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Involvement of *N*-Methyl-D-Aspartate (NMDA) Receptors in Noncompetitive NMDA Receptor Antagonist-Induced Hyperlocomotion in Mice

MASAHIRO IRIFUNE, TAKAO SHIMIZU, MASAHIRO NOMOTO AND TAKEO FUKUDA[1]

Department of Pharmacology, Faculty of Medicine, Kagoshima University, Kagoshima 890, Japan

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IRIFUNE, M., T. SHIMIZU, M. NOMOTO AND T. FUKUDA. *Involvement of* N-*methyl-D-aspartate (NMDA) receptors in noncompetitive NMDA receptor antagonist-induced hyperlocomotion in mice.* PHARMACOL BIOCHEM BEHAV **51**(2/3) 291–296, 1995.—The role of the *N*-methyl-D-aspartate (NMDA) receptors in hyperlocomotion induced by (+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine hydrogen maleate (MK-801), a potent and selective noncompetitive NMDA receptor antagonist, was examined in male ddY mice. A low dose of MK-801 [0.2 mg/kg, intraperitoneally (IP)] produced a marked increase in locomotor activity without obvious staggering gait. In contrast, a high dose (1 mg/kg, IP) induced a typical motor syndrome characterized by increased locomotor activity, stereotyped behavior, and severe ataxia. NMDA (60–120 mg/kg, IP), an NMDA receptor agonist, dose dependently antagonized hyperlocomotion induced by a low dose of MK-801 (0.2 mg/kg). However, even a high convulsive dose of NMDA (240 mg/kg, IP) could not completely antagonize the hyperactivity induced by MK-801. On the other hand, neither a high dose of *N*-methyl-L-aspartate (400 mg/kg, IP), a stereoisomer of NMDA, nor a critical subconvulsive dose of kainate (10 mg/kg, IP), a non-NMDA receptor agonist, reversed MK-801-induced hyperlocomotion. The activity induced by MK-801 was potently suppressed by low doses of haloperidol (0.05–0.1 mg/kg, IP), a dopamine (DA) receptor antagonist, in a dose-dependent manner. These data for MK-801 were similar to those for phencyclidine and ketamine, other noncompetitive NMDA receptor antagonists. These results suggest that noncompetitive NMDA receptor antagonist-induced hyperlocomotion is mediated, at least in part, by NMDA receptor antagonism, although this hyperactivity may also involve dopaminergic mechanisms through indirect (perhaps by reducing NMDA receptor-mediated neurotransmission) and/or direct (by inhibiting DA uptake) effects on DA neurons.

Locomotor activity *N*-Methyl-D-aspartate receptor Dopamine receptor MK-801 Phencyclidine Ketamine Haloperidol Mouse

MK-801[(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine hydrogen maleate] was originally described as a potential anticonvulsant agent with an unknown mechanism of action (6). More recently, it has been shown that MK-801 is a highly potent and selective noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist (28). MK-801 produces a complex behavioral syndrome in rodents, including hyperlocomotion (15,17), as in other noncompetitive NMDA receptor antagonists such as phencyclidine and ketamine (1,5). It is well known that dopaminergic mechanisms play an important role in mediating locomotor activity (10). Phencyclidine and ketamine inhibit the uptake of dopamine (DA), and are also able to enhance the release of DA less potently (13,16). Therefore, these indirect DA receptor agonist actions of phencyclidine and ketamine may cause an increase in locomotor activity. In contrast, MK-801 is strikingly less potent than phencyclidine as an inhibitor of DA uptake (26), whereas MK-801 increases locomotor activity much more intensely than does phencyclidine (11). These findings indicate that MK-801-induced hyperlocomotion involves other neuronal mechanisms than indirect DA receptor agonist actions.

The excitatory amino acid (EAA) receptors are classified into two major classes: NMDA receptors and non-NMDA receptors. MK-801 is known to be a selective noncompetitive NMDA receptor antagonist that has been identified through electrophysiologic (21) and behavioral (29) techniques. Therefore, in this study, to elucidate the role of the NMDA receptor in MK-801-induced hyperlocomotion, we examined behaviorally whether the NMDA receptor agonist could antagonize hyperactivity induced by MK-801.

[1] To whom requests for reprints should be addressed.

METHOD

Animals

Adult male ddY mice (Kuroda Junkei Doubutsu Ltd., Kumanoto, Japan) weighing 36–52 g were used. Each animal was used only once, and we conducted only one trial per animal. The animals were housed with free access to food and water in an air-conditioned room with a temperature of 22–24°C and humidity of 45–55% and maintained under a constant 12 L : 12 D cycle (lights on at 0700 h). All behavioral experiments were performed between 1000 and 1800 h. This study was carried out after approval from the Committee of Animal Experimentation, Faculty of Medicine, Kagoshima University.

Locomotor Activity

Locomotor activity was measured with four circular activity cages (49 cm diameter × 26.5 cm high). Each cage was equipped with three photocell sensor units mounted on the outer wall at equal distances 2 cm above the floor. Interruptions of the infrared light beams were recorded on electromechanical counters located at a distance from the activity cages and automatically printed every 10 min. Mice were individually placed in their cages and acclimatized to the cage for 30 min, administered MK-801 IP (0.05–1 mg/kg), phencyclidine (5 mg/kg), ketamine (30 mg/kg), or 0.9% saline, and then returned for an additional 3-h test period.

Righting Reflex and Ataxia

Mice were examined individually in a circular glass beaker (13.5 cm diameter × 19 cm high). After IP administration of MK-801 (0.2–1 mg/kg), phencyclidine (5 mg/kg), or ketamine (30 and 150 mg/kg), we hand-inclined the beaker three times at each recording time. Righting reflex and ataxia were recorded and scored every 3 min after the injection for 2 h. These behavioral changes were evaluated according to the rating scale of Boast et al. (2) with minor modifications: a score of 0 indicated no obvious ataxia; +1 indicated staggering gait during locomotion but a normal righting reflex; +2 indicated that the mouse righted itself within 2 s on all three trials but the hindlimb was raised (slightly impaired righting reflex); +3 indicated that the latency to righting was > 2 s but < 10 s at the best response in three trials (moderately or severely impaired righting reflex); +4 corresponded to the absence of this reflex (no righting within 10 s on all three trials).

Drugs

MK-801 hydrogen maleate and ketamine hydrochloride were purchased from Research Biochemicals Inc. (Wayland, MA); *N*-methyl-D-aspartic acid (NMDA), *N*-methyl-L-aspartic acid (NMLA), and kainic acid (KA) were from Sigma Chemical Co. (St. Louis, MO); haloperidol was from Yoshitomi Pharmaceutical Co. (Osaka, Japan). Phencyclidine hydrochloride was generously supplied by Dr. Toru Nishikawa (Division of Mental Disorder Research, National Institute of Neuroscience, NCNP, Tokyo, Japan).

All drugs were dissolved in 0.9% saline solution and administered IP in a volume of 5–10 ml/kg. In a preliminary study, critical subconvulsive doses of NMDA and KA were determined as follows: first, a high dose of NMDA or KA was administered one by one. When the mouse showed convulsions, we lowered the dose and tried it again. After some repetitions of this procedure, the dose that did not cause convulsions in several mice was considered to be the critical subconvulsive dose. The following behavioral changes induced by IP injection of various doses of NMDA were observed. Typically, lower doses of NMDA (60–120 mg/kg) produced tail licking or biting and hindlimb scratching. No mice showed convulsions. Higher doses (200–300 mg/kg) produced, in rapid order, tail licking, scratching, wild running, clonic convulsions, tonic seizures, and death. The episodes began several minutes after injection and evolved within 30 min. These observations are almost consistent with the data of Leander et al. (19). Subconvulsive doses of NMDA (60–120 mg/kg) were used in this study. A critical subconvulsive dose (10 mg/kg) was also used for KA, because NMDA receptor antagonists do not prevent KA-induced convulsions.

Statistical Analysis

The data were analyzed by one-way analysis of variance (ANOVA) with the wholly significant difference (WSD) test for cumulative data and two-way ANOVA with repeated measures on the treatment and time factors for time-course data. The results were considered statistically significant when $p < 0.05$.

RESULTS

Effects of MK-801 on Locomotor Activity

An IP administration of MK-801 in mice increased total locomotor counts for 3 h in a dose-dependent fashion [$F(5, 56) = 12.36$, $p < 0.01$], and these effects were significant at doses of 0.2–1 mg/kg (Fig. 1A). Figure 1B shows the time-course effects on locomotor activity. At a dose of 0.2 mg/kg, locomotor activity was unchanged during the first 10 min, after which activity rapidly increased reaching a peak at 50 min. Thereafter, the activity gradually declined and returned to the control level at 150 min after the injection. No obvious staggering gait was seen at this dose. In contrast, 1 mg/kg of MK-801 very gradually increased locomotor activity, and the activity reached a peak at approximately 3 h after the injection. The mice showed stereotyped behavior and severe ataxia, and exhibited a slightly impaired righting reflex.

Effects of Noncompetitive NMDA Receptor Antagonists on Righting Reflex and Ataxia

Figure 2 shows the time-course effects of MK-801, phencyclidine, and ketamine on the righting reflex and ataxia. MK-801 at a dose of 0.2 mg/kg induced no evident effect. MK-801 at 1 mg/kg produced a peak effect at 18 min postinjection. Thereafter, the effect declined gradually; however, the mice did not return to normal throughout the recording for 2 h. At the peak, the mice showed a score of +2, which indicates continuous staggering gait and slightly impaired righting reflex. However, no mice showed the absence of righting reflex (Fig. 2A). Phencyclidine at 5 mg/kg induced no obvious ataxia. Ketamine at 30 mg/kg produced slight and continuous staggering gait during the first 10 min, but the mice returned to a normal condition within 15 min. In contrast, ketamine at 150 mg/kg produced a peak at 6 min; at the peak the mice completely lost their righting reflex (shown as a score of +4). A score of +4 was considered to indicate sleeping. The sleeping time from 150 mg/kg of ketamine was 19.0 ± 3.1 min (mean ± SEM, $n = 6$). Thereafter, the effect declined gradually and the mice returned to normal at approximately 90 min after the injection (Fig. 2B).

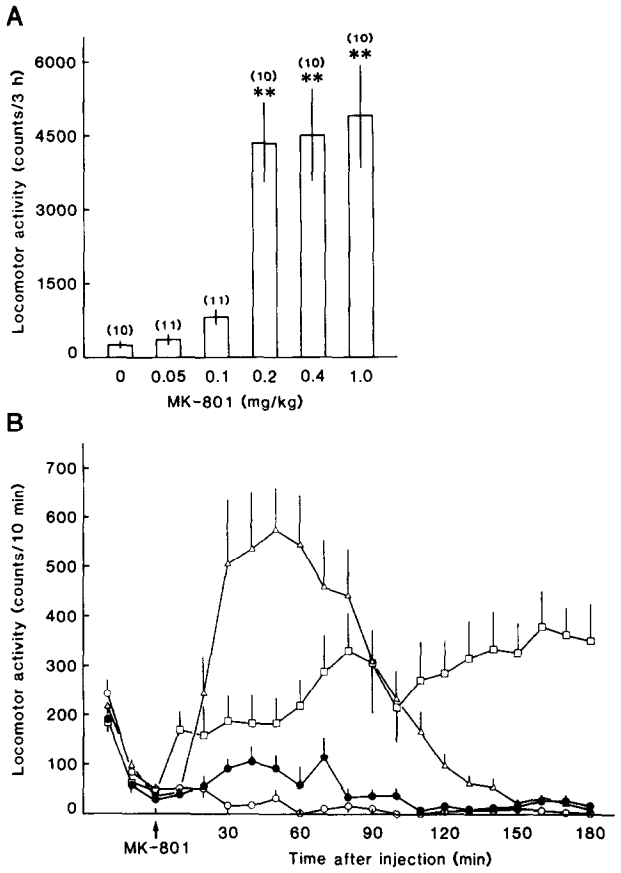

FIG. 1. Effects of MK-801 on locomotor activity in mice. Animals were administered IP with various doses of MK-801 [●, 0.1 mg/kg; △, 0.2 mg/kg; and □, 1 mg/kg; (B)] or vehicle saline [○; (B)] 30 min after mice were placed in the test cage for acclimatization. (A) Cumulative data. The cumulative locomotor counts were determined to be the total of each 10-min count up to 3 h. Each bar represents the mean ± SEM. Numbers in parentheses indicate the number of animals used in each experiment. $^{**}p < 0.01$ compared to vehicle control mice, one-way ANOVA with WSD test. (B) Time-course data. Each point represents the mean ± SEM of 10–11 animals. For points without a vertical bar, SEM is within the symbol.

Effects of EAA Receptor Agonists on MK-801-Induced Hyperlocomotion

Figure 3 demonstrates the time-course effects of NMDA on hyperlocomotion induced by an IP injection of 0.2 mg/kg of MK-801, which produced no obvious ataxia. NMDA (60–120 mg/kg, IP) antagonized MK-801-induced hyperactivity in a dose-dependent manner, resulting in a significant dose × time interaction with respect to saline [$F(17, 431) = 2.01$, $p < 0.05$] and [$F(17, 431) = 3.90$, $p < 0.01$] for 60 and 120 mg/kg, respectively. A higher dose of NMDA (120 mg/kg) was more potent than a lower dose (60 mg/kg). The lower dose had a shorter effect, but was equipotent to the higher dose up to 40 min after the injection. The effect of the higher dose continued up to 100 min. However, even the higher dose of NMDA could not completely reverse the action of MK-801. At these doses, on its own NMDA did not change the animals' spontaneous locomotor activity [$F(2, 26) = 0.74$, $p > 0.05$]. In contrast, neither a high dose of NMLA (400 mg/kg, IP), a stereoisomer of NMDA, nor a critical subconvulsive dose of KA (10 mg/kg, IP), a non-NMDA receptor agonist, reversed MK-801-induced hyperlocomotion [$F(2, 24) = 0.61$, $p > 0.05$] (Fig. 4).

Effects of NMDA on Phencyclidine- and Ketamine-Induced Hyperlocomotion

An IP injection of 5 mg/kg of phencyclidine, another noncompetitive NMDA receptor antagonist, produced peak locomotion within the first 20 min. Thereafter, the activity gradually declined and returned to the control level at 110 min after the injection. This dose of phencyclidine was almost equivalent to 0.2 mg/kg of MK-801, regarding effects on locomotor activity, although phencyclidine was slightly less potent. Total locomotor activity counts for 3 h produced by phencyclidine (5 mg/kg) vs. those by MK-801 (0.2 mg/kg) were 3425.3 ± 396.1 ($n = 15$) vs. 4443.4 ± 507.2 ($n = 11$). Phencyclidine at 5 mg/kg, as well as MK-801 at 0.2 mg/kg, did not induce ataxic gait (Fig. 2). NMDA (60–120 mg/kg, IP) dose dependently reversed phencyclidine-induced hyperactivity, resulting in a significant dose × time interaction between a dose of 120 mg/kg and saline [$F(17, 431) = 4.39$, $p < 0.01$]. No significant dose × time interaction between a dose of 60 mg/kg and saline was detected [$F(17, 431) = 1.16$, $p > 0.05$] (Fig. 5A). The peak locomotion of 30 mg/kg of ketamine occurred within the first 20 min, with a rapid decline afterward. At this dose, the mice showed slight and continuous staggering gait during the first 10 min (Fig. 2). Locomotion induced by this dose of ketamine was much less than that produced by either

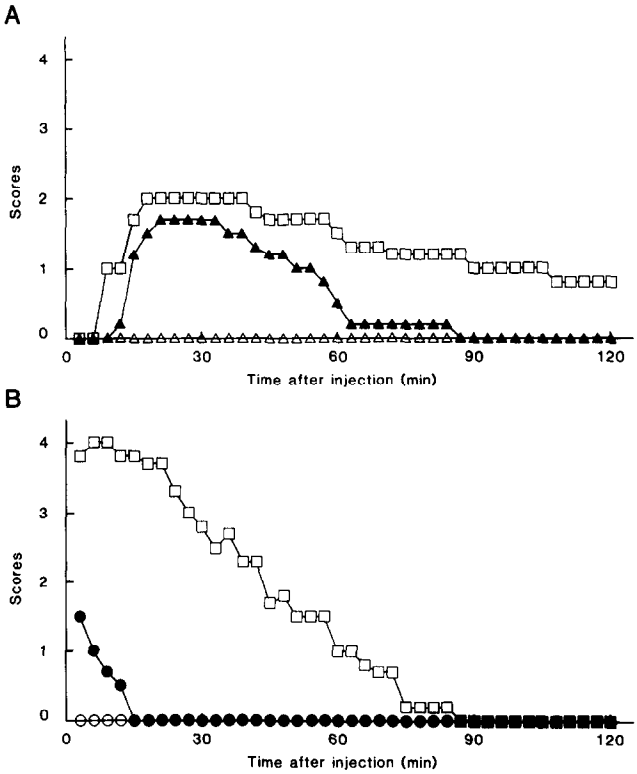

FIG. 2. Time-course effects of MK-801, phencyclidine, and ketamine on righting reflex and ataxia in mice. Animals were administered IP with MK-801 [△, 0.2 mg/kg; ▲, 0.4 mg/kg; and □, 1 mg/kg; (A)], phencyclidine [○, 5 mg/kg; (B)] or ketamine [●, 30 mg/kg; and □ 150 mg/kg; (B)]. Each point represents the mean score of six animals.

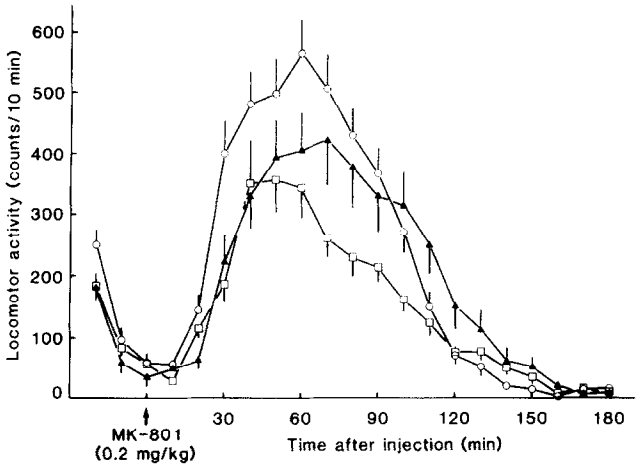

FIG. 3. Time-course effects of NMDA on hyperlocomotion induced by IP administration of 0.2 mg/kg of MK-801 in mice. Various doses of NMDA (▲, 60 mg/kg; and □ 120 mg/kg) or vehicle saline (○) were administered IP simultaneously with MK-801. Each point represents the mean ± SEM of 12 animals. For points without a vertical bar, SEM is within the symbol.

phencyclidine (5 mg/kg) or MK-801 (0.2 mg/kg). In contrast, a higher dose of ketamine (150 mg/kg) produced hyperlocomotion equipotent to 5 mg/kg of phencyclidine. Total counts by 150 mg/kg of ketamine vs. those by 5 mg/kg of phencyclidine were 3056.6 ± 531.4 (n = 10) vs. 3425.3 ± 396.1 (n = 15). However, the higher dose of ketamine also induced anesthesia (Fig. 2), and hyperlocomotion occurred after anesthetic phase in contrast to hyperactivity caused by a low dose of either ketamine (30 mg/kg), phencyclidine (5 mg/kg), or MK-801 (0.2 mg/kg). Therefore, the properties of hyperlocomotion produced by an anesthetic dose of ketamine may be different from those produced by a lower dose. For this reason,

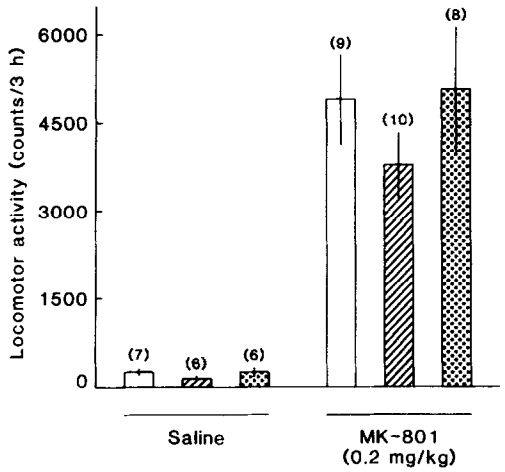

FIG. 4. Effects of NMLA (hatched bars, 400 mg/kg) and kainate (dotted bars, 10 mg/kg) on hyperlocomotion induced by IP administration of 0.2 mg/kg of MK-801 in mice. All drugs or vehicle saline (open bars) were administered IP simultaneously with MK-801 or saline. The cumulative locomotor counts were determined as the total of each 10-min count up to 3 h. Each bar represents the mean ± SEM. Numbers in parentheses indicate the number of animals used in each experiment.

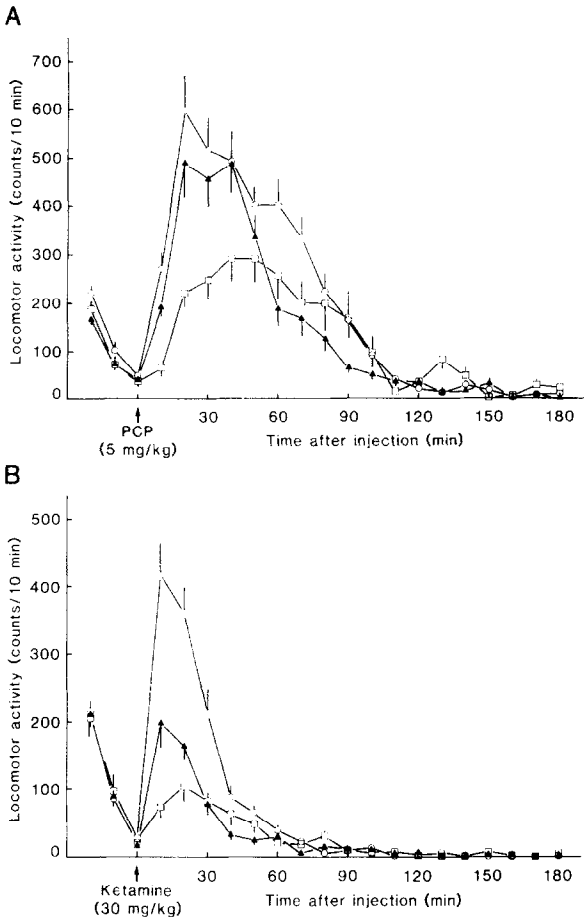

FIG. 5. Time-course effects of NMDA on hyperlocomotion induced by IP administration of 5 mg/kg of phencyclidine (PCP) (A) and 30 mg/kg of ketamine (B) in mice. Various doses of NMDA (▲, 60 mg/kg; and □, 120 mg/kg) or vehicle saline (○) were administered IP simultaneously with phencyclidine or ketamine. Each point represents the mean ± SEM of 10–17 animals. For points without a vertical bar, SEM is within the symbol.

a dose of 30 mg/kg was used for ketamine in subsequent experiments. NMDA (60–120 mg/kg) also antagonized 30 mg/kg of ketamine-induced hyperlocomotion. Two-way ANOVA revealed that both the lower and higher doses of NMDA induced a significant dose × time interaction with respect to saline [$F(17, 503) = 5.77$, $p < 0.01$] and [$F(17, 359) = 12.48$, $p < 0.01$] for 60 and 120 mg/kg, respectively (Fig. 5B).

Effects of Haloperidol on Noncompetitive NMDA Receptor Antagonist-Induced Hyperlocomotion

Figure 6 shows the effects of the DA receptor antagonist, haloperidol, on MK-801-, phencyclidine-, and ketamine-induced hyperlocomotion in mice. The locomotor stimulatory effects produced by MK-801 (0.2 mg/kg, IP), phencyclidine (5 mg/kg, IP), and ketamine (30 mg/kg, IP) were potently suppressed at pretreatment with low doses of haloperidol (0.05–0.1 mg/kg, IP) in a dose-dependent manner [$F(2, 28) = 21.87$, $p < 0.01$], [$F(2, 33) = 12.95$, $p < 0.01$], and [$F(2, 46) = 13.58$, $p < 0.01$], respectively. Haloperidol at 0.05 or 0.1 mg/kg produced no overt behavioral change [$F(2, 47) = 2.85$, $p > 0.05$].

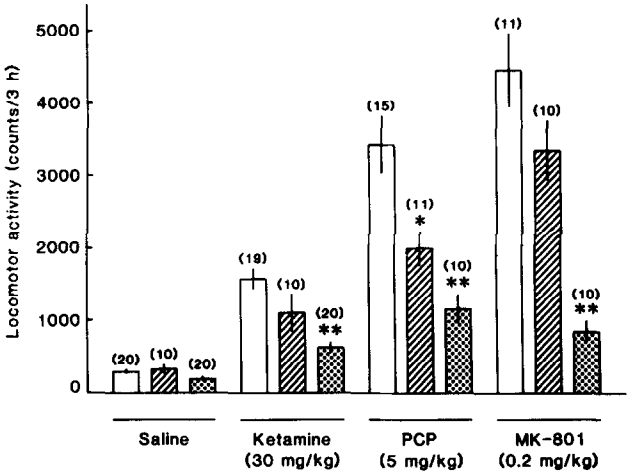

FIG. 6. Effects of haloperidol on hyperlocomotion induced by IP administration of 0.2 mg/kg of MK-801, 5 mg/kg of phencyclidine (PCP), and 30 mg/kg of ketamine in mice. Various doses of haloperidol (hatched bars, 0.05 mg/kg or dotted bars, 0.1 mg/kg) or vehicle saline (open bars) were given 30 min before MK-801, phencyclidine, or ketamine. The cumulative locomotor counts were determined as the total of each 10-min count up to 3 h. Each bar represents the mean ± SEM. Numbers in parentheses indicate the number of animals used in each experiment. $*p < 0.05$; $**p < 0.01$ compared to vehicle control mice, one-way ANOVA with WSD test.

DISCUSSION

The present study demonstrated that NMDA, an NMDA receptor agonist, antagonized MK-801-induced hyperlocomotion in a dose-dependent fashion in mice (Fig. 3). However, even the highest dose used could not completely antagonize the hyperactivity induced by MK-801; this may partly be due to the noncompetitive NMDA receptor antagonism of MK-801. By contrast, neither a high dose of NMLA, a stereoisomer of NMDA, nor a critical subconvulsive dose of KA, a non-NMDA receptor agonist, reversed MK-801-induced hyperlocomotion (Fig. 4). As shown in Fig. 5, NMDA also antagonized the hyperactivity induced by phencyclidine and ketamine, other noncompetitive NMDA receptor antagonists, in a dose-dependent manner. These results indicate that NMDA selectively antagonizes noncompetitive NMDA receptor antagonist-induced hyperlocomotion and that the effects of NMDA are stereoselective.

In this study, we administered NMDA IP. Moreau et al. (23) pointed out that neurologic and behavioral changes induced by the systemic administration of NMDA are not very reproducible, whereas changes induced by intracerebroventricular (ICV) injection of NMDA are. However, many tests on convulsions, anesthesia, learning, and memory have been performed by the use of an IP injection of NMDA (8,9,14,18,24). As shown in METHOD, we also observed that NMDA dose dependently produces a variety of behavioral changes, whereas an ICV injection of a very low dose of NMDA (1 nmol in 1 μl) yields seizures in <1 min (23). Furthermore, it has been reported that in learning and memory tests, even lower doses of NMDA (10–50 mg/kg, IP) are sufficiently effective (24). Therefore, we did not use the ICV injection technique but IP administration.

The NMDA receptor-channel complex consists of an agonist recognition site and a modulatory glycine site, which interact with their respective ligands in a cooperative manner to open an ion channel through which the influx of Ca^{2+} and Na^+ and efflux of K^+ take place. Inside the channel are Mg^{2+} and phencyclidine binding sites that, when occupied, prevent the ionic fluxes from occurring. It has been reported that high doses of glycine block phencyclidine-induced hyperactivity in mice (27) and that D-serine, a selective agonist at the glycine binding site, antagonizes phencyclidine- and MK-801-induction of stereotyped behavior and ataxia in rats (7). These findings seem to support the present study.

The density of NMDA binding sites is high in the CA1 region of the hippocampus and in superficial layers of the cerebral cortex, and is low in the striatum, cerebellum, and brainstem. The distribution of phencyclidine binding sites, which are believed to be the sites within the NMDA receptor channel, is similar to that of the NMDA receptors. Comparisons of NMDA receptor distribution with binding sites for the more selective phencyclidine binding ligand, MK-801, also show a high degree of correspondence (22). Recently, however, the presence of two high affinity binding sites for phencyclidine has been described: one is coupled to the NMDA receptor-channel complex and the other is associated with the DA uptake site. Phencyclidine is essentially nonselective between the two sites but has higher affinity for the site of the DA transporter. By contrast, MK-801 is the most selective for the NMDA recognition site but shows very low affinity for the DA uptake site (20,25). These binding data may support the neurochemical observation that MK-801 is strikingly less potent than phencyclidine as an inhibitor of DA uptake (26). Behaviorally, however, MK-801 produces hyperlocomotion (which is one of behavioral indices of postsynaptic DA receptor stimulation) much more intensely than does phencyclidine (11) (Fig. 6). These findings suggest that MK-801-induced hyperlocomotion is due to other neuronal mechanisms rather than indirect DA agonist actions.

It has been reported that MK-801 causes a pronounced locomotor stimulation in mice independently of catecholaminergic neurons (4). We also confirmed this by the finding that MK-801-induced hyperlocomotion was antagonized by NMDA. However, it might be that the locomotor activity induced by a reduction of NMDA receptor-mediated neurotransmission is not very strong, because even a high convulsive dose of NMDA (240 mg/kg, IP) did not antagonize entirely MK-801-induced hyperactivity (data not shown).

In contrast, low doses of haloperidol, a DA receptor antagonist, potently inhibited the hyperlocomotion induced by MK-801 as well as phencyclidine and ketamine (Fig. 6). These findings suggest that the interaction between dopaminergic and glutamatergic neurons is involved in NMDA receptor antagonist-induced hyperlocomotion. Several hypotheses on the interaction between dopaminergic and glutamatergic systems have been developed. First, activation of NMDA receptors located on nerve terminals of DA neurons may inhibit DA release. Consequently, NMDA receptor antagonism may result in increased DA release (12). Second, glutamate and DA may operate independently of each other on GABAergic inhibition of the excitatory thalamocortical pathway. This pathway forms an important part of a cortico-striato-thalamo-cortical feedback loop serving to protect the cortex from an overload of information and hyperarousal (3). These hypotheses may be applied to explain the actions of phencyclidine and ketamine, because these drugs have both properties of NMDA receptor antagonism and indirect DA receptor agonist actions. From the present study, however, these hypotheses seem insufficient to explain the mechanism of hyperactivity induced

by MK-801, because MK-801 is selective for the NMDA recognition site. To elucidate the exact mechanism of the selective NMDA receptor antagonist-induced hyperlocomotion, further investigations will be required.

In conclusion, noncompetitive NMDA receptor antagonist-induced hyperlocomotion involves, at least in part, a reduction of NMDA receptor-mediated neurotransmission.

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