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$GABA_B$ receptor agonist baclofen improves methamphetamine-induced cognitive deficit in mice

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ABSTRACT

In this study, we investigated the effects of $GABA_A$ and $GABA_B$ receptor agonists on the methamphetamine-induced impairment of recognition memory in mice. Repeated treatment with methamphetamine at a dose of 1 mg/kg for 7 days induced an impairment of recognition memory. Baclofen, a $GABA_B$ receptor agonist, ameliorated the repeated methamphetamine-induced cognitive impairment, although gaboxadol, a $GABA_A$ receptor agonist, had no significant effect. $GABA_B$ receptors may constitute a putative new target in treating cognitive deficits in patients suffering from schizophrenia, as well as methamphetamine psychosis.

1. Introduction

Methamphetamine is a highly addictive drug of abuse, and addiction to methamphetamine has increased to epidemic proportions worldwide (Cretzmeyer et al., 2003; Rawson et al., 2002). Chronic use of methamphetamine causes psychiatric symptoms, such as hallucination and delusions, and long-term cognitive deficits (Simon et al., 2000; Kalechstein et al., 2003; Nordahl et al., 2003; Srisurapanont et al., 2003), which are indistinguishable from paranoid schizophrenia (Yui et al., 2002; Srisurapanont et al., 2003). In a previous study, we demonstrated that repeated methamphetamine treatment caused an enduring impairment of recognition memory in a novel object recognition test in mice, and that methamphetamine-induced cognitive impairment was reversed by an atypical antipsychotic, clozapine, but not haloperidol (Kamei et al., 2006). Furthermore, the same treatment in rats resulted in a significant impairment of spatial working memory, which was ameliorated by clozapine but not haloperidol (Nagai et al., 2007). Thus, methamphetamine-induced memory impairment in rodents may be a useful model for cognitive deficits in methamphetamine abusers and schizophrenic patients.

The GABA receptor system is known to play a significant role in modulating the dopamine system (Tepper and Lee, 2007). Several studies have demonstrated that GABA receptor agonists can inhibit the effects of drugs of abuse. For example, baclofen has been shown to attenuate amphetamine-induced increase in dopamine levels in the nucleus accumbens (Brebner et al., 2005), and $GABA_A$ receptors on ventral tegmental area dopamine neurons play a significant role in attenuating the effects of drugs of abuse in a similar manner to that of $GABA_B$ receptors (Westerink et al., 1996). Although many studies have examined the effects of GABA receptor agonists on hyperdopaminergic conditions induced by psychostimulant drugs, few studies have investigated the effects of GABA receptors on cognitive deficits induced by drugs of abuse.

Recent studies suggest that alterations of GABA systems are related to the pathophysiology of schizophrenia (Lewis, 2000; Benes and Berretta, 2001). Moreover, it is suggested that impairment in GABA-mediated inhibition in the prefrontal cortex may provide a mechanism of disturbance in cognitive processes, such as working memory, in individuals with schizophrenia (Lewis, 2000; Benes and Berretta, 2001). Cognitive dysfunction is considered a core feature of schizophrenia (Elvevåg and Goldberg, 2000), and the degree of cognitive deficit may be the best predictor of long-term functional outcome for individuals with schizophrenia (Green, 1996). Despite the clinical

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importance of cognitive dysfunction in schizophrenia, there are no appropriate drug therapies.

In this study, to develop novel pharmacotherapy for cognitive deficits in schizophrenia patients and methamphetamine abusers, we examined the effects of $GABA_A$ and $GABA_B$ receptor agonists on methamphetamine-induced impairment of recognition memory in mice.

2. Materials and methods

Male ICR mice (7–8 weeks old) were obtained from Japan SLC Inc. (Shizuoka, Japan). The animals were housed in plastic cages and kept in a regulated environment (23±1 °C, 50±5% humidity) with a 12 h light–dark cycle (lights on at 9:00 am). Food and tap water were available ad libitum. All animal care and use was in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and was approved by the Institutional Animal Care and Use Committee of Kanazawa University.

Methamphetamine hydrochloride (Dainippon Sumitomo Pharma Co. Ltd., Osaka, Japan), *R*(+)-baclofen hydrochloride (Sigma-Aldrich Co., St Louis, MO) and gaboxadol hydrochloride (Sigma-Aldrich) were dissolved in saline. All drugs were administered in a volume of 0.1 ml/10 g body weight. Mice were given methamphetamine (1 mg/kg, s.c.) daily once for 7 days. One day after the last treatment of methamphetamine, novel object recognition test commenced as described below.

Novel object recognition test was carried out as described previously (Kamei et al., 2006; Mizoguchi et al., 2008). The experimental apparatus consisted of a Plexiglas box (30×30×35 cm high), with a sawdust-covered floor. The apparatus was located in a sound-attenuated room and was illuminated with a 20 W bulb.

The novel object recognition test procedure consisted of three sessions: habituation, training, and retention. Each mouse was individually habituated to the box, with 10 min of exploration in the absence of objects for 3 consecutive days (habituation session, days 1–3). During the training session, two novel objects were symmetrically fixed to the floor of the box, 8 cm from the walls, and each animal was allowed to explore the box for 10 min (day 4). The objects were a golf ball, a wooden column and a wall socket, which were different in shape and color but similar in size. The animals were considered to be exploring the object when the head of the animal was facing the object or the animal was touching or sniffing the object. The time spent exploring each object was recorded. After training, mice were immediately returned to their home cages. During the retention sessions, the animals were placed back into the same box 24 h (day 5) after the training session, in which one of the familiar objects used during training was replaced by a novel object. The animals were then allowed to explore freely for 5 min and the time spent exploring each object was recorded. Throughout the experiments, the objects were used in a counterbalanced manner in terms of their physical complexity and emotional neutrality. A preference index in the retention session, the ratio of the amount of time spent exploring the novel object over the total time spent exploring both objects, was used to measure cognitive function. In the training session, the preference index was calculated as a ratio of the time spent exploring the object that was replaced by the novel object in the retention session, over the total exploring time.

Baclofen (1 and 2 mg/kg, s.c.) and gaboxadol (1 and 3 mg/kg, s.c.) were administered once 15 min before the training session in novel object recognition test (day 4). No drugs were given during the habituation (day 1–3) and the retention sessions (day 5) in the novel object recognition test.

To investigate effect of baclofen on motor function, locomotor activity was measured. Mice were given saline or methamphetamine at a dose of 1 mg/kg for 7 days. Mice were placed in home cage for 15 min following injection of saline or baclofen (2 mg/kg, s.c.) after the 3 day-withdrawal of repeated methamphetamine treatment, and then locomotor activity was measured for 10 min in a standard transparent rectangular rodent cage (25×30×18 high cm) using an infrared sensor (NS-AS01; Brainscience, Osaka, Japan) placed over the cage (Kamei et al., 2006; Mizoguchi et al., 2008).

All data were expressed as the mean±S.E.M.. Statistical analysis was carried out by one-way or two-way ANOVA, followed by Student–Newman–Keuls test for multigroup comparisons. *P* values less than 0.05 were taken to indicate significant differences.

3. Results

Repeated methamphetamine treatment (1 mg/kg, s.c.) for 7 days resulted in a significant reduction of the preference index in the retention session but not training session as compared with saline-treated control (Figs. 1A and 2A) although it had no effect on total exploratory time (Figs. 1B and 2B). The $GABA_A$ receptor agonist, gaboxadol, at doses of 1 mg/kg, failed to ameliorate the methamphetamine-induced reduction of exploratory preference to the novel object in the retention session of novel object recognition test (Fig. 1A). Although there was no difference between gaboxadol 1 mg/kg and 3 mg/kg in methamphetamine-treated animal ($P=0.10$), there was a tendency of recovery in gaboxadol-treated group at 3 mg/kg ($P=0.06$). Thus, we

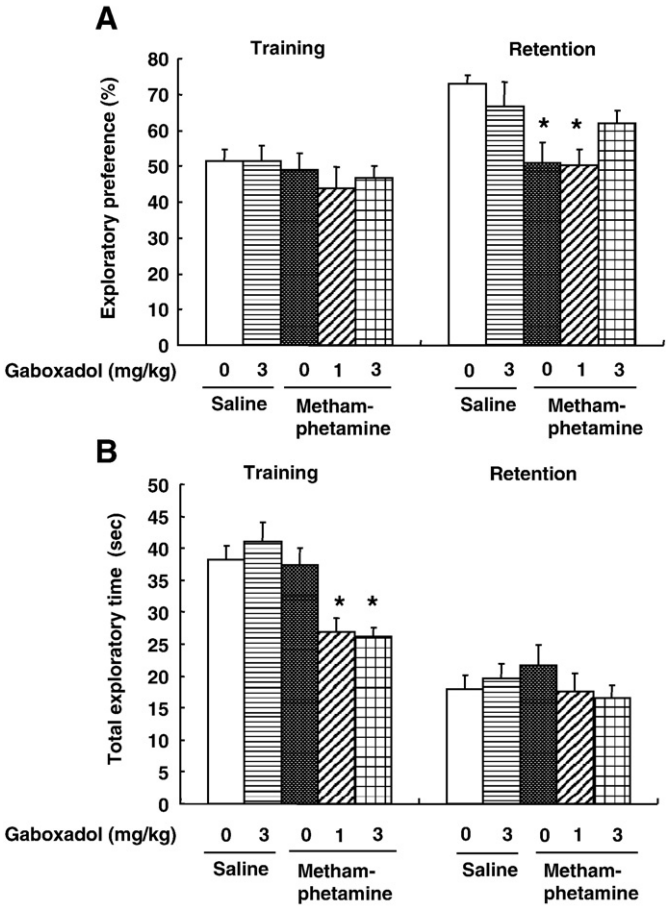

Fig. 1. Effect of gaboxadol on methamphetamine-induced impairment of recognition memory in mice. After the cessation of repeated methamphetamine (1 mg/kg, s.c.) treatment for 7 days, mice were subjected to the novel-object recognition test. Gaboxadol (1 and 3 mg/kg, s.c.), or saline was administered 15 min before the training session. (A) Exploratory preference. (B) Total exploration time. Values indicate the mean±S.E.M. (saline/saline, $n=13$; saline/Gaboxadol 3 mg/kg, $n=8$; methamphetamine/saline, $n=12$; methamphetamine/Gaboxadol 1 mg/kg, $n=7$; methamphetamine/Gaboxadol 3 mg/kg, $n=14$). ANOVA: (A, training) $F(4,49)=0.488$, $P=0.7448$; (A, retention) $F(4,49)=4.6$, $P<0.01$; (B, training) $F(4,49)=7.876$, $P<0.01$; (B, retention) $F(4,49)=0.637$, $P=0.6389$. $^*P<0.05$ compared with the saline/saline-treated group (Student–Newman–Keuls test).

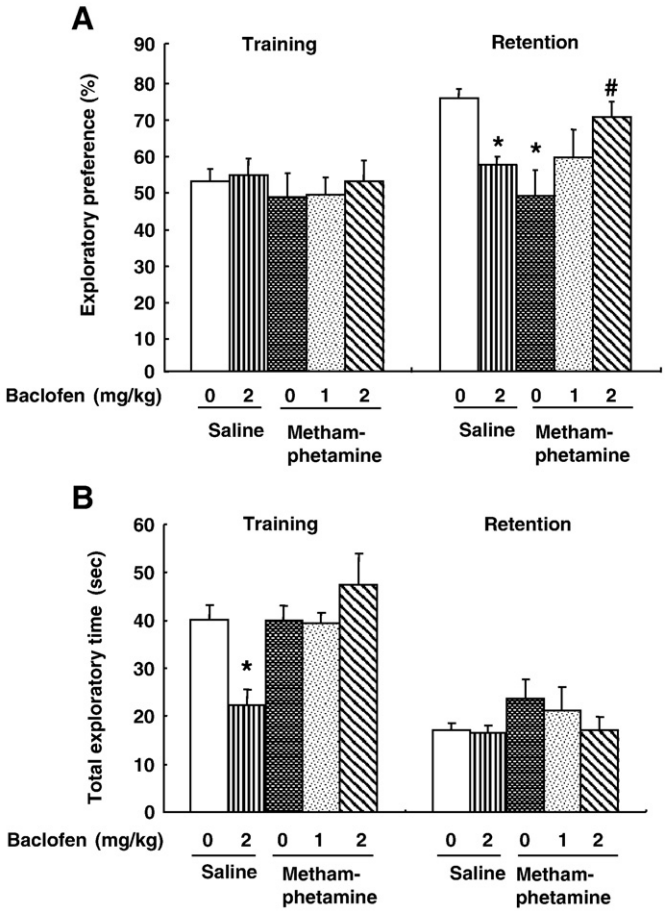

Fig. 2. Effect of baclofen on methamphetamine-induced impairment of recognition memory in mice. After the cessation of repeated methamphetamine (1 mg/kg) treatment for 7 days, mice were subjected to the novel-object recognition test. Baclofen (1 and 2 mg/kg, s.c.) or saline was administered 15 min before the training session. (A) Exploratory preference. (B) Total exploration time. Values indicate the mean ± S.E.M. (saline/saline, $n=12$; saline/Baclofen 2 mg/kg, $n=13$; methamphetamine/saline, $n=8$; methamphetamine/Baclofen 1 mg/kg, $n=8$; methamphetamine/Baclofen 2 mg/kg, $n=10$). ANOVA: (A, training) $F(4,46)=0.242$, $P=0.9133$; (A, retention) $F(4,46)=5.56$, $P<0.01$; (B, training) $F(4,46)=7.752$, $P<0.01$; (B, retention) $F(4,46)=1.2$, $P=0.3238$. $^*P<0.05$ compared with the saline/saline-treated group. $\#P<0.05$ compared with the methamphetamine/saline-treated group (Student–Newman–Keuls test).

also examined the effect of gaboxadol at 10 mg/kg. However, because high-dose gaboxadol at 10 mg/kg markedly reduced the exploratory activity of mice in the training session, they were not subjected to novel object recognition test (data not shown). Gaboxadol at 3 mg/kg had no effect on the exploratory preference (Fig. 1A) and total exploratory time (Fig. 1B) in both training and retention sessions in saline-treated control mice.

Next, we examined the effect of baclofen on methamphetamine-induced cognitive impairment. The $GABA_B$ receptor agonist dose-dependently improved the reduction of exploratory preference to the novel object in methamphetamine-treated mice (Fig. 2A). Baclofen at 2 mg/kg significantly ameliorated methamphetamine-induced cognitive impairment (Fig. 2A). Baclofen had no effect on the level of exploratory preference for the novel object in the training session or the total exploration time in both the training and retention sessions in methamphetamine-treated mice. Treatment with baclofen at 2 mg/kg in saline-treated control group resulted in a significant decrease in total exploratory time to novel objects in the training session (Fig. 2B), leading to a significant impairment of novel object recognition in the retention session (Fig. 2A). This is probably due to an insufficient exploratory behaviors in the training session, which could result in a poor discrimination of a novel object.

4. Discussion

We have previously demonstrated that repeated methamphetamine treatment in mice induces enduring recognition memory impairment, which is associated with dysfunction of the dopamine D_1 receptor-ERK1/2 pathway in the prefrontal cortex. Clozapine, but not haloperidol, completely restored the cognitive impairment induced by methamphetamine treatment when repeatedly administered for 7 days after withdrawal from methamphetamine, although acute treatment with these antipsychotics had no effect (Kamei et al., 2006). The data are consistent with clinical evidence that clozapine is superior to typical neuroleptics in improving cognitive deficits in schizophrenic patients (Lee et al., 1999). Thus, we propose that methamphetamine-induced cognitive impairment in mice may be a useful model for cognitive deficits in methamphetamine abusers and schizophrenic patients. In this study, we found that acute treatment with baclofen improved methamphetamine-induced cognitive deficit without affecting motor function, whereas repeated treatment was necessary for the effect of clozapine. These results suggest that $GABA_B$ receptor agonists may be more useful for the treatment of cognitive deficit in schizophrenia patients and methamphetamine abusers than clozapine and other antipsychotic drugs. In contrast, gaboxadol, a $GABA_A$ receptor agonist, had no effect on methamphetamine-induced cognitive deficits. However, gaboxadol is known to preferentially activate the $GABA_A$ receptor subtype containing the delta subunit, which mediated tonic inhibition. Therefore, gaboxadol may not be an ideal agonist for a global activation of $GABA_A$ receptors. Further studies are required to test this assumption.

Additionally, we think that the ameliorating effect of baclofen is not related to the effect on motor function. In fact, we examined the effect of baclofen at a dose of 2 mg/kg on locomotor activity of mice that had been treated with saline or methamphetamine (1 mg/kg) for 7 days. Baclofen had no effect on behavioral locomotion of repeated methamphetamine-treated group (saline/saline group ($n=7$), 399 ± 39.9 counts/10 min; saline/baclofen group ($n=7$), 343.7 ± 51.4 counts/10 min; methamphetamine/saline group ($n=7$), 429.1 ± 21.4 counts/10 min; methamphetamine/baclofen group ($n=7$), 346.3 ± 41.6 counts/10 min; $F(3,24)=1.08$, $P=0.37$). In Figs. 1 and 2, we showed the total exploratory time, which means locomotor activity in training and retention phase, respectively. Baclofen had no effect on the level of exploratory preference for the novel object in the training session or the total exploration time in both the training and retention sessions in methamphetamine-treated mice. These results suggest that baclofen has no effect on motor function in methamphetamine-treated mice. There was an apparent difference in sensitivity to baclofen between saline-treated control and methamphetamine-treated group: Baclofen at 2 mg/kg significantly reduced the total exploratory time in the training session in control mice, while the drug had no effect in the methamphetamine-treated mice. Regarding to this phenomenon, it is reported that repeated cocaine treatment decreases baclofen-stimulated [^{35}S]GTPγS binding to G protein in the nucleus accumbens, indicating desensitization of $GABA_B$ receptors (Xi et al., 2003). Thus, it is possibly that repeated methamphetamine treatment causes desensitization of $GABA_B$ receptor as does cocaine treatment.

There are some studies suggesting that $GABA_B$ receptors play an important role in regulating dopamine neurons, while the role of $GABA_A$ receptors has been unclear. For example, previous studies showed that baclofen reduced the reinforcing effects of many substances of abuse, such as cocaine, nicotine, heroin, and alcohol (Cousins et al., 2002), possibly through $GABA_B$-mediated modulation of mesolimbic dopamine transmission (Bartholini, 1985). In fact, baclofen is known to stabilize the firing pattern of dopamine neurons (Erhardt et al., 2002). It was demonstrated that chronic coadministration of baclofen and amphetamine blocked the development of sensitization to the locomotor stimulation effect of amphetamine

(Bartoletti et al., 2005), and acute treatment with baclofen inhibited the expression of amphetamine-induced locomotor sensitization (Bartoletti et al., 2004). Moreover, a recent study showed that acute treatment with baclofen ameliorated ethanol-induced memory deficit in mice (Escher and Mittleman, 2004). Moreover, we have recently demonstrated that baclofen, but not gaboxadol, ameliorates methamphetamine- and MK-801-induced impairment of prepulse inhibition of the acoustic startle reflex in mice (Arai et al., 2008). These results support our findings that baclofen ameliorates repeated methamphetamine treatment-induced cognitive deficits. Taken together, the ameliorating effect of baclofen on cognitive impairment in methamphetamine-treated mice may be attributable to its effects on $GABA_B$ receptors in midbrain dopamine neurons.

In conclusion, we demonstrated that baclofen acutely ameliorated the cognitive deficit in repeated methamphetamine-treated mice, an animal model for cognitive deficits in methamphetamine abuse and schizophrenia. Our results suggest that baclofen may be superior to clozapine and other antipsychotic drugs that mainly affect dopamine D_2 and 5-HT_2 receptors. $GABA_B$ receptors may constitute a putative new target for treating cognitive deficits in patients suffering from schizophrenia, as well as methamphetamine psychosis. Further studies are necessary to clarify the molecular mechanisms of the action of baclofen.

Conflict of interest

There are no conflicts of interest in this study.

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