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Competitive and Noncompetitive NMDA Antagonists Block Sensitization to Methamphetamine

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OHMORI, T., T. ABEKAWA, A. MURAKI AND T. KOYAMA. *Competitive and noncompetitive NMDA antagonists block sensitization to methamphetamine.* PHARMACOL BIOCHEM BEHAV **48**(3) 587–591, 1994.—The present study examined the effects of both competitive (D-CPP-ene) and noncompetitive (MK-801) NMDA antagonists on behavioral sensitization to methamphetamine (MA). Behavioral effects of repeated administration of NMDA antagonists were also examined. Rats treated with MA according to an escalating dose schedule (2.5, 5, 7.5, and 10.0 mg/kg, SC, twice a day on days 1, 3, 5, and 7, respectively) indicated behavioral supersensitivity. Pretreatment with either MK-801 (0.5 mg/kg, IP) or D-CPP-ene (20 mg/kg, IP) prior to MA administration prevented the development of the supersensitivity. Rats treated with MK-801 showed a decrease in the motor activity when subsequently challenged with MK-801 compared with saline-treated rats. Likewise, rats administered with D-CPP-ene showed decreased motor activity when challenged with D-CPP-ene. There was no cross-sensitization nor tolerance between MA and MK-801 or D-CPP-ene. These results suggest that both competitive and noncompetitive NMDA antagonists block sensitization to MA and that repeated administration with NMDA antagonists results in behavioral tolerance.

Methamphetamine Behavioral sensitization *N*-methyl-D-aspartate MK-801 D-CPP-ene Glutamate Tolerance

REPEATED administration of amphetamine or methamphetamine (MA) results in an augmentation of its locomotor activating effects, a phenomenon known as behavioral sensitization [for reviews, (14,26)]. In humans, the chronic use of the drug elicits a progressive augmentation in paranoid symptoms that closely resemble schizophrenia [for reviews, (14,26)]. Therefore, understanding the neural mechanism of sensitization in rodents may provide insight into the pathogenesis of both amphetamine-induced psychosis and schizophrenia. It was recently demonstrated that behavioral sensitization to amphetamine is blocked by MK-801, a noncompetitive *N*-methyl-D-aspartate (NMDA) antagonist (15,16,33,37,38). This finding, which indicates an involvement of NMDA receptors in the development of behavioral supersensitivity, is of interest because NMDA receptors have been reported to be associated with other forms of neural plasticity such as kindling and long-term potentiation (4).

On the other hand, blockade of the NMDA receptor per se has been suggested to produce psychotic symptoms. It has long been known that phencyclidine (PCP) causes a schizophrenia-like psychosis (1,13). Recent studies indicate that the psychotropic effect of phencyclidine is mediated by blockade of the NMDA receptor (13,24). In rodents, PCP causes hyperlocomotion, stereotyped behavior, and ataxia (3,34). Several studies have examined behavioral effects of repeated administration of phencyclidine (3,12,22,30,34). However, PCP has a property as a dopamine reuptake blocker as well as a noncompetitive NMDA antagonist (24,31). It is possible that the former property was related to the behavioral alteration observed after chronic treatment with PCP. Unlike PCP, MK-801 lacks an action as a dopamine reuptake blocker (24,31) and, therefore, provides a more specific agent to investigate the behavioral consequence after repeated pharmacological blockade of the NMDA receptor.

In the present study, we reexamined and confirmed the inhibitory effect of MK-801 on behavioral sensitization to MA. Moreover, it was revealed that D-CPP-ene, a competitive NMDA antagonist, also blocked the development of the behavioral supersensitivity. We also examined whether repeated administration of MK-801 and D-CPP-ene would result in

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supersensitivity or tolerance in their locomotor activating effects and whether cross-sensitization would occur between MA and MK-801 or D-CPP-ene.

METHOD

Animals

Male Wistar-King rats (200–250 g) were housed individually under controlled conditions of light (from 0630 to 1830 h), temperature (24°C), and humidity (50%), and were allowed free access to standard laboratory diet and tap water.

Experimental Procedure

Experiment 1. Half of the rats were first pretreated with MK-801 (0.5 mg/kg, IP) and half were pretreated with saline (1 ml/kg, IP) twice a day (6–7 h apart) on days 1, 3, 5, and 7. Thirty minutes later, half of each of these groups were subcutaneously treated with methamphetamine hydrochloride (MA) and the other half treated with saline (1 ml/kg). The dose of MA was gradually increased (2.5, 5, 7.5, and 10 mg/kg on days 1, 3, 5, and 7, respectively). On day 14 or 15, MA (1 mg/kg, SC) was readministered to all four groups (saline, MA, MK-801, and MK-801 + MA, n = 15–18 for each group) and motor activity was measured. On day 17 or 18, MK-801 (0.25 mg/kg, IP) was administered to all groups.

Experiment 2. Half of the rats were first pretreated with D-CPP-ene (20 mg/kg, IP) and half were pretreated with saline (1 ml/kg, IP) twice a day on days 1, 3, 5, and 7. Thirty minutes later, half of each of these groups were treated with MA and the other half treated with saline in the same manner as Experiment 1. All four groups (saline, MA, D-CPP-ene, and D-CPP-ene + MA, n = 9 for each group) were tested with MA (1 mg/kg, SC) on day 14 or 15, and with D-CPP-ene (10 mg/kg, IP) on day 17 or 18.

Apparatus

Motor activity was measured by an apparatus with an infrared sensor that detect thermal radiation from animals. The apparatus was a modification of that of Shirakawa and Oikawa (28). Horizontal movements of the rat were digitized and fed into a computer every 10 min. Locomotion predominantly contributed to the count, but repeated rearing, head weaving, and other nonspecific body movements could also contribute to the count when these movements had substantial horizontal components. Preliminary experiments showed that there was a good dose-response relationship in the count elicited by MA in the dose range from 0.5 to 1.5 mg/kg (SC), MK-801 from 0.1 to 0.5 mg/kg (IP), or D-CPP-ene from 5 to 20 mg/kg (IP, data not shown). A higher dose of MA that predominantly caused stereotyped behavior produced smaller counts than the dose of 1.5 mg/kg. Measurement was started 2 h after the home cage of the rat was placed under the sensor. It is a major advantage of this method that the motor activity is able to be measured in the home cage of the rat.

Drugs

Methamphetamine HCl (Dainippon Pharmaceuticals Ltd., Japan), MK-801 [(+)-5-methyl-10,11-dihydroxy-5H-Dibenzo (a,d)-cycloheptan-5,10-imine, Merck & Co. Inc., Japan] and D-CPP-ene [(e)-4-(3-phosphonoprop-2-enyl) piperazine-2-carboxylic acid: SDZ EAA 494, Sandoz Ltd., Basel, Switzerland] were dissolved in saline.

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 $p < 0.05$). In the analysis of the motor activity elicited by D-CPP-ene, cumulated motor activity was used for the analysis.

RESULTS

Figures 1 and 2 show the results of Experiment 1. Figure 1 illustrates the motor activity induced by MA on day 14 or 15. Two-way ANOVA indicated a significant interaction between the group and time in the motor activity induced by MA ($p < 0.001$). Post hoc Duncan new multiple range tests revealed that MA-treated rats showed significantly greater motor activity than other three groups (saline, MK-801, and MA + MK-801). One-way ANOVA with the post hoc tests conducted at each time revealed that the motor activity was significantly enhanced in MA group at time 20 to 100 min compared with other three groups. Figure 2 indicates the motor activity elicited by MK-801 on day 17 or 18 in all four groups. There was a significant interaction between the group and time (two-way ANOVA, $p < 0.001$). The post hoc tests revealed that both MK-801 and MK-801 + MA groups significantly differed from saline as well as MA group. One-way ANOVA

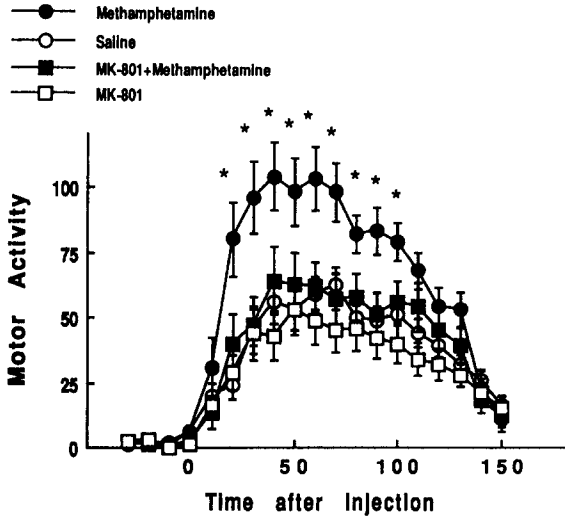

FIG. 1. Rats treated repeatedly with saline, methamphetamine (MA), MK-801, and MK-801 + MA were challenged with MA (1 mg/kg, SC) at time 0 on day 14 or 15. Each point represents the mean ± SEM for 15–18 rats per group. MA group showed a significant difference in the motor activity compared with saline, MK-801 and MK-801 + MA group (* < 0.05).

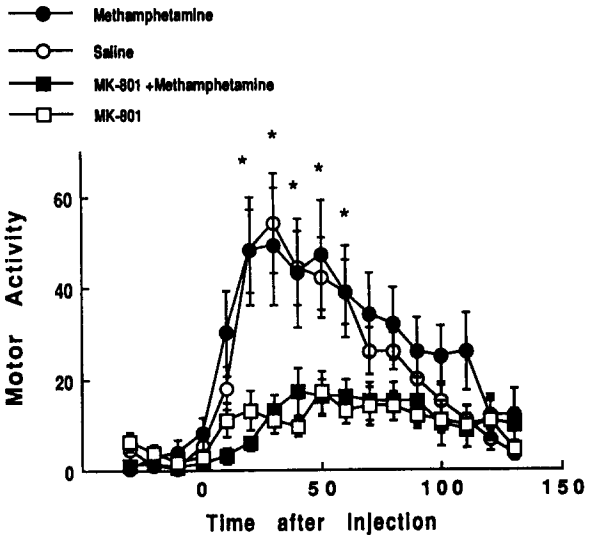

FIG. 2. Rats treated repeatedly with saline, methamphetamine (MA), MK-801, and MK-801 + MA were challenged with MK-801 (0.25 mg/kg, IP) at time 0 on day 17 or 18. Each point represents the mean ± SEM for 15–18 rats per group. MK-801 group and MK-801 + MA group showed a significant difference in the motor activity compared with saline as well as MA group (* < 0.05).

followed by the post hoc tests conducted at each time revealed that the motor activity was significantly reduced from 20 to 60 min in both MK-801 and MA + MK-801 groups compared with saline as well as MA group.

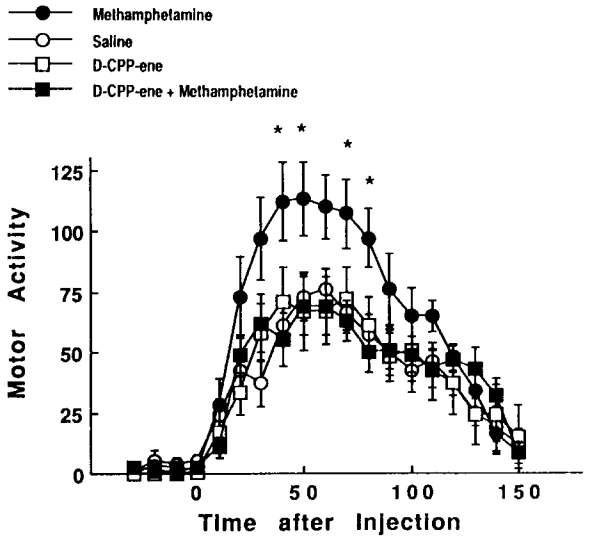

FIG. 3. Rats treated repeatedly with saline, methamphetamine (MA), D-CPP-ene, and D-CPP-ene + MA were challenged with MA (1 mg/kg, SC) at time 0 on day 14 or 15. Each point represents the mean ± SEM for nine rats per group. MA group showed a significant difference in the motor activity compared with saline, D-CPP-ene, and D-CPP-ene + MA group (* < 0.05).

Figures 3 and 4 show the results of Experiment 2. Figure 3 illustrates the motor activity induced by MA on day 14 or 15. Two-way ANOVA indicated a significant interaction between the group and time in the motor activity induced by MA ($p < 0.001$). Post hoc Duncan new multiple range tests revealed MA-treated rats showed significantly greater motor activity than other three groups (saline, D-CPP-ene, and MA + D-CPP-ene). One-way ANOVA with the post hoc tests conducted at each time revealed that the motor activity was significantly enhanced in MA group at time 40, 50, 70, and 80 min compared with other three groups. Figure 4 indicates the motor activity elicited by D-CPP-ene on day 17 or 18 in all four groups. There was a significant interaction between the group and time (two-way ANOVA, $p < 0.001$). The post hoc tests revealed that D-CPP-ene and MA + D-CPP-ene groups produced significantly decreased motor activity compared with MA group. The difference between D-CPP-ene or MA + D-CPP-ene group and saline group did not reach a statistical significance. However, when the cumulated motor activity from 140 to 230 min was analyzed by one-way ANOVA with post hoc Duncan new multiple range tests, it was found that both D-CPP-ene group and MA + D-CPP-ene group produced significantly reduced motor activity compared with saline as well as MA group.

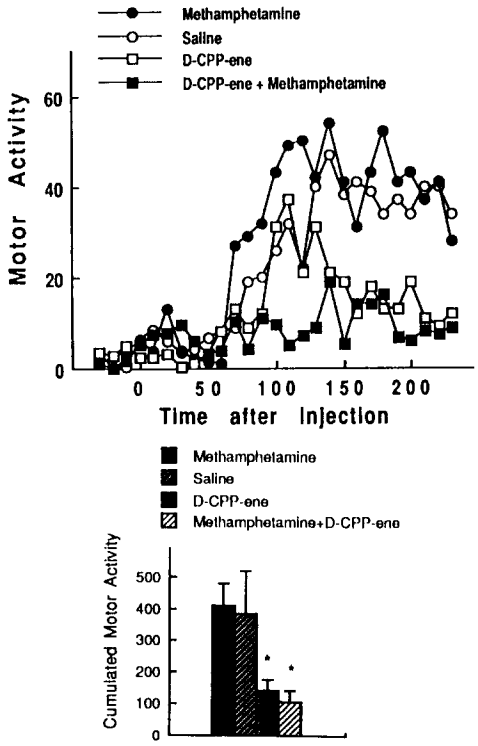

FIG. 4. Rats treated repeatedly with saline, methamphetamine (MA), D-CPP-ene, and D-CPP-ene + MA were challenged with D-CPP-ene (10 mg/kg, IP) at time 0 on day 17 or 18. Each point represents the mean for nine rats per group. The SEM is omitted for simplicity. The histogram represents the cumulated motor activity of each group from 140 to 230 min. D-CPP-ene and D-CPP-ene + MA group produced significantly reduced motor activity compared with saline as well as MA group (* < 0.05).

DISCUSSION

Recent studies (15,16,33,37,38) have reported that coadministration of MK-801 prevented the behavioral sensitization produced by repeated administration of amphetamine. Consistent with these studies, we demonstrated that coadministration of MK-801 completely blocked the development of sensitization tested 7 to 8 days after the escalating dose schedule of MA treatment. This treatment regime has been used in our laboratory for behavioral and biochemical studies (21,23). A lower dose of MA (1 mg/kg) was used on test days than treatment days (2.5–10 mg/kg) to avoid the induction of stereotypy which could nonspecifically inhibit the motor activity measured by the infrared sensor. A novel finding of the present study is that D-CPP-ene, a competitive NMDA antagonist, also blocked the development of behavioral supersensitivity. Competitive and noncompetitive NMDA antagonists block the receptor at different sites. The former acts at the agonist recognition site and the latter acts at the PCP site of the NMDA receptor-channel complex. Thus, our finding that both competitive and noncompetitive NMDA antagonists blocked behavioral sensitization strengthens the hypothesis that the development of behavioral sensitization requires stimulation of NMDA receptors.

The mechanism by which both MK-801 and D-CPP-ene block sensitization is unknown. It is unlikely that the two agents interfere with the release of dopamine from mesolimbic dopamine nerve terminals. Although MK-801 was reported to significantly reduce the massive increase in extracellular dopamine in the striatum after systemic injection of MA (36), the NMDA antagonist was shown not to reduce the increase in extracellular dopamine in the nucleus accumbens after amphetamine (10). Recent studies have also shown that MK-801 does not prevent MA-stimulated DA release from striatal slices (2), consistent with the fact that MK-801 is a poor inhibitor of DA uptake in vitro (24,31).

It is also unlikely that behavioral sensitization was blocked by MK-801 or D-CPP-ene through interference with the development of conditioning of the effect of MA to a specific environment where the drug was given. The rats were repeatedly treated with MA and/or NMDA antagonists, and readministered with MA in their home cages. The dose of MA during the repeated treatment and that used in the challenge test were different. Therefore, it is assumed that conditioning variables were minimized in the present experiment.

In addition to blocking behavioral sensitization to amphetamine or MA, MK-801 has been shown to prevent MA-induced dopaminergic and serotonergic neurotoxicity (25,32) and MA-induced decreases in the number of DA uptake sites (21) and corticosteroid receptors (19). The NMDA antagonist has also been reported to prevent morphine tolerance and dependence (35), sensitization (11,15), and tolerance (8) to cocaine, tolerance to ethanol (17), sensitization to nicotine (29), and behavioral changes induced by chronic treatment with an antidepressant (7,9), a dopamine (5) and a serotonin agonist (27). All these findings suggest a role of excitatory amino acids in behavioral changes and neuronal plasticity produced by long-term exposure to different psychotropic drugs.

Although interpretation from an animal model to a human psychosis must be extrapolated with great caution, it can be speculated that the NMDA receptor stimulation plays a role for the process of the evolution and recurrence of amphetamine-induced psychosis and that NMDA antagonists may have a potential to block the process. Recent evidence suggests that overactivity of glutamatergic neurons may contribute to the progress of neurodegenerative diseases such as Parkinson's disease, and antagonists of glutamate receptors may modify the neurodegenerative process (20).

The present study also examined whether repeated administration of NMDA antagonists would result in supersensitivity or tolerance in their locomotor activating effects. Consistent with Dall'Olio et al. (6), who showed that MK-801-induced hyperactivity was no longer observed either during 21 daily treatment or 5 days after the treatment, we observed the rats treated with MK-801 exhibited a marked decrease in the motor activity elicited by subsequent MK-801 as compared to the rats treated with saline. Similarly, the rats treated with D-CPP-ene showed a reduction in the motor activity when subsequently challenged with D-CPP-ene compared with the rats treated with saline. Lower doses of MK-801 and D-CPP-ene (0.25 and 10 mg/kg, IP, respectively) were used on test days than treatment days (0.5 and 20 mg/kg, IP, respectively) to avoid ataxia and stereotyped behavior which could nonspecifically inhibit the motor activity measured by the infrared sensor. These results suggest that repeated treatments with both noncompetitive (MK-801) and competitive (D-CPP-ene) NMDA antagonists produce behavioral tolerance. The tolerance appeared to be long lasting, because it was observed 10–12 days after the end of the treatment. The results also suggest that treatment with MA 30 min following MK-801 or D-CPP-ene does not block the development of the behavioral tolerance, because the rats treated with MA in combination with each of the NMDA antagonists also showed a marked reduction in the motor activity induced by MK-801 or D-CPP-ene. The reason for the discrepancy with the report of Wolf and Khansa (37), indicating behavioral sensitization to MK-801 following repeated administration with MK-801, may reside in a difference of the treatment and challenge schedule with MK-801. Kuribara et al. (18) recently reported that repeated administration with MK-801 induced either argumentation or reduction in ambulation, depending on the doses of MK-801 given during treatment.

We also examined whether cross-sensitization would occur between MA and MK-801 or D-CPP-ene. It was demonstrated that repeated administration of MA produces neither behavioral supersensitivity nor tolerance to NMDA antagonists, because the rats treated with MA did not show a difference compared with those treated with saline in the motor activity elicited by either MK-801 or D-CPP-ene. Likewise, repeated administration with NMDA antagonists appears to induce neither behavioral supersensitivity nor tolerance in the sensitivity to MA, because the rats treated with either MK-801 or D-CPP-ene indicated a similar response to MA compared with those treated with saline. It seems that sensitization to MA and tolerance to NMDA antagonists occur via different mechanisms.

In summary, the present study suggests that both competitive and noncompetitive NMDA antagonists block sensitization to MA and that repeated administration with NMDA antagonists results in behavioral tolerance. Sensitization to MA and tolerance to NMDA antagonists seem to occur via different mechanisms.

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