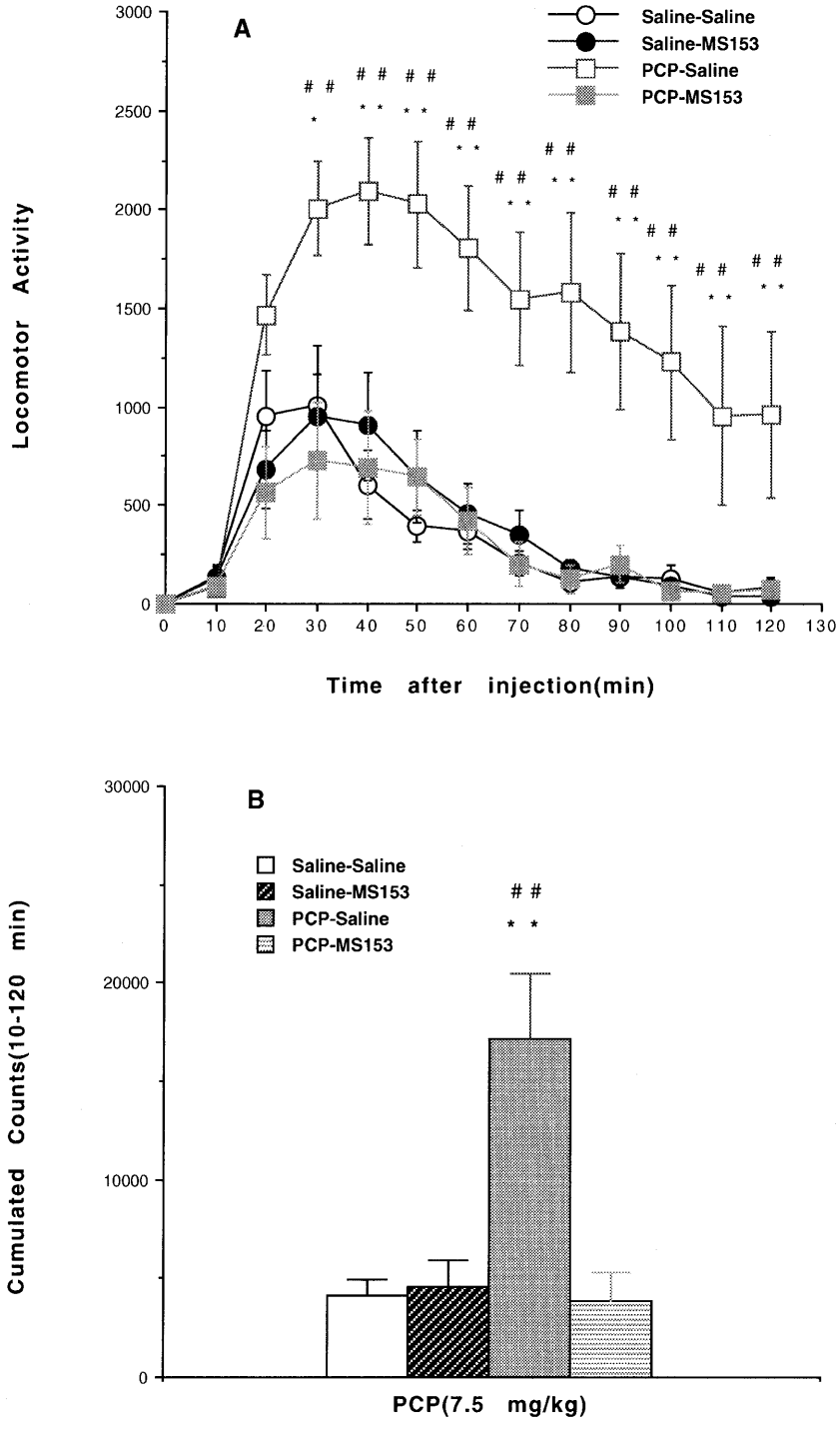

Fig. 4 Effects of MS-153 on the development of behavioral sensitization to locomotion-inducing effect of PCP. Locomotion (**A**) and cumulated counts of locomotion (**B**) of PCP-Saline group were higher than those of the other three groups, i.e. Saline-Saline group, Saline-MS153 group, and PCP-MS153 group. **P*<0.05, ***P*<0.01 Saline-Saline group versus PCP-Saline group, ##*P*<0.01 PCP-Saline group versus PCP-MS153 group. The number of animals for each group was six to eight

respectively. Mann-Whitney *U*-test revealed that ataxia was enhanced in MS-153 (1)-PCP group, MS153 (10)-PCP group, or MS153 (100)-PCP group compared with Saline-PCP group at 30, 40 min, 30–120 min, and 30–140 min, respectively.

Furthermore, one-way ANOVA followed by the post-hoc Duncan test revealed that cumulated ratings of ataxia (20–140 min) of Saline-PCP group, MS153 (1)-PCP group, MS153 (10)-PCP group, or MS153 (100)-PCP group were higher than those of Saline-Saline group. One-way ANOVA followed by the post-hoc test revealed that cumulated ratings of ataxia were enhanced in MS153 (10)-PCP group and MS153 (100)-PCP group compared with Saline-PCP group.

Effect of MS-153 on stereotypy

One-way ANOVA followed by the post-hoc Duncan test revealed that cumulated rating scores of stereotypy after PCP injection were 5.12±1.30 (Saline-Saline group), 22.67±2.03 (Saline-PCP group), 26.83± 3.85 (MS153

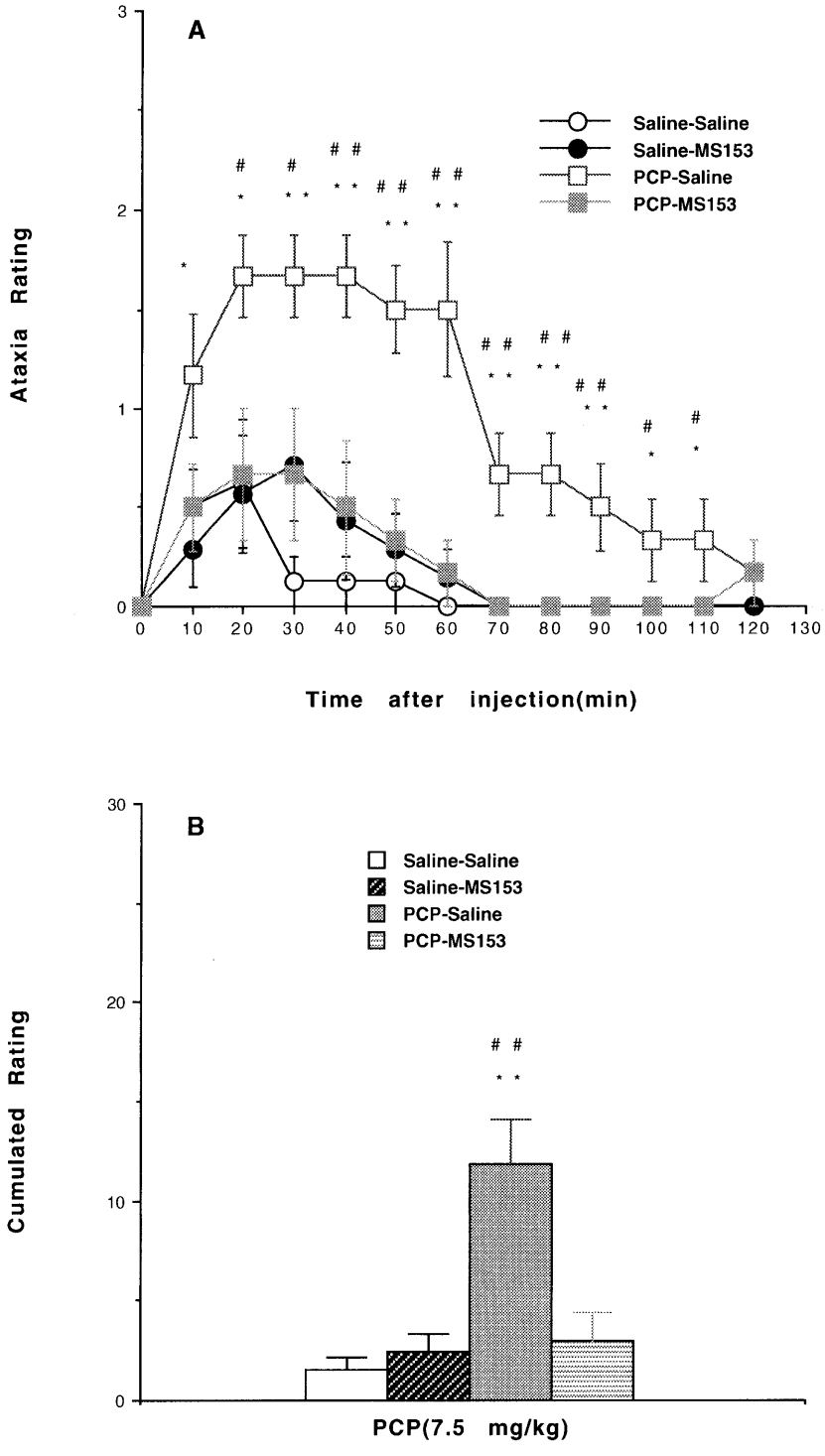

Fig. 5 Effects of MS-153 on the development of behavioral sensitization to ataxia-inducing effect of PCP. Ataxia (**A**) and cumulated rating scores of ataxia (**B**) of PCP-Saline group were higher than those of other three groups, i.e. Saline-Saline group, Saline-MS153 group, and PCP-MS153 group. **P*<0.05, ***P*<0.01 Saline-Saline group versus PCP-Saline group, #*P*<0.05, ##*P*<0.01 PCP-Saline group versus PCP-MS153 group. The number of animals for each group was six to eight

(1)-PCP group), 35.33±3.04## (MS153 (10)-PCP group), and 48.29± 2.04## (MS153 (100)-PCP group), ##*P*<0.01 versus Saline-PCP group).

Effects of MS-153 on behavioral sensitization

Figure 4 shows locomotion (A) and cumulated counts of locomotion (10–120 min) (B) induced by challenge with PCP (7.5 mg/kg) 4 days after the repeated PCP-treatment (20 mg/kg, once in every day, for 5 days). A repeated two-way ANOVA indicated significant effects for interaction between the group and time in locomotion induced by PCP [$F(33,253)=2.65$, $P<0.01$], an effect for group [$F(3,23)=11.91$, $P<0.01$], and an effect for time [$F(11,253)=25.33$, $P<0.01$]. The post-hoc Duncan new multiple range test revealed that locomotion of PCP-Saline group was higher than Saline-Saline group, PCP-MS153 group, and Saline-MS153 group at 30–120 min. One-way ANOVA followed by the post-hoc test revealed

that cumulated counts of PCP-Saline group were higher than Saline-Saline group, PCP-MS153 group, and Saline-MS153 group.

Figure 5 shows ataxia (A) and cumulated ratings of ataxia (10–120 min) (B) induced by challenge with PCP (7.5 mg/kg) 4 days after repeated PCP treatment (20 mg/kg, once in every day, for 5 days). Kruskal-Wallis tests revealed that a significant difference among the four groups from 10 to 110 min. Mann-Whitney *U*-test revealed that ataxia of PCP-Saline group was higher than Saline-Saline group at 10–110 min, was higher than PCP-MS153 group at 20–110 min, and was higher than Saline-MS153 group at 10–120 min. Furthermore, one-way ANOVA followed by the post-hoc Duncan test revealed that cumulated ratings of ataxia of PCP-Saline group were higher than those of Saline-Saline group, PCP-MS153 group, and Saline-MS153 group.

One-way ANOVA followed by the post-hoc Duncan test revealed that cumulated rating scores of stereotypy after PCP administration as a challenge were 17.00±1.65 (Saline-Saline group), 18.43±2.09 (Saline-MS153 group), 48.17± 3.60$^{\#\#}$ (PCP-saline group), and 19.50±3.48 (PCP-MS153 group), ##P<0.01 versus other three groups.

Discussion

Effect of MS-153 on acute effect of PCP

Pretreatment with MS-153 (10 or 100 mg/kg) enhanced acute PCP (7.5 mg/kg)-induced both locomotion and ataxia, suggesting that the MS-153-induced exacerbation of locomotion is not attributed to the attenuation of PCP-induced ataxia. Furthermore, in a preliminary experiment, MS-153 did not induce the attenuation of PCP-induced stereotypy, which could enhance the PCP-induced locomotion, rather enhanced PCP-induced stereotypy. Since PCP primarily blocks *N*-methyl-D-aspartate (NMDA) receptors non-competitively (Johnson and Jones 1990), it is possible that PCP blocks NMDA receptors on GABAergic interneurons to disinhibit glutamatergic pyramidal neurons from GABAergic tonic inhibition in the prefrontal cortex (PFC), inducing an increase in glutamate release in the PFC (Adams and Moghaddam 1998; Moghaddam and Adams 1998). As a result, glutamatergic output originating from the PFC, and projecting to the ventral tegmental area (VTA) or nucleus accumbens (NAC), may be activated to enhance dopaminergic neural transmission, which increases locomotion (McCullough and Salamone 1992; Steinpreis and Salamone 1992; Adams and Moghaddam 1998; Jentsch et al. 1998; Moghaddam and Adams 1998). MS-153 enhanced the acute PCP effect. We could explain these findings by suggesting that MS-153 attenuates the glutamatergic neural transmission by reducing extracellular level of glutamate, which enhances the PCP-induced reduction of glutamatergic transmisson via blocking NMDA receptors. As a result, MS-153 may enhance PCP-induced locomotion.

Effect of MS-153 on development of sensitization to PCP

On the other hand, in the present study, repeated PCP administration led to behavioral sensitization to both locomotion- and ataxia-inducing effects of PCP when tested 4 days after withdrawal from the last PCP treatment. Since behavioral sensitization developed not only to PCP-induced locomotion but also ataxia, it is hard to explain the development of sensitization to locomotion in terms of the attenuation of ataxia. Furthermore, MS-153 (10 mg/kg) given 60 and 120 min after every PCP treatment, blocked the development of behavioral sensitization to PCP-induced both forms of behavior. In addition, MS-153 did not enhance PCP-induced stereotypy, which could attenuate the augmentation of PCP-induced locomotion. Rather, in a preliminary experiment, MS-153 inhibited the development of stereotypy sensitization to PCP. These results suggest an important role of glutamatergic neural transmission in the development of behavioral sensitization to both locomotion- and ataxia-inducing effects of PCP.

Regimen of dosing of PCP

According to the regimen of Johnson et al. (1998), we employed a protocol in which PCP (20 mg/kg)-injection was repeated once in every day for 5 days, and after 4 days withdrawal, PCP (7.5 mg/kg) was administered as a challenge. Almost all the experiments on behavioral sensitization to PCP did not employ sufficient withdrawal of more than 24 h (Smith et al. 1981; Greenberg and Segal 1986; Nabeshima et al. 1987; Xu and Domino 1994). However, since the present work employed 4 days withdrawal, we can rule out the possibility of an acute action of the drug. In addition, Johnson et al. (1998) observed that the behavioral sensitization continued for at least 8 days. Once the behavioral sensitization to PCP has developed, it may continue for a long time, an effect attributed to neuronal plastic changes. We adopted 7.5 mg/kg PCP as an acute or a challenge injection dose, since this dose is reported to increase effectively locomotor activity with minimal induction of ataxia (Sturgeon et al. 1979). Furthermore, we employed 20 mg/kg PCP as a repeated treatment dose, since this treatment is reported to produce neuronal damage in the corticolimbic regions (Johnson et al. 1998), which areas are also structurally and/or developmentally damaged in schizophrenia. In addition, in our preliminary experiment, treatment with lower dose (PCP 7.5 mg/kg, once in every day, for 7 days) did not produce behavioral sensitization to PCP (7.5 mg/kg).

Dissociation between acute and repeated co-administration of MS-153 and PCP

An acute treatment of MS-153 30 min prior PCP injection enhanced abnormal behaviors induced by a single injection of PCP (7.5 mg/kg). Contrarily, repeated treatment of MS-153, 60 and 120 min after PCP injection blocked the development of behavioral sensitization to PCP. Interestingly, there is the discrepancy between the effects of acute and repeated administration of MS-153 on PCP-induced behavioral changes. To explain this dissociation, we should focus on the time course of dosing treatment.

Single administrations of non-competitive NMDA receptor antagonists such as PCP (Adams and Moghaddam 1998) and ketamine (Moghaddam et al. 1997) have been reported to increase extracellular glutamate levels in the PFC or NAC, which continue to rise for more than 60 min. This continuous increase in extracellular concentration of glutamate in the PFC or NAC may induce some neural plastic changes via excitatory amino acid receptors, and then induce some irreversible changes of dopaminergic transmission, which interacts with glutamatergic transmission (Nishijima et al. 1996; Takahata and Moghaddam 1998), leading to the development of behavioral sensitization to PCP. In the cerebral ischaemic model, occlusion of middle cerebral artery (MCA) induces continuous increases in glutamate levels for at least 180 min, which was blocked by 24-h IV infusion, but not IV bolus injection of MS-153 after MCA occlusion (Umemura et al. 1996). This blocking reduced the size of ischaemic cerebral infarction (Umemura et al. 1996; Kawazura et al. 1997). In the case of the PCP model, since MS-153 has a very short half-life in serum (around 70 min) when given as a single injection (Umemura et al. 1996; Kawazura et al. 1997), the present study employed a single injection of MS-153 30 min prior to PCP treatment to reduce basal level of glutamate and employed two injections of MS-153 60 min and 120 min after PCP treatment to block effectively PCP-induced increase in glutamate level. By these treatments, MS-153 may reduce the basal level of glutamate to enhance the acute effect of PCP or, contrarily, may inhibit PCP-induced increase in glutamate level to block the development of behavioral sensitization to PCP.

Repeated stimulation of excitatory amino acid receptors such as NMDA receptor (Karler et al. 1989; Ohmori et al. 1994), AMPA receptor (Karler et al. 1991; Li et al. 1997), and metabotropic glutamate receptor (mGluR) (Kim and Vezina 1998) as well as the production of nitric oxide via NMDA receptor stimulation (Abekawa et al. 1995; Itzhak et al. 1997) play essential roles in the development of behavioral sensitization to amphetamines (Wolf 1998). Since the primary pharmacological action of PCP is the blockade of the NMDA receptor (Johnson and Jones 1990; Javitt and Zukin 1991), the stimulation of excitatory amino acid receptors other than NMDA receptor, such as AMPA receptor or mGlu R may be necessary for developing behavioral sensitization to PCP.

Effects of MS-153 on some aspects related to PCP sensitization

Similar to the case with amphetamines (Stewart and Druhan 1993), behavioral sensitization to PCP develops context-independently (Xu and Domino 1993). From the data of the present study, it is unlikely that behavioral sensitization was blocked by MS-153 through interference with the development of conditioning of the effect of PCP to a specific environment where the drug was given. In the present study, the rats were repeatedly treated with PCP and/or MS-153 in home cages, and re-administered with PCP in activity chambers. Therefore, it is assumed that conditioning variables were minimized in the present experiment.

In summary, repeated administration of PCP (20 mg/kg×5) led to behavioral sensitization to both locomotion- and ataxia-inducing effects of PCP (7.5 mg/kg). Co-administration of PCP with MS-153, which has the ability to enhance glutamate uptake or to inhibit glutamate release blocked the development of behavioral sensitization to PCP-induced both locomotion and ataxia, suggesting an important role of glutamatergic neural transmission in PCP sensitization. Since the present study showed only data for behavioral changes, the precise mechanism by which MS-153 blocked sensitization is unknown. Therefore, additional experiments should be performed to determine possible changes in dopamine or glutamate release in the PFC and/or NAC.

Acknowledgements This work was supported in part by Grant-in-Aid No 09670968 and No 11670925 for Scientific Research from the Ministry of Education, Science and Culture, Japan.

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