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Clonazepam Prevents the Development of Sensitization to Methamphetamine

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ITO, K. T. OHMORI, T. ABEKAWA AND T. KOYAMA. *Clonazepam prevents the development of sensitization to methamphetamine.* PHARMACOL BIOCHEM BEHAV **58**(4) 875–879, 1997.—The GABA–benzodiazepine neurotransmission has been implicated in various forms of plasticity such as kindling and learning. The present study examined the effects of clonazepam (CZP), a GABA–benzodiazepine agonist, on the development of behavioral sensitization to methamphetamine (MA). Rats treated with MA (1 mg/kg, SC) for 10 days displayed significantly enhanced motor activity when tested with MA (1 mg/kg) after a 7–8-day withdrawal, indicating the development of behavioral sensitization. Pretreatment with CZP (0.5 and 2.0 mg/kg) prior to MA administration prevented the development of the phenomenon. Rats treated with CZP alone showed no difference in the motor activity compared to those treated with saline. These results suggest that stimulation of GABA–benzodiazepine receptors plays a role in the development of behavioral sensitization. © 1997 Elsevier Science Inc.

Methampetamine Sensitization Clonazepam Benzodiazepine GABA

REPEATED administration of amphetamine or methamphetamine (MA) results in an augmentation of its locomotor activating effects, a phenomenon known as behavioral sensitization (11,29). In humans, the chronic use of the drug elicits a progressive augmentation in paranoid symptoms that closely resemble schizophrenia (11,29). 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 (13,22,34,39), protein synthesis inhibitors (14,30), and scopolamine, an antagonist of the muscarinic cholinergic receptor (24,25). NMDA antagonists have been shown to block or retard the development of kindling, learning as well as LTP (4,15,20). Protein synthesis inhibitors have also been reported to inhibit learning and LTP (2,26,27). Scopolamine has been known to inhibit kindling, learning as well as LTP (6,8,38).

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 (1,10,21). We found that clonazepam (CZP), a potent GABA-benzodiazepine agonist with high selectivity to the central types of benzodiazepine receptors, completely prevented the development of the stimulant-induced 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 to 1830 h), 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.

Effect of CZP on MA-induced Motor Activity

Rats received a single injection of either saline (1 ml/kg), MA (1 mg/kg), or CZP. Another group received MA (1 mg/kg) 10 min after CZP administration. Three doses of CZP were tested in three separate experiments (0.125, 0.5, and 2.0

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mg/kg). Because 0.5 mg/kg CZP was tested first and found to have no effect on motor activity, CZP group (rats to receive CZP alone) was omitted in the experiment with the smallest dose of CZP. The acute effects of coadministration with CZP on MA-induced motor activity was observed on day 1 of the 10-day treatment phase in some of the rats used in the experiments described below. Motor activity was observed as described below.

Effect of CZP on Behavioral Sensitization to MA

Rats were randomly assigned to one of the following four groups ($n = 12$ per group). First group was treated with MA (1 mg/kg). Second group received CZP (0.5 mg/kg). Third group received MA (1 mg/kg) 10 min after the injection of CZP (0.5 mg/kg). 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 (1 mg/kg) was injected to all four groups (MA, CZP, CZP+MA, and saline) in their home cages and motor activity was observed. In separate experiments, a smaller (0.125 mg/kg) and a greater (2 ml/kg) doses of CZP were also tested by using the same experimental design. However, the second group (rats to receive CZP alone repeatedly) was omitted in the experiment with 0.125 mg/kg CZP ($n = 12$ or 8 per group), because the experiments with large doses of CZP (0.5 and 2.0 mg/kg) were conducted first and the 10-day treatment with CZP alone was found to have no effect on MA-induced motor activity on day 17 or 18.

In complementary experiments, rats were randomly assigned to one of the two groups ($n = 8$). The first group received vehicle (0.5% sodium carboxymethylcellulose) and the second group received CZP (0.5 mg/kg). Ten minutes later, both groups received MA (1 mg/kg). Drugs were injected daily from day 1 to day 10 in their home cages. On day 17, MA (1 mg/kg) was injected to both groups. Motor activity was observed on day 1, day 6, and day 10 of the 10-day treatment phase as well as on day 17.

Motor Activity Measurement

When MA was injected on day 17 or 18, behavior of the animals was examined by visual observation, as previously described (23), using the rating scale devised by Dougherty and Ellinwood (5) with minor modifications. Each animal was assigned a rating score of 1–9 according to the scale every 10 min for 90 min after MA injection. Ratings were made by two observers, one of whom was unaware of the treatment conditions. In most cases, the two observers gave the same score. Interscore reliability of two observers calculated using data from present experiments 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 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 locomotion 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 Ltd, Japan) were dissolved in saline. CZP (Roche Pharmaceuticals Ltd., Japan) were suspended in 0.5% sodium carboxymethylcellulose. All doses refer to salts. All injections were given subcutaneously in the morning.

Statistics

The cumulated behavioral scores of each rat during the 90-min period were analyzed by Kruskal–Wallis tests. When there was a statistically significant difference, Mann–Whitney U-tests was used to determine which group differed from others (defined as $p < 0.05$).

RESULTS

Effects of CZP on MA-induced Motor Activity

Figure 1 shows the effect of CZP on MA-induced motor activity. Three doses of CZP were tested in three separate experiments (0.125, 0.5, and 2.0 mg/kg). Results represents median and interquartile range of the cumulated rating score from 10 to 90 min for each group of rats. Kruskal–Wallis tests indicated a significant difference in all three separate experiments. Mann–Whitney U-tests revealed that both MA and CZP+MA groups showed significant enhancement in the cumulated rating score compared to saline group ($*p < 0.05$) in all three experiments.

Pretreatment with 0.125 mg/kg CZP significantly enhanced MA-induced behavioral score ($\#p < 0.05$), while pretreatment with either 0.5 or 2.0 mg/kg CZP produced no significant effect on MA-induced behavior. CZP (0.5 mg/kg) alone showed no significant behavioral effects compared with saline, although the higher does (2.0 mg/kg) significantly reduced the score compared with saline ($*p < 0.05$).

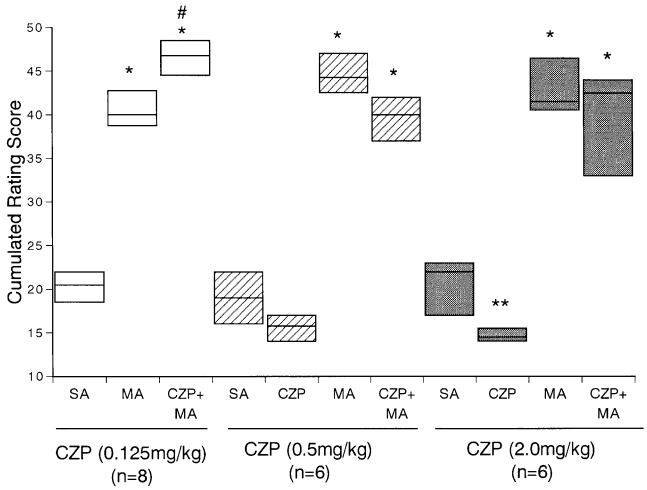

FIG. 1. Effect of CZP on MA-induced motor activity; Rats received a single injection of either saline (1 ml/kg), MA (1 mg/kg), or CZP. Another group received MA (1 mg/kg) 10 min after CZP administration. Three doses of CZP were tested in three separate experiments (0.125, 0.5, and 2.0mg/kg). In the experiment with the smallest dose of CZP, CZP group was omitted. Results represent median and interquartile range of the cumulated rating score for six or eight rats per group. $*p < 0.05$ vs. saline group; $\#p < 0.05$ vs. MA group; $**p < 0.05$ vs. saline (Mann–Whitney *U*-tests).

Effects of CZP on Behavioral Sensitization to MA

Figure 2 shows the effects of CZP on behavioral sensitization to MA. Three doses of CZP were tested in three separate experiments (0.125, 0.5, and 2.0 mg/kg). MA (1 mg/kg) was injected to all four group on day 17 or 18. Results represents median and interquartile range of the cumulated rating score from 10 to 90 min for each group. Kruskal–Wallis tests indicated a significant difference in all three separate experiments. Mann–Whitney *U*-tests revealed that MA group showed a significant enhancement in the cumulated rating score compared with respective saline group ($*p < 0.05$) in all three experiments.

Rats pretreated with 0.125 mg/kg CZP prior to MA injection during the 10-day treatment phase also showed significantly enhanced scores compared with saline-treated rats ($*p < 0.05$). There was no significant difference between MA and CZP (0.125 mg/kg)+MA groups.

However, rats pretreated with 0.5 and 2.0 mg/kg CZP prior to MA injection during the treatment phase failed to show an enhancement in the behavioral score. CZP (either 0.5 or 2.0 mg/kg)+MA showed no significant difference compared with respective saline group. CZP alone at either 0.5 or 2.0 mg/kg showed no significant behavioral effect compared with saline.

Figure 3 shows the cumulative behavioral score on days 1, 6, and 10 during the treatment phase as well as the score on day 17 in Veh+MA and CZP+MA groups. The score of day 10 as well as day 17 showed significant enhancement compared with that of day 1 in Veh+MA group ($*p < 0.05$), whereas no significant change was shown at either day 6, 10 or 17 compared with day 1 in CZP+MA group. In the score of day 17, Veh+MA group showed significant enhancement compared with CZP+MA group ($*p < 0.05$).

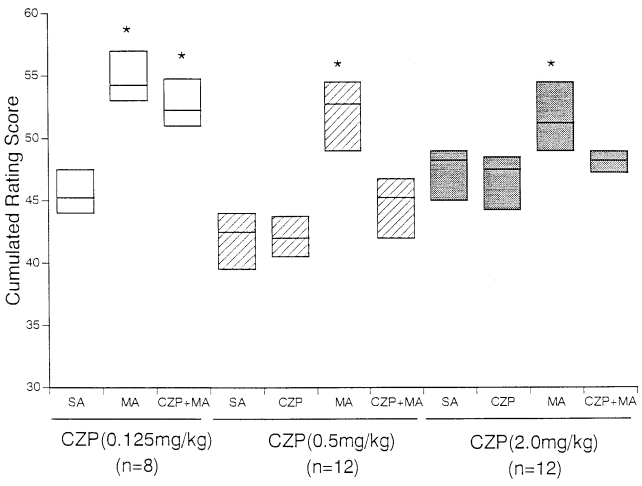

FIG. 2. Effect of CZP on behavioral sensitization to MA; rats were randomly assigned to one of the following four groups. First group was treated with MA (1 mg/kg). Second group received CZP (0.5 or 2.0 mg/kg). Third group received MA (1 mg/kg) 10 min after the injection of CZP (0.125, 0.5, or 2.0 mg/kg). 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 (1 mg/kg) was injected to all four groups (MA, CZP, CZP+MA, and saline). There doses of CZP were tested in separate experiments with respective control groups. CZP group was omitted in the experiment with 0.125 mg/kg CZP. Results represent median and interquartile range of the cumulated rating score for 8 or 12 rats per group. $*p < 0.05$ vs. saline group (Mann–Whitney *U*-tests).

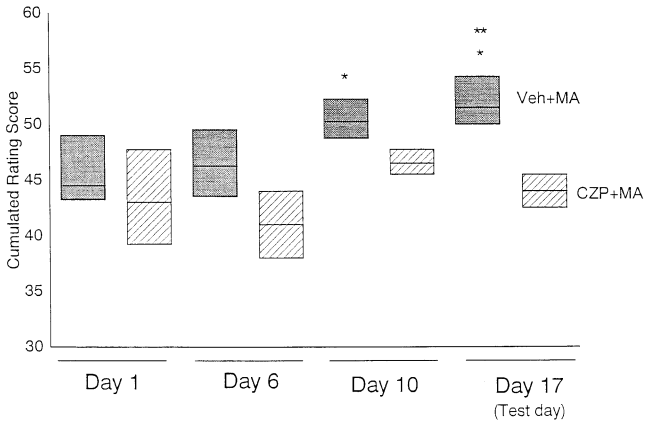

FIG. 3. Behavioral scores during the 10-day treatment phase and on the test day. Veh+MA group received vehicle (1 ml/kg) and CZP+MA group received CZP (0.5 mg/kg) 10 min prior to MA injection (1 mg/kg) from day 1 to day 10. Both groups were given MA (1 mg/kg) on day 17. Behavior was scored on day 1, 6, 10, and 17. Results represent median and interquartile range of the cumulated rating score for eight rats per group. $*p < 0.05$ vs. Veh+MA on day 1; $**p < 0.05$ vs. CZP+MA on day 17 (Mann–Whitney *U*-tests).

DISCUSSION

Rats treated with MA (1 mg/kg, SC) for 10 days showed significantly enhanced motor activity compared to those treated with saline when injected wtth MA (1 mg/kg) after 7–8 days withdrawal, indicating the development of behavioral sensitization. Rats pretreated with CZP (0.5 and 2.0 mg/kg) prior to MA administration showed no difference in the motor activity from saline-treated rats when tested with MA (1 mg/kg), while the activity of those pretreated with a smaller dose of CZP (0.125 mg/kg) was not significantly different from that of those treated with MA alone. Rats treated with CZP alone showed no difference in the motor activity compared to those treated with saline. These results suggest that pretreatment with CZP prior to MA administration prevented the development of behavioral sensitization in a dose-related manner.

Similar to our results, Weiss et al. have found that diazepam, a benzodiazepine agonist, inhibited the development of behavioral sensitization to cocaine (37). In their study, rats that received cocaine on day 1 showed an increased locomotor response to the stimulant on day 2. This effect was found to be context dependent. They showed that diazepam prevented cocaine-induced hyperactivity on day 1 as well as subsequent sensitization on day 2. They interpreted that diazepam blocked sensitization though interference with the development of conditioning of the effect of cocaine to a specific environment by blocking acute motor effect on day 1. The same interpretation cannot be applied to our results for two reasons. First, conditioning variables to a specific environment were minimized in the present experiment, because the rats were repeatedly treated with MA and/or CZP, and tested with MA, in their home cages. Secondly and more importantly, pretreatment with CZP prior to MA administration did not inhibit MA-induced behavioral activity. Our findings that pretreatment with the small dose (0.125 mg/kg) produced enhancement and the greater doses (0.5 and 2.0 mg/kg) of CZP showed no change or nonsignificant tendency toward reduction in the acute behavioral effect of MA are consistent with previous studies (31,36).

Benzodiazepines are known to have interoceptive stimulus properties and induce state-dependent learning (20,27). However, in the complementary experiments, CZP (0.5 mg/kg)+MA group showed no enhancement in the behavioral score on day 10 compared with day 1 of the 10-day treatment phase, while Veh+MA group showed significant enhancement on day 10 compared with day 1. Taking this observations into consideration, it is unlikely that CZP served as an interoceptive stimuli associated with MA effect, and that the absence of CZP on the MA challenge day (day 17 or 18) might account for the failure of CZP+MA group to show enhanced behavior.

One possible problem of the present study is that CZP plus MA group received two injections, while other groups received only one. Considering that CZP was suspended in 0.5% sodium carboxymethylcellulose vehicle, it is possible that the vehicle treatment might have some influence on MA-induced behavior. However, the vehicle injection showed no behavioral effects compared to saline injection (data not shown). Moreover, the inhibitory effect of CZP on behavioral sensitization to MA was dose related. Pretreatment with the small dose of CZP (0.125 mg/kg) showed no effect on sensitization. Therefore, it is unlikely that the vehicle treatment or the difference in the number of injection contributed to the results. In support for this interpretation, the results of MA challenge in Veh+MA and CZP+MA groups in the complementary experiments are consistent with other results.

It is known that the benzodiazepine receptor binding site is an integral component of $GABA_A$ receptor complex (32). CZP has high affinity and high selectivity to central types of benzodiazepine receptors (16,17). GABA is a major inhibitory neurotransmitter in the mammalian brain and is present in all brain regions, both in interneurons as well as in projection neurons such as striatonigral and striatopallidal pathways (19).

GABA and benzodiazepines has been known to modulate dopamine release in the central nervous system (9,33). Stimulation of DA receptors in the nucleus accumbens has been shown to reduce extracellular concentrations of GABA in the ventral pallidum (3). These DA–GABA interactions may be related with acute behavioral effects of psychostimulants. However, because CZP (0.5 and 2.0 mg/kg) did not reduce acute behavioral effects of MA, it is unlikely that CZP decreased MA-induced DA release during repeated treatment and subsequently inhibited the development of sensitization.

GABAergic neurons in both the nucleus accumbens and ventral pallidum project to the ventral tegmental area (VTA) (7), a region that may play an important role in the initiation of behavioral sensitization (12). These afferents to dopamine cells in the VTA are thought to synapse primarily onto $GABA_B$ receptors (35). A study has shown that microinjection of $GABA_B$ agonist into VTA inhibits the development of sensitization. Therefore, it is not conceivable that CZP acted in VTA to prevent sensitization.

The exact site of action of CZP to prevent the development of behavioral sensitization to MA is unknown. However, as mentioned in the Introduction, glutamatergic systems, cholinergic systems, 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 (13,22,24,25,30,34,39). The present findings, taken together with the role of GABAergic systems in kindling, learning, and LTP, support a notion that behavioral sensitization to stimulants drugs shares a common property with other forms of neural plasticity. It may be that a neuronal circuit including glutamatergic, cholinergic, GABAergic, and dopaminergic systems is involved in the development of behavioral sensitization.

In summary, the present study indicates that CZP, a GABA-benzodiazepine agonist, prevents sensitization to MA, suggesting a possible role for GABA-benzodiazepine transmission in the development of behavioral sensitization.

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