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NMDA Receptor Antagonists Enhance 5-HT_2 Receptor-Mediated Behavior, Head-Twitch Response, in PCPA-Treated Mice

Hack-Seang Kim, In-Sook Park, Hwa-Kyung Lim and Hong-Seork Choi

College of Pharmacy, Chungbuk National University, Cheongju 361-763, Korea

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Previous work in our laboratory has shown that the N-methyl-D-aspartate (NMDA) receptor antagonists, AP-5, CPP, MK-801, ketamine, dextrorphan and dextromethorphan cause a pronounced enhancement of 5-hydroxytryptamine (5-HT)-induced head-twitch response (HTR) in intact mice, suggesting the involvement of NMDA receptors in the glutamatergic modulation of serotonergic function at the postsynaptic 5-HT_2 receptors. The purpose of this study was to extend our previous work on the behavioral interaction between glutamatergic and serotonergic receptors. In the present study, both competitive (AP-5 and CPP) and noncompeti- tive (MK-801, ketamine, dextrorphan and dextromethorphan) NMDA receptor antagonists markedly enhanced 5-HT-induced selective serotonergic behavior, HTR, in *p*-chlorophenylalanine (PCPA)-treated mice which were devoid of any involvement of indirect serotonergic function, to establish the involvement of the NMDA receptor in 5-HT-induced HTR at the postsynaptic 5-HT_2 receptors. In addition, the enhancement of 5-HT-induced HTR was inhibited by a dopamine agonist, apomorphine, NMDA receptor antagonist, NMDA and a serotonin 5-HT_2 receptor antagonist, cyproheptadine, in PCPA-treated mice. Therefore, the present results support our previous conclusion that the NMDA receptors play an important role in the glutamatergic modulation of serotonergic function at the postsynaptic 5-HT_2 receptors.

Key words : 5-Hydroxytryptamine, Head-twitch response, NMDA receptor antagonists, *p*-Chlorophenylalanine

INTRODUCTION

The *N*-methyl-*D*-aspartate (NMDA) receptor antagonists (AP-5, MK-801 and phencyclidine) induce a characteristic behavioral syndrome in rats and mice, including hyperlocomotion, lateral head weaving, circling and ataxia (Kelley and Throne, 1992, Löscher *et al.*, 1993 and 1991, Löscher and Hönack, 1993 and 1992, Tricklebank *et al.*, 1989, Yamaguchi *et al.*, 1987). At least a part of these behavioral syndromes is thought to relate to interactions between glutamatergic and dopaminergic neurotransmission. There are evidences that the excitatory amino acids participate in the mechanism of release of dopamine and dopamine metabolism in several brain regions including the striatum (Bouyer *et al.*, 1984, Cheramy *et al.*, 1986, Krebs *et al.*, 1991). The potential interaction between glutamatergic and dopaminergic system has attracted much interest because of its possible implications for diseases such as schizophrenia and Parkinson's disease (Kulkarni and Verma, 1991, Lodge and Johnson, 1990).

Correspondence to: Hack-Seang Kim, Ph. D., Professor of Pharmacology, College of Pharmacy, Chungbuk National University, Cheongju 361-763, Korea

However, there are several studies showing that MK-801, in addition to its effects on dopaminergic pathways, may also affect other monoamine transmitter systems in the brain. Only a few studies investigated the possibility that MK-801 might also interact with the serotonergic system, although several of the motor syndromes, e.g. head weaving, flat body posture, forepaw treading and hyperlocomotion, induced by MK-801 in rodents resemble the characteristic pattern induced by 5-hydroxytryptamine (5-HT).

While an interaction with dopaminergic pathways contributes to these actions induced by the NMDA receptor antagonists, there are also evidences for an involvement of serotonergic mechanisms. The infusion of NMDA into the caudate of anaesthetized cats caused a decrease in extracellular 5-HT and NMDA receptor antagonists stimulate 5-HT turnover in several brain regions. In addition, several of the behavioral alterations such as head weaving, forepaw treading and flat body posture, induced by the NMDA receptor antagonist closely resemble the behavioral syndromes induced by 5-HT_{1A} receptor agonists (Goodwin and Green, 1985, Löscher *et al.*, 1993 and 1991, Löscher and Hönack, 1993 and 1992, Tricklebank *et al.*, 1985a and 1985b, Yamaguchi *et al.*, 1987).

The behavioral serotonergic syndromes induced by MK-801 were blocked by a 5-HT_{1A} receptor antagonist, ipsapirone but not by a 5-HT_2 receptor antagonist, ritanserin (Löscher and Hönack, 1992). Thus, it is likely that these behavioral interactions may be closely related to the serotonergic 5-HT_{1A} activation mediated via the glutamatergic receptor. However, behavioral interaction between glutamatergic and serotonergic 5-HT_2 receptors has not been well characterized yet.

Meanwhile, it has been recognized that the head-twitch response (HTR) induced by 5-HT in mice was mediated via 5-HT_2 receptor but not via 5-HT1A receptor. Our previous studies have shown that the NMDA receptor antagonists (AP-5, CPP, MK-801, ketamine, dextrorphan and dextromethorphan) markedly enhanced 5-HT-induced HTR in intact mice, whereas NMDA, cyproheptadine and apomorphine inhibited 5-HT-induced HTR in intact mice (Kim *et al.*, 1998).

In the present study, in order to devoid of any involvement of indirect serotonergic function and to establish the involvement of the NMDA receptor in 5-HT-induced HTR at the postsynaptic 5-HT_2 receptors, we investigated whether or not the NMDA receptor antagonists inhibited 5-HT-induced HTR in mice pretreated with *p*-chlorophenylalanine (PCPA), the irreversible tryptophan hydroxylase inhibitor.

MATERIALS AND METHODS

Animals

The animals used were ICR male mice (Samyuk Laboratory Animal Inc., Osan, Korea) weighing 20~25 g in a group of 12~15. They were housed in acrylfiber cages at a controlled room (temperature 22±3°C) and were maintained on a 12 hr light/dark cycle. They were given a solid diet and tap water ad libitum.

Drugs

(+) MK-801 hydrogen maleate, ketamine hydrochloride, dextrorphan tartrate, dextromethorphan hydrobromide, AP-5 [D(-)-2-amino-5-phosphonopentanoic acid], and CPP [D(-)-3-(2-carboxypiperazine-4-yl)-propylphosphonate] were obtained from Research Biochemical International (Boston MA, USA). Cyproheptadine hydrochloride, apomorphine hydrochloride, *p*-chlorophenylalanine, 5-hydroxytryptamine creatinine sulfate and *N*-methyl-*D*-aspartate were obtained from Sigma Chemical (St. Louis, MO, USA). PCPA was dissolved in 1% tween 80 in deionized water. Except for apomorphine that was dissolved in saline containing 0.1% ascorbic acid, all drugs were dissolved in physiological saline.

Measurement of 5-HT-induced head-twitch response (HTR) in mice

Intracerebral injection was made by insertion of Hamilton injection needle perpendicularly (3/8 in., 27 gauge) through the soft bone 1.5 mm to the right of the bregma on the coronal suture. The needle was attached to a Hamilton microsyringe and was inserted through a stainless-steel tube that acted as a stopper. The animal was placed into transparent plexiglas cylinders (20 cm diameter; 25 cm height) (Grahame-Smith, 1971). The HTR frequency was scored by an observer who was blind to the drug treatment for 2 min at 10 min after the injection of 5-HT. The various challenge injections alone did not induce any HTR. Therefore, the data of those are not presented in each figure.

To deplete serotonergic stores, all mice were pretreated with PCPA (400 mg/kg, ip) 6 hr and 30 min before the injection of 5-HT (Singleton and Marsden, 1981, Matsumoto *et al.*, 1997). Especially when examined the effects of AP-5, CPP and NMDA, intracerebral injections of 5-HT were made right after the injections of AP-5, CPP and NMDA through the soft bone 1.5 mm to the left of bregma. Apomorphine (sc) was administered to mice 5 min before, ketamine and dextromethorphan (ip) were 30 min before, and dextrorphan and cyproheptadine (ip) were 1 hr before the icv injection of 5-HT, respectively. The intracerebral injections were verified after each experiment by gross examination of the brain following injection of dye.

In our previous study, 80 μg/mouse of 5-HT (icv) appeared to be a submaximal dose for inducing HTR in intact mice (Kim *et al.*, 1998). However, present experiment established the dose-response characteristics for stimulation of the HTR by a single administration of 5-HT (12.5, 25, 30 and 50 μg/10 μl/mouse, icv) in PCPA-treated mice when compared to saline group because the postsynaptic 5-HT_2 receptor supersensitivity was developed in PCPA-treated mice (data not shown). 50 μg/mouse of 5-HT showed the maximal effects of HTR in PCPA-treated mice, and the test of inhibition of HTR was conducted with this dose of 5-HT. Enhancement of HTR was assessed using a dose of 30 μg of 5-HT/mouse, at which about 40% of maximal HTR was observed in PCPA-treated mice.

Statistics

The data are expressed as means±SEM. The statistical significance of drug effects was analyzed by non-parametric Mann-Whitney U-test.

RESULTS

Enhanced effects of competitive NMDA receptor antagonists on 5-HT-induced HTR in PCPA-treated mice

AP-5 (0.25, 0.5 and 1.0 μg/10 μl/mouse, icv) administered just prior to the injection of 5-HT (30 μg/10 μl/mouse, icv) increased the HTR compared to that of control group (Fig. 1A). 5-HT-induced HTR was also

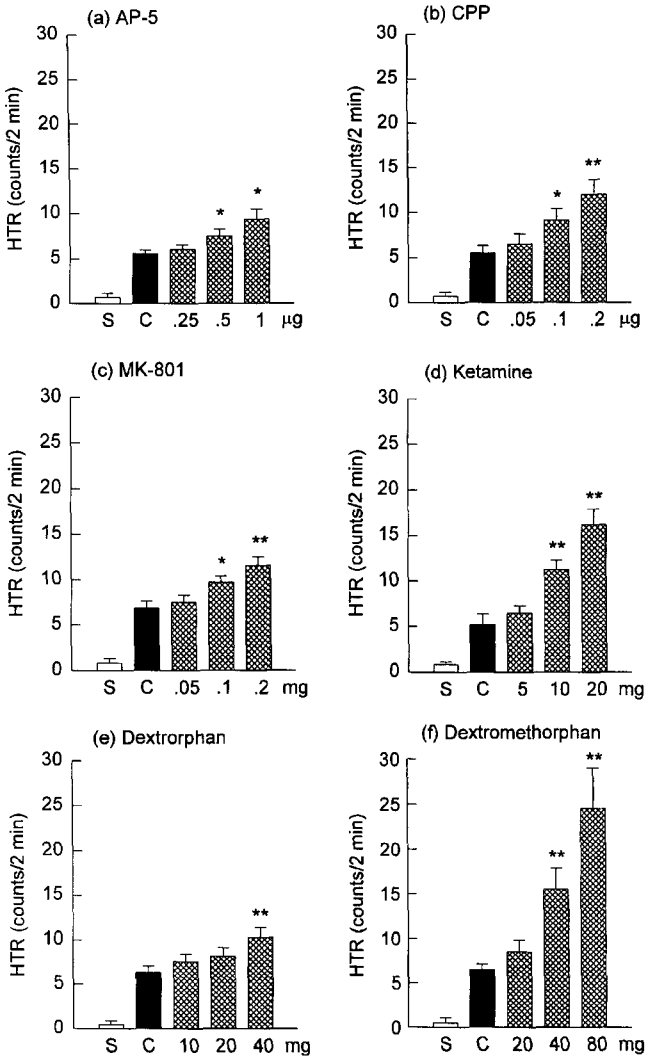

Fig. 1. Effects of AP-5, CPP, MK-801, ketamine, dextrorphan and dextromethorphan on 5-HT-induced head-twitch response (HTR) in PCPA-treated mice. AP-5 and CPP were administered (icv) to PCPA-treated mice just before the injection of 5-HT (30 μg/10 μl/mouse, icv). MK-801, ketamine and dextromethorphan were administered (ip) to PCPA-treated mice 30min before the injection of 5-HT but dextrorphan was administered 1 hr before. PCPA (400 mg/kg, ip) was administered to mice twice 6 hr and 30 min prior to the test of HTR. Each value is expressed at the mean±SEM of at least 15 mice. *p<0.05, **p <0.01, compared with the control group (C). S; Saline.

enhanced by injection of CPP (0.05, 0.1 and 0.2 μg/mouse, icv) when compared to that of control group (Fig. 1B).

Enhanced effects of noncompetitive NMDA receptor antagonists on 5-HT-induced HTR in PCPA-treated mice

The noncompetitive NMDA receptor antagonist, MK-801 (0.05, 0.1 and 0.2 mg/kg, ip) administered 30 min before the injection of 5-HT (30 μg/10 μl/mouse, icv) increased the 5-HT-induced HTR at lower doses in PCPA-pretreated mice (Fig. 1C). In addition, it appeared that 5-HT-induced HTR was also markedly enhanced by low doses of three different noncompetitive NMDA receptor antagonists, ketamine (5, 10 and 20 mg/kg, ip), dextrorphan (10, 20 and 40 mg/kg, ip) and dextromethorphan (20, 40 and 80 mg/kg, ip) (Fig. 1D, E and F).

Decreased effects of 5-HT2 antagonist cyproheptadine, dopaminergic receptor agonist apomorphine on 5-HT-induced HTR in PCPA-treated mice

The 5-HT_2 receptor antagonist, cyproheptadine (0.3, 1 and 3 mg/kg, ip), administered 1 hr prior to the injection of 5-HT (50 μg/10 μl/mouse, icv) inhibited the 5-HT-induced HTR when compared to that of control group (Fig. 2A). In addition, the dopaminergic receptor agonist, apomorphine (0.5, 1 and 2 mg/kg, sc) administered 30 min before the injection of 5-HT also attenuated the 5-HT-induced HTR in PCPA-pretreated mice (Fig. 2B).

Decreased effects of NMDA receptor agonist NMDA on 5-HT-induced HTR in PCPA-treated mice

The NMDA receptor agonist, NMDA (0.01, 0.025 and 0.05 μg/mouse, icv), administered just prior to the injection of 5-HT (50 μg/10 μl/mouse) inhibited the 5-HT-induced HTR in PCPA-pretreated mice compared to that of control group (Fig. 2C).

DISCUSSION

The present results demonstrated that the NMDA receptor antagonists (AP-5, CPP, MK-801, ketamine, dextrorphan and dextromethorphan) markedly enhanced 5-HT-induced HTR in mice pretreated with PCPA, a depletor of 5-HT. While the NMDA receptor agonist (NMDA), the 5-HT_2 receptor antagonist (cyproheptadine) and the dopaminergic receptor agonist (apomorphine) inhibited 5-HT-induced HTR in PCPA-treated mice. The HTR induced by 5-HT in mice is due to the stimulation of 5-HT_2 receptors in the central nervous system. Previous work in our laboratory has shown that the NMDA receptor antagonists (AP-5, CPP, MK-801, ketamine, dextrorphan and dextromethorphan) markedly enhanced 5-HT-induced HTR in intact mice (Kim *et al.*, 1998). These enhancements of 5-HT-induced HTR suggest the involvement of NMDA receptors in the glutamatergic modulation of serotonergic function at the postsynaptic 5-HT_2 receptors. In addition, 5-HT-induced HTR was inhibited by a dopaminergic receptor agonist, apomorphine, a 5-HT receptor antagonist, cyproheptadine and a NMDA agonist, NMDA in the present study.

The results suggest that the blockade of NMDA receptor resulted in enhancement of 5-HT-induced

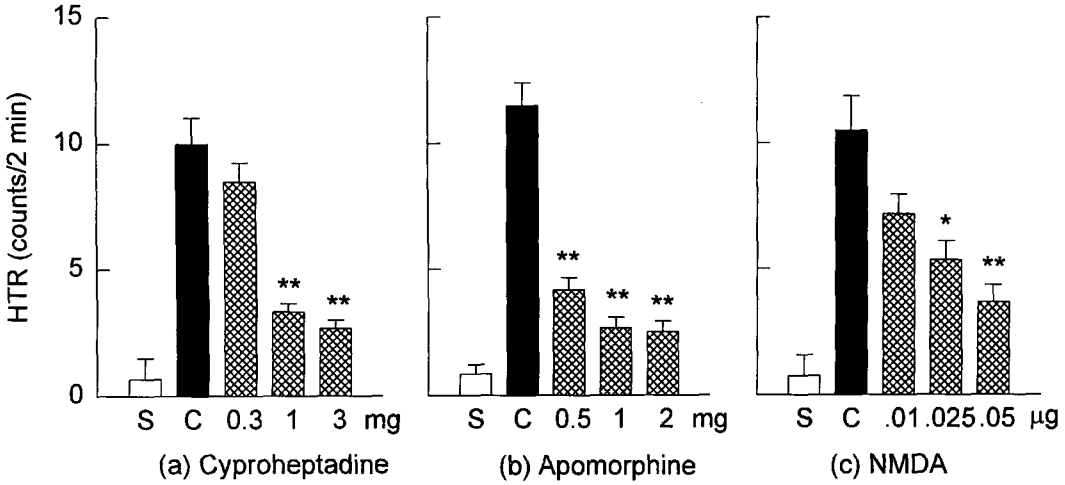

Fig. 2. Effects of cyproheptadine, apomorphine and NMDA on 5-HT-induced head-twitch response (HTR) in PCPA-treated mice. Cyproheptadine (sc), apomorphine (ip) and NMDA (icv) were administered to PCPA-treated mice 1 hr, 5 min and just before the injection of 5-HT (50 μg/10 μl/mouse, icv), respectively. PCPA (400 mg/kg, ip) was administered to mice twice 6 hr and 30 min prior to the test of HTR. Each value is expressed at the mean±SEM of at least 15 mice. *p<0.05, **p<0.01 compared with the control group (C). S; Saline.

HTR and 5-HT_2 receptor supersensitivity was developed in PCPA-treated mice. The enhancement of NMDA receptor antagonists on 5-HT-induced HTR in PCPA-treated mice without any involvement of indirect monoamines support the notion that NMDA receptors play important roles in the glutamatergic modulation of serotonergic function at 5-HT_2 receptors in intact mice (Kim *et al.*, 1998).

It is thought that the HTR induced by 5-HT in mice is due to stimulation of CNS 5-HT_2 receptors (Goodwin and Green, 1985). Therefore, the present results suggest that glutamatergic neurotransmission may modulate 5-HT function at the 5-HT_2 receptor. These are the first data available regarding glutamatergic modulation of serotonergic function at the 5-HT_2 receptors in PCPA-treated mice. However, this study raises several issues concerning the synaptic arrangement of the interaction between glutamate and 5-HT_2 receptors. Their precise relationship is as yet undefined. However, it has been reported that dopamine receptor agonists, such as apomorphine, inhibit 5-HT-induced HTR in mice (Bedard and Pycock, 1977).

In addition, there is evidence that an enhancement of dopaminergic tone at the striatal level could be related to the reduced HTR to quipazine, a serotonergic receptor agonist (Dall'ollio *et al.*, 1989). These results are consistent with the present study, indicating that the enhancement of dopaminergic tone at the striatal level by apomorphine inhibits 5-HT-induced HTR in mice. Furthermore, it has been proposed that both glutamatergic and dopaminergic corticostriatal terminals make contact with the dendrites of striatal output cells, and this arrangement forms the basis of glutamatergic modulation of incoming dopaminergic cortical signals and subsequent influence on its outgoing signals (Bouyer *et al.*, 1984; Freund *et al.*, 1984; Kim *et al.*, 1996 and 1999; Smith and Bolam, 1990; Somogyi *et al.*, 1981; Totterdell and Smith, 1989). In considering the hypothesis of glutamatergic-dopaminergic axodendritic interaction, we presumed that apomorphine, a dopamine agonist, induces local dopaminergic activation and thus selectively amplifies information from its cortico-limbic area. Blockade of NMDA receptors attenuates activation of the output pathway and thereby lowers the general level of dopamine-induced activation (Hamilton *et al.*, 1986; Kelley and Throne, 1992; Kim *et al.*, 1996 and 1999). In support of this, it has been reported that apomorphine-induced climbing behavior in mice, representative of dopaminergic behavior, is inhibited by noncompetitive NMDA receptor antagonists (Kim *et al.*, 1996 and 1999). In addition to the direct glutamatergic-serotonergic interactions, indirect glutamatergic-serotonergic interactions via dopaminergic neurons might be also involved in alterations of serotonergic turnover produced by NMDA receptor antagonists (Löscher *et al.*, 1993 and 1991; Löscher and Hönack, 1993).

The lowered general level of dopaminergic tone at the striatal level as a result of treatment with the NMDA receptor antagonists results in an increased intensity of serotonergic tone, explaining the behavioral serotonergic syndromes induced by NMDA receptor antagonists. In addition, inhibitory effects of NMDA receptor antagonists on 5-HT uptake could play a role in the enhancement of 5-HT-induced behaviors as Hiramatsu *et al.* (1989) have suggested that MK-801 inhibits 5-HT uptake. These appear to be neuroanatomical substrates for both potentiating and anta-

gonistic effects of NMDA receptor antagonists on dopaminergic stimulation (Alexander and Crutcher, 1990, Pan *et al.*, 1985). On this basis, the inhibitory effects of NMDA receptor antagonists on dopaminergic stimulation might also be involved in the enhancement of 5-HT-induced HTR in mice. Interneuronal substrates might thus exist for both potentiating effects of NMDA receptor antagonists on serotonergic stimulation and their inhibitory effects on dopaminergic stimulation. Consistent with this hypothesis, 5-HT-induced HTR was inhibited by a dopaminergic receptor agonist, apomorphine, and an NMDA receptor agonist, NMDA, as well as by a serotonergic 5-HT_2 receptor antagonist, cyproheptadine, in the present study.

The functional interactions between glutaminergic and serotonergic pathways are less well characterized than that with dopaminergic pathways, but, in the striatum, serotonin release seems to be under inhibitory glutamatergic control (Becquet *et al.*, 1990; Whitton *et al.*, 1994). Microdialysis experiments have shown that MK-801 increases not only serotonin metabolism but also its release in brain regions including the striatum (Löscher *et al.*, 1993 and 1991; Löscher and Hönack, 1993 and 1992; Whitton *et al.*, 1994). These results suggest that attenuation of glutamatergic-serotonergic interaction by NMDA receptor antagonists enhances serotonergic transmission at both 5-HT_{1A} receptors and 5-HT_2 receptors. Although postsynaptic 5-HT_{1A} receptors are thought to play a primary role in the behavioral syndromes induced by increased brain 5-HT level, 5-HT_2 receptors are also involved to a much lesser extent (Tricklebank *et al.*, 1985). The degree of serotonergic stimulation that induces head weaving through activation of the 5-HT_{1A} receptor is not sufficient to induce HTR activation of the 5-HT_2 receptor. Following treatment with NMDA antagonists, it is much easier to induce HTR when the 5-HT_2 receptors are stimulated by administration of additional 5-HT. In support of these observations, the behavioral serotonergic syndromes induced by the NMDA receptor antagonist, MK-801 are blocked by 5-HT_{1A} receptor antagonists including ipsapirone (Löscher and Hönack, 1992), (+)-WAY10035 (Löscher and Hönack, 1993) and CGP39551 (Löscher *et al.*, 1993), but not by 5-HT_2 receptor antagonist, ritanserin (Bedard and Pycock, 1977). Phencyclidine mainly produces head weaving at low doses and head twitches at high doses, respectively. Phencyclidine-induced head twitches and head weaving are blocked by pretreatment with ritanserin, a selective 5-HT_2 receptor antagonist, and with pindolol, a 5-HT_{1A} receptor antagonist, respectively (Yamaguchi *et al.*, 1987).

Therefore, the present results strongly support our previous conclusion that the NMDA receptors play important roles in the glutamatergic modulation of serotonergic function at the postsynaptic 5-HT_2 receptors.

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