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The Role of Benzodiazepine Receptors in the Acquisition and Expression of Behavioral Sensitization to Methamphetamine

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ITO, K., T. OHMORI, T. ABEKAWA AND T. KOYAMA. *The role of benzodiazepine receptors on the acquisition and expression of behavioral sensitization to methamphetamine.* PHARMACOL BIOCHEM BEHAV **65**(4) 705–710, 2000.—The GABA–benzodiazepine neurotransmission has been reported to be implicated in various forms of plasticity such as kindling and learning. In a previous study, we have shown that clonazepam (CZP), a GABA–benzodiazepine agonist, prevents the acquisition of behavioral sensitization to methamphetamine (MA). The present study was conducted to extend this finding by examining the effect of flumazenil (Flu), a GABA–benzodiazepine antagonist on the prevention by CZP. Rats (male Wistar–King rats) treated with MA (1 mg/kg, SC) for 10 days showed significantly enhanced motor activity compared to those treated with saline when tested with MA (1 mg/kg) after a 7–8-day withdrawal, indicating the acquisition of behavioral sensitization. Representing the previous finding, pretreatment with CZP (0.5 mg/kg) prior to MA administration prevented the acquisition of the phenomenon. Pretreatment with Flu (10 mg/kg) prior to MA administration has no influence on the acquisition of sensitization. However, pretreatment with Flu prior to CZP administration reversed the inhibitory effect of CZP. CZP showed no effect on the expression of sensitization in the sensitized rats when given prior to the MA readminisiration. These results strengthen the suggestion that stimulation of GABA–benzodiazepine receptors plays a role in the acquisition but not in the expression of behavioral sensitization to MA. © 2000 Elsevier Science Inc.

Methamphetamine Sensitization Clonazepam Flumazenil Benzodiazepine GABA

REPEATED administration of amphetamine or methamphetamine (MA) results in an augmentation of its locomotor activating effects, a phenomenon known as behavioral sensitization. In humans, the chronic use of the drug elicits a progressive augmentation in paranoid symptoms that closely resemble schizophrenia (15,32). 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 (17,26,36,39), protein synthesis inhibitors (18,33), and scopolamine, an antagonist of the muscarinic cholinergic receptor (27,28). NMDA antagonists have been shown to block or retard the development of kindling, learning, as well as LTP (7,21,24). Protein synthesis inhibitors have also been reported to inhibit learning and LTP (2,29,30). Scopolamine has been known to inhibit kindling, learning as well as LTP (8,11,38).

These phenomenological and pharmacological similarities led us to examine whether behavioral sensitization would be blocked by GABA–benzodiazepine agonists, known to inhibit kindling, learning, as well as LTP (1,14,25). We have previously reported that clonazepam (CZP), a potent GABA–benzodiazepine agonist with high selectivity to the central types of benzodiazepine receptors, completely prevented the acquisition of the stimulant-induced sensitization (13). In the present study, we aimed to extend our previous

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study. First, we examined the effect of flumazenil (Flu), a GABA–benzodiazepine antagonist, on the acute motor effect of MA as well as on the acquisition of MA-induced sensitization. Second, it was tested whether Flu would reverse the inhibitory effect of CZP on MA sensitization. Finally, it was examined whether CZP would also inhibit the expression of sensitization.

METHOD

Animals

Male Wistar–King rats (Hokkaido University Animal Facility), weighing 190–270 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 0630–1830 h), with temperature at 24°C), and humidity at 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 guide for the care and use of laboratory animals regulated by Hokkaido University School of Medicine, and NIH guidelines on animal care.

Experiment 1: Effect of Flu on the Acquisition of Behavioral Sensitization to MA

Rats were randomly assigned to one of the following four groups (n = 20–24 per group). Each rat received two injections. The second injection was given 10 min after the first injection. The first group was treated with vehicle (1 ml/kg) + MA (1 mg/kg). The second group received Flu (10 mg/kg) + saline (SA). The third group received Flu + MA. The fourth group received vehicle (Veh) + SA. Drugs were injected daily from day 1 to day 10 in their home cages. On day 17 or 18, MA (1 mg/kg) was injected to all four groups (Veh + MA, Flu + SA, Flu + MA, and Veh + SA) in their home cages. Motor activity was measured on day 1 and day 17 or 18.

Experiment 2: Effect of Flu and CZP on the Acquisition of Behavioral Sensitization to MA

Rats were randomly assigned to one of the four groups (n = 24). Each rat received three injections. The second and third injections were given 10 min and 15 min after the first injection, respectively. The first group was treated with Veh (1 ml/kg) + Veh + MA (1 mg/kg). The second group received Veh + CZP (0.5 mg/kg) + MA. The third group received Flu (10 mg/kg) + CZP + MA. The fourth group received Veh + Veh + SA (1 ml/kg). Drugs were injected daily from day 1 to day 10 in their home cages. On day 17 or 18, MA (1 mg/kg) was injected to all four groups (Veh + Veh + MA, Veh + CZP + MA, Flu + CZP + MA, and Veh + Veh + SA) in their home cages. Motor activity was measured on day 1 in most of experiments (n = 16) and day 17 or 18 in all experiments (n = 24). Flu + Veh + SA, Veh + CZP + SA and Flu + Veh + MA were not included, because data from Experiment1 and our previous study (13) suggest these treatments would have no effect.

Experiment 3: Effect of CZP on the Expression of Behavioral Sensitization to MA

Rats daily received either MA (1 mg/kg) or SA (1 ml/kg) from day 1 to day 10 in their home cages. On day 17 or 18 (challenge day), each rat received two injections. The second injection (MA) was given 10 min after the first injection (Veh or CZP). Those animals treated with MA were assigned to one of the two groups (n = 8). First group received Veh (1 ml/kg) + MA (1 mg/kg), and second group received CZP (1 mg/kg) + MA. Those treated with SA received Veh + MA. Motor activity was measured in the three groups after MA injection. Because a small dose (0.125 mg/kg) of CZP significantly enhanced, a medium dose (0.5 mg/kg) showed no change, and a greater dose (2.0 mg/kg) slightly tended to reduce the acute motor effect of MA in a previous study (13) as well as a preliminary study, 1.0 mg/kg of CZP was used in this experiment.

Motor Activity Measurement

The observation room was located near the animal room and kept with the same condition. 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 that detects thermal radiation from animals (Supermex: Muromachi Kikai, Tokyo, Japan). 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 contribute to the count when these movements had substantial horizontal components.

Drugs

Methamphetamine hydrochloride (Dainippon Pharmaceuticals Ltd, Japan) was dissolved in saline. Flumazenil (Yamanouti Pharmaceuticals Ltd, Japan) and clonazepam (Roche Pharmaceuticals Ltd, Japan) were suspended in 0.5% sodium carboxymethylcellulose. All doses refer to salts. All injections were given subcutaneously in the morning (0900–0930).

Statistics

The motor activity was analyzed by a two-way analysis of variance (ANOVA) using the treatment group as the between-subject variable and time as a repeated-measures variable. When the group–time interaction was statistically significant, a post hoc Duncan new multiple range test was used to determine which group differed from others (defined as $p < 0.05$). Then a one-way ANOVA with a post hoc Duncan new multiple range test were performed at each time to determine when a significant difference was observed (defined as $p < 0.05$).

RESULTS

Experiment 1

The effects of FLU on MA-induced motor activity as well as on the acquisition of sensitization were examined.

On day 1, There was no significant difference either between the Veh + MA group and the Flu + MA group or between the Veh + SA group and the Flu + SA group (Fig. 1). On day 17 or 18 (challenge day), two-way ANOVA indicated a significant interaction between the group and time, $F(3, 30) = 1.730$, $p < 0.01$. The Veh + MA group from 20–40 min and the Flu + MA group from 30–40 showed a significant enhancement in MA-induced sensor counts compared to the Veh + SA group. There was no difference in MA-induced sensor counts between the Veh + MA group and the

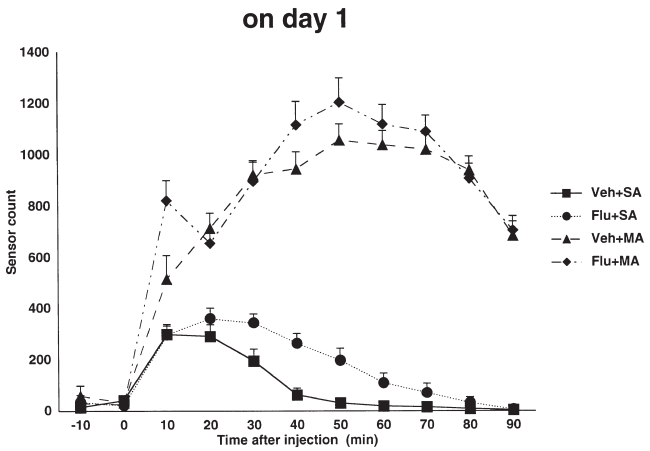

FIG. 1. Effects of Flu on MA-induced motor activity on the first day. Rats were randomly assigned to one of the following four groups. Each rat received two injections. The first group was treated with Veh (1 ml/kg) + MA (1 mg/kg). The second group received Flu (10 mg/kg) + SA. The third group received Flu + MA. The fourth group received Veh + SA. Each point represents the mean ± SEM at each time for 20–24 rats per group. There was no difference between the Veh + MA group and the Flu + MA group.

Flu+MA group. The Flu+SA group showed no difference from the Veh+SA group (Fig. 2).

Experiment 2

It was examined whether Flu would reverse the inhibitory effect of CZP on the MA sensitization. On day 1, there were no differences among the Veh + Veh + MA, Veh + CZP + MA, and Flu + CZP + MA groups (Fig. 3). When MA was readministered on day 17 or 18 (challenge day), two-way ANOVA indicated a significant interaction between the group and time, $F(3, 39) = 3.380$, $p < 0.01$. The Veh + Veh + MA, as well as Flu + CZP + MA group, showed a significant enhancement in sensor counts compared to Veh + Veh + SA group from 20 to 90 min (Fig. 4). There was no difference between the Veh + CZP + MA group and the Veh + Veh + SA group.

Experiment 3

Figure 5 shows the effect of CZP on the expression of behavioral sensitization to MA. Two-way ANOVA indicated a significant interaction between the group and time, $F(3, 30) = 26.488$, $p < 0.01$). CZP was given 10 min prior to MA challenge on day 17 or 18. CZP showed no effect on MA-induced motor activity in sensitized rats.

DISCUSSION

In the previous study, we have shown that CZP, a GABA–benzodiazepine agonist, prevents the development of MA-induced behavioral sensitization (13). The present study aimed to further clarify the role of GABA–benzodiazepine receptors in the behavioral sensitization. In Experiment 1, the effect of Flu, a GABA–benzodiazepine antagonist, on MA-induced acute motor changes as well as sensitization was examined. Pretreatment with Flu (10 mg/kg) had no effect on MA-induced acute motor changes. Animals pretreated with Flu prior to each MA administration showed no difference in the MA-induced motor activity on day 17 or 18 from those treated with MA alone. These results suggest that pretreatment with Flu prior to MA administration has no effect on not only the acute motor changes but also the acquisition of behavioral sensitization.

Similar to our results, Britton et al. (5) have reported that Flu (12 mg/kg IP) showed no intrinsic activity, and failed to antagonize the locomotor activating effects of amphetamine (0.75 mg/kg, IP). Although initial studies in animals failed to reveal any intrinsic pharmacological activity of Flu, subse-

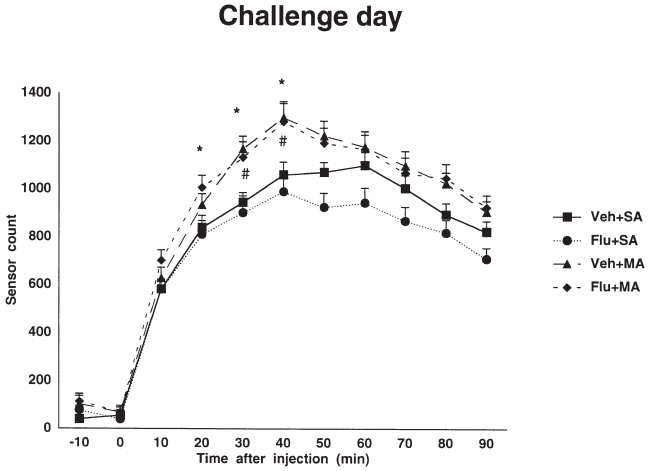

FIG. 2. Effects of Flu on the acquisition of behavioral sensitization to MA. On day 17 or 18, MA (1 mg/kg) was injected to all four groups (Veh + MA, Flu + SA, Flu + MA, and Veh + SA) in their home cages, and motor activity was measured. Each point represents the mean ± SEM at each time in each group. Veh + MA group from 20 to 40 min ($*p < 0.05$) and Flu + MA group from 20 to 30 ($\#p < 0.05$) showed a significant enhancement in sensor counts compared to Veh + SA group. There was no difference between the Veh + MA group and the Flu + MA group.

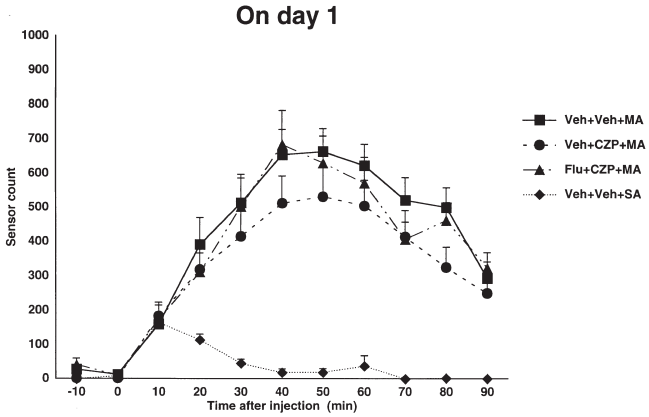

FIG. 3. Effects of Flu and CZP on MA-induced motor activity on the first day. Rats were randomly assigned to one of the four groups. Each rat received three injections. The first group was treated with Veh +Veh + MA (1 mg/kg). The second group received Veh + CZP (0.5 mg/kg) + MA. The third group received Flu (10 mg/kg) + CZP + MA. The fourth group received Veh + Veh + SA. Each point represents the mean ± SEM at each time for 16 rats per group. There was no difference among the Veh + Veh + MA group, the Veh + CZP + MA group, and the Flu + CZP + MA group.

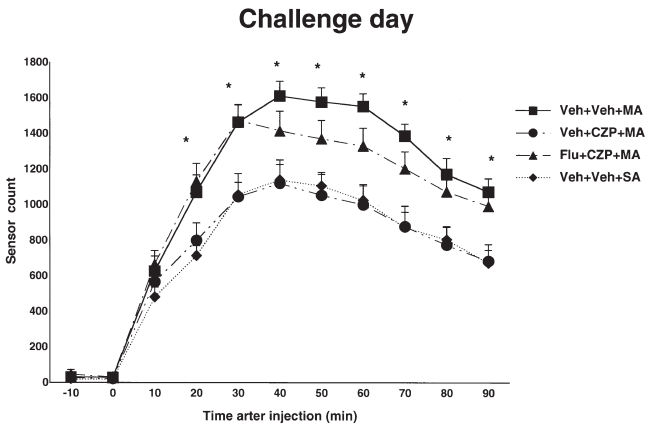

FIG. 4. Effect of CZP or Flu + CZP on the acquisition of sensitization to MA. On day 17 or 18, MA (1 mg/kg) was injected to all four groups (Veh + Veh + MA, Veh + CZP + MA, Flu + CZP + MA, and Veh + Veh + SA) in their home cages. Each point represents the mean ± SEM at each time in each group. There was no difference between the Veh + CZP + MA group and the Veh + Veh + SA group. The Veh + Veh + MA as well as the Flu + CZP + MA group showed a significant enhancement in sensor counts compared to the Veh + Veh + SA group from 20 to 90 min ($*p < 0.05$).

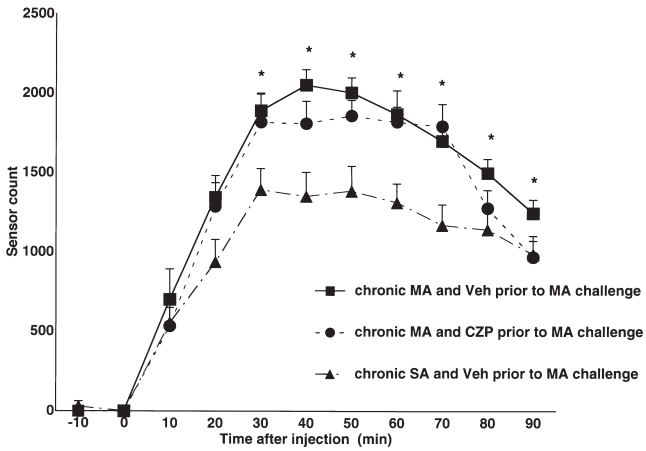

FIG. 5. Effects of CZP on the expression of sensitization to MA. Rats received daily either MA (1 mg/kg) or SA (1 ml/kg) from day 1 to day 10 in their home cages. On day 17 or 18 (challenge day), each rat received two injections. The second injection (MA) was given 10 min after the first injection. Those treated with MA were assigned to one of the two groups. First group received Veh (1 ml/kg) + MA (1 mg/kg), and second group received CZP (1 mg/kg) + MA. Those treated with SA received Veh + MA. Motor activity was measured in the three groups after MA injection. Each point represents the mean ± SEM at each time for eight rats per group. Both MA-treated rats showed enhance motor activity from 20 to 90 min compared to SA-treated rats ($*p < 0.05$).

quent behavioral studies have suggested both a partial agonist and an inverse agonist activities (9). However, Brogden et al. (6) has summarized that partial agonist effects are observed usually with high doses of Flu (30–50 mg/kg), while inverse agonist-like activity is evident most often at lower doses. This latter activity has often been observed only under particular test and environmental conditions. Thus, it can be assumed that Flu at the dose used in the present study (10 mg/kg) primarily acted as an antagonist without intrinsic activity. In addition, this dose has been proved to adequately reverse the behavioral and pharmacological effect of benzodiazepine agonists (4,6). Several studies have suggested the presence of endogenous benzodiazepine agonists and inverse agonists (10,20). The present results may indicate that those endogenous ligands, if present, have no modulatory role in the acute motor effect of MA and in the process of the acquisition of sensitization to MA.

Consistent with the previous study, rats pretreated with CZP (0.5 mg/kg) prior to MA administration showed no difference in the MA-induced motor activity from saline treated rats, suggesting that CZP prevented the acquisition of behavioral sensitization. Rats pretreated with Flu prior to CZP and MA showed significantly enhanced motor activity compared to those treated with saline (Experiment 3). Thus, These results suggest that Flu reversed the inhibitiory effect of CZP and strengthen the notion that stimulation of GABA–benzodiazepine receptors play a role in the acquisition of behavioral sensitization.

CZP has high affinity and high selectivity to central types of benzodiazepine receptors (22,23). Taken together with the result that Flu reversed the effect of CZP, it is highly likely that the inhibitory effect of CZP on the acquisition of sensitization to MA is mediated by benzodiazepine receptors. Considering that the benzodiazepine receptor-binding site is an integral component of the $GABA_A$ receptor complex (34), it is assumed that facilitation of the neurotransmission through $GABA_A$ receptors by stimulating benzodiazepine receptors is relevant to the blockade of sensitization.

GABA and benzodiazepines have been known to modulate dopamine release in the central nervous system (12,35). However, as discussed in our previous report (13), it is unlikely that CZP decreased MA-induced DA release during repeated treatment and subsequently inhibited the development of sensitization, because CZP (0.5 mg/kg) did not reduce acute behavioral effects of MA. Considering GABAergic afferent to dopamine cells in the VTA are thought to synapse primarily onto GABAB receptors (37), and microinjection of $GABA_B$ agonist into the VTA has been shown to inhibit the acquisition of sensitization (16), it is also unlikely that CZP acted in the ventral tegmental area (VTA), an area that contains a dopaminergic cell body, and may play an important role in the acquisition of behavioral sensitization (16).

One possibility is that CZP prevented the acquisition of behavioral sensitization by acting at GABA–benzodiazepine receptors in the frontal cortex. Consistent with this speculation, Karler et al. (19) reported that intracortical administration of 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol (THIP), a $GABA_A$ agonist, blocked the acquisition of behavioral sensitization to amphetamine in the mice (19). The same group has shown that THIP itself produce stereotypy when locally applied in the striatum (3). However, they also showed intrastriatal injection of bicuculline, a $GABA_A$ antagonist, blocked the acquisition of sensitization. It seems that $GABA_A$ receptors have different roles in different brain regions. Their finding that not only intrastriatal but also systemic injection of the $GABA_A$ antagonist prevented sensitization is not easily reconciled with our finding. It is possible that systemic injection of CZP in the rat and that of bicculline in the mice may predominantly work in the cortex and striatum, respectively. Studies with local administration of CZP are necessary to elucidate the exact site of action.

The present study also examined the effect of CZP on the expression of sensitization (Experiment 3). Rats pretreated with CZP (1 mg/kg) prior to MA challenge (1 mg/kg) showed as much enhanced motor activity as those pretreated with Veh prior to MA. These results suggest that treatment with CZP prior to MA challenge does not prevent the expression of behavioral sensitization. Our previous study has shown that the dose of 0.5 or 2.0 mg/kg of CZP does not significantly change the acute motor effect of MA in naive rats. The present results suggest that CZP (1.0 mg/kg) does not alter the magnitude of enduring enhanced response in sensitized animals.

The responsible site of the expression of sensitization has been claimed to be the striatum or the nucleus accumbence, because the direct infusion of amphetamine to those areas produce enhanced response in the animals that received repeated systemic injections of the stimulant (15,31). Bedingfield et al. (3) have reported that systemic as well as intrastriatal injection of bicuculline blocked the expression of sensitization. Considering their results together with ours, blockade rather than facilitation of GABA–benzodiazepine in the striatum may block the expression.

As mentioned in the Introduction, glutamatergic neurotransmission, cholinergic neurotransmission and protein synthesis, 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. Considering the role of GABAergic systems in kindling, learning, and LTP, the present findings support a notion that behavioral sensitization to psychostimulants shares a common property with other forms of neural plasticity. Taken together, it may be that a neuronal circuit including glutamatergic, cholinergic, GABAergic and dopaminergic systems are involved in the development of behavioral sensitization.

In summary, the present study replicated our previous finding that CZP, a GABA–benzodiazepine agonist, prevents the development of behavioral sensitization to MA. Furthermore, Flu, a GABA–benzodiazepine antagonist, was shown to reverse the prevention of sensitization by CZP, although Flu alone has no effect on sensitization. CZP showed no effect on the expression of sensitization. These results suggest that GABA–benzodiazepine transmission is associated with the development of behavioral sensitization to MA.

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