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Involvement of nitric oxide in phencyclidine-induced hyperlocomotion in mice

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Abstract

The present study was undertaken to investigate the involvement of nitric oxide (NO) in the behaviors induced by 1-(1-phenylcyclohexyl) piperidine (phencyclidine; PCP) in mice, using N^G-nitro-L-arginine methyl ester (L-NAME), an inhibitor of NO synthase. PCP (1, 3, and 10 mg/kg s.c.) dose dependently induced hyperlocomotion and stereotyped behaviors, including sniffing, head movement, and ataxia, in mice. PCP also caused a marked deficit of motor coordination in mice, the effect being exerted in a dose-dependent manner. Although pretreatment with L-NAME (50 mg/kg i.p.) slightly enhanced the ataxia induced by PCP (3 mg/kg), it failed to modify other stereotyped behaviors and the lack of motor coordination induced by PCP (3 mg/kg). The hyperlocomotion induced by PCP (3 mg/kg) was significantly enhanced by L-NAME (5 and 50 mg/kg) and 7-nitro indazole (25 mg/kg), but not by D-NAME (50 mg/kg), a less active enantiomer of L-NAME. However, the behavioral changes induced by PCP, at the high dose, 10 mg/kg, were not enhanced by L-NAME and D-NAME. The enhancing effects of L-NAME on the PCP (3 mg/kg)-induced hyperlocomotion were significantly prevented by L-arginine (1 g/kg i.p.). However, D-arginine (1 g/kg i.p.) and L-lysine (1 g/kg i.p.) had no effect in this regard. These results suggested the involvement of central NO production in the mediation of PCP-induced behaviors, hyperlocomotion in particular, in mice.

Keywords: Phencyclidine; Nitric oxide (NO) synthase inhibitor; Ataxia; Locomotion; (Mouse)

1. Introduction

1-(1-Phenylcyclohexyl) piperidine (phencyclidine; PCP), a drug that is subject to widespread abuse, has been reported to induce psychomimetic effects in humans and a pattern of excitation and/or depression in animals. PCP has been reported to interact with many neurotransmitters, including catecholamines (Nabeshima et al., 1983; Tonge and Leonard, 1972), serotonin (Nabeshima et al., 1984, 1985, 1987; Smith et al., 1977; Tonge and Leonard, 1971), acetylcholine (Domino and Wilson, 1972), and opiates (Hiramatsu et al., 1986). Further, PCP also has potent non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonistic properties (Hiramatsu et al., 1989; Sagratella et al., 1987). In animals, PCP induces a characteristic behavioral syndrome, with ataxia, hyperactivity, lack of motor coordination, and stereotyped behaviors (Castellani and Adams, 1981; Sturgeon et al., 1979), which is thought to result, at least in part, from an interaction between glutamatergic and dopaminergic transmission (Kulkarni and Verma, 1991; Lodge and Johnson, 1990). This interaction suggests that an imbalance between glutamate and dopamine may be the underlying cause of neuropsychiatric disorders such as schizophrenia (Carlsson and Carlsson, 1990; Kulkarni and Verma, 1991; Wachtel and Turski, 1990). Further, the behavioral syndrome induced by PCP in animals has been proposed as an animal model of schizophrenia, being particularly suited to the search for antipsychotic drugs that are capable of abolishing symptoms caused by deficient glutamatergic transmission (Carlsson and Carlsson, 1990; Tiedtke et al., 1990). However, there is some evidence that PCP produces its behavioral effects not only through the reduction of neurotransmission at NMDA receptors or interactions between glutamatergic and dopaminergic systems, but also via other sys-

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tems, such as those described above (Carlsson and Carlsson, 1990; Löscher et al., 1991).

It has recently been reported that nitric oxide (NO) may be an important intracellular messenger in the nervous and immune systems (Collier and Vallance, 1989) and that NO may also operate as a neurotransmitter, particularly in the central nervous system (CNS) (Garthwaite et al., 1988). NO is produced from L-arginine by NO synthase (Palmer et al., 1988). This enzyme has been found in various neuronal populations, in particular in regions of the brain, such as the cerebellum, hippocampus, striatum, cortex, hypothalamus, mid brain, and medulla in the rat (Föstermann et al., 1990). NO formation can be blocked by selective enzyme inhibitors, such as N^G-nitro-L-arginine methyl ester (L-NAME) (Hecker et al., 1990). In the CNS, the activation of NMDA receptors has been shown to induce NO synthesis, which then activates soluble guanylate cyclase and leads to the formation of cyclic GMP. Further, NO synthase inhibitors prevent hippocampal long-term potentiation (O'Dell et al., 1991; Schuman and Madison, 1991) and NMDA-mediated neurotoxicity (Dawson et al., 1993; Haberny et al., 1992). Such effects have also been reported to be commonly induced by NMDA receptor antagonists such as 5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (dizocilpine; MK-801) and PCP, and these effects have been suggested to result from a reduced function of glutamatergic systems. Thus, it is possible that PCP and NO synthase inhibitors have some similar pharmacological properties in animals.

The present study was undertaken to investigate the possible role played by endogenous NO in PCP-induced behavioral changes by modulating the L-arginine/NO pathway.

2. Material and methods

2.1. Animals and environment

Male mice of the *ddY* strain (Japan SLC, Shizuoka, Japan), weighing 25–30 g at the beginning of the experiments, were used. The animals were housed in plastic cages, were given food (CE2, Clea Japan, Tokyo, Japan) and tap water ad libitum and were kept in a regulated environment (23 ± 1°C, 50 ± 5% humidity), with a 12/12 h light-dark cycle (light on at 9:00 a.m.).

2.2. Drugs

The following compounds were purchased from commercial sources: N^G-nitro-L-arginine methyl ester (L-NAME; Sigma, St. Louis, MO, USA), N^G-nitro-D-arginine methyl ester (D-NAME; Sigma), 7-nitro inda-

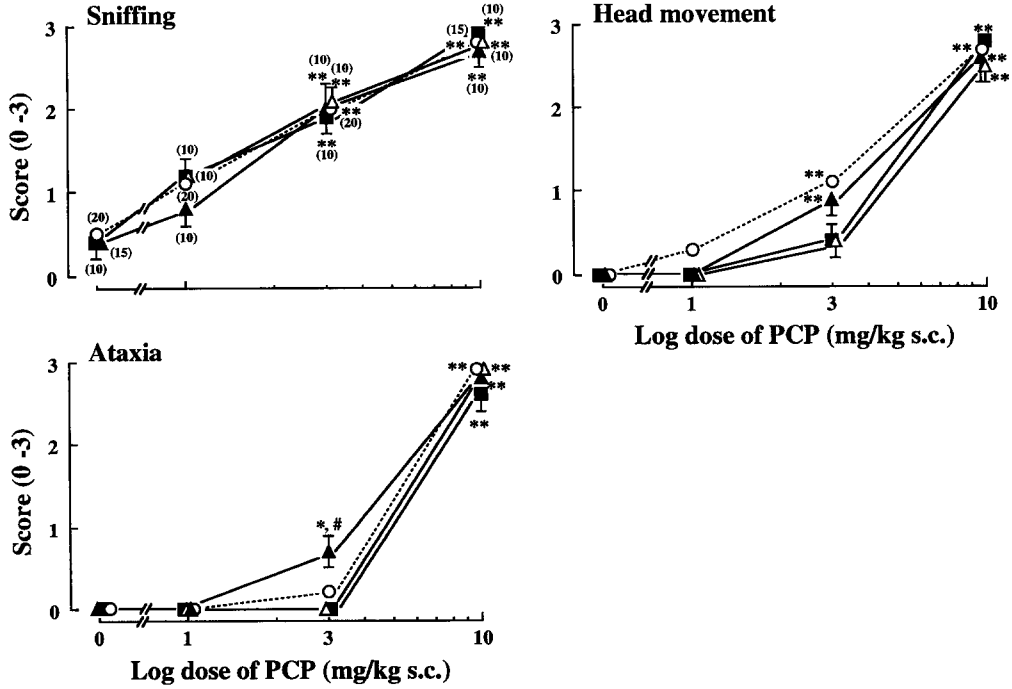

Fig. 1. Effects of L-NAME and D-NAME on stereotyped sniffing, head movement, and ataxia induced by PCP in mice. L-NAME (5 and 50 mg/kg i.p.), D-NAME (50 mg/kg i.p.), or saline was administered 15 min before treatment with PCP (1, 3 or 10 mg/kg s.c.). These behaviors were observed over a 3-min period beginning 30 min after PCP or saline treatment. Numbers in parentheses show the number of animals used. (○) saline, (△) L-NAME 5 mg/kg, (▲) L-NAME 50 mg/kg, (■) D-NAME 50 mg/kg. * $P < 0.05$, ** $P < 0.01$ vs. saline + saline. # $P < 0.01$ vs. saline + PCP (Dunn's multiple comparisons test).

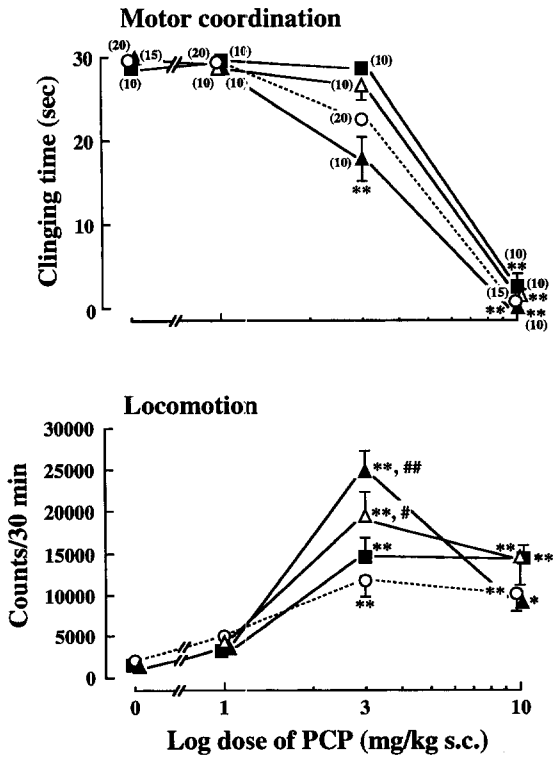

Fig. 2. Effects of L-NAME and D-NAME on the lack of motor coordination and the hyperlocomotion induced by PCP in mice. L-NAME (5 and 50 mg/kg i.p.), D-NAME (50 mg/kg i.p.), or saline was administered 15 min before treatment with PCP (1, 3 or 10 mg/kg s.c.). The locomotor count was recorded over a 30-min period beginning 30 min after PCP treatment, and the motor coordination test was carried out immediately after locomotion was scored, as described in the Materials and methods section. Numbers in parentheses show the number of animals used. (○) saline, (△) L-NAME 5 mg/kg, (▲) L-NAME 50 mg/kg, (■) D-NAME 50 mg/kg. * $P < 0.05$, ** $P < 0.01$ vs. saline + saline. # $P < 0.05$, ## $P < 0.01$ vs. saline + PCP (Dunnett's multiple comparisons test).

zole (Lancaster Synthesis, Lancashire, UK), L-arginine (Sigma), D-arginine (Sigma), and L-lysine (Sigma). 1-(1-Phenylcyclohexyl) piperidine hydrochloride (phencyclidine; PCP) was synthesized by us.

All compounds were dissolved in a 0.9% saline solution, except for 7-nitro indazole, which was suspended in arachis oil (Katayama Chem., Osaka, Japan) by sonication, and were administered intraperitoneally (i.p.) in a volume of 0.1 ml/10 g body weight, except for PCP, which was administered subcutaneously (s.c.).

All experiments were performed in accordance with the Guidelines for Animal Experiments of the Nagoya University School of Medicine.

2.3. Experimental schedule

The animals received saline, L-NAME (5 and 50 mg/kg i.p.), D-NAME (50 mg/kg i.p.), or 7-nitro indazole (5 and 25 mg/kg i.p.) 15 min before PCP (1, 3, and 10 mg/kg s.c.) treatment, and they were placed individually in a transparent acrylic cage (26 × 44 × 40 cm) immediately after the PCP treatment. Thirty minutes later, the degree of sniffing, head movement, and ataxia was assessed over a 3-min observation period in terms of scores ranging from 0 to 3 (0, none; 1, slight; 2, moderate; 3, marked). The locomotor count was recorded simultaneously, over a 30-min period, using digital counters with infrared cell sensors placed on the walls (SCANET SV-10, Toyo Sangyou, Toyama, Japan) (Kitaichi et al., 1994). Immediately after the measurement of locomotion, the animals were placed on a horizontal bar (30 cm high), and the time that each mouse clung to the bar in 3 trials was measured (cut-off time: 3 min).

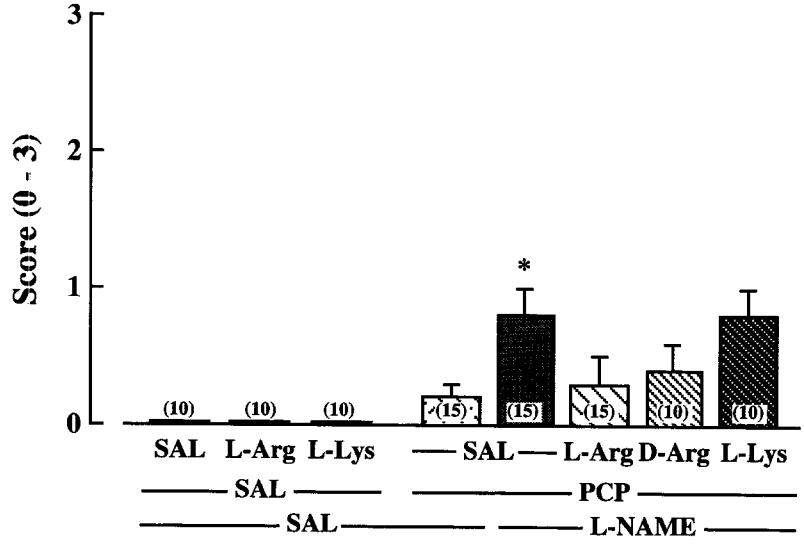

Fig. 3. Effects of L-arginine, D-arginine and L-lysine on the enhancement of PCP-induced ataxia induced by L-NAME in mice. L-Arginine (1 g/kg i.p.), D-arginine (1 g/kg i.p.), and L-lysine (1 g/kg i.p.) were administered 20 min before PCP (3 mg/kg) treatment. SAL, saline; L-Arg, L-arginine; D-Arg, D-arginine; and L-Lys, L-lysine. Numbers in parentheses show the number of animals used. * $P < 0.05$ vs. saline + PCP (Dunn's multiple comparisons test).

Table 1
Effect of 7-nitro indazole on PCP-induced hyperlocomotion in mice

Treatment	Dose (mg/kg)	n	Counts/30 min
Control	–	10	1142.6± 360.4
7-Nitro indazole alone	25	10	1058.7± 156.6
PCP alone	3	15	10439.4±1018.1 **
+7-Nitro indazole	5	10	9728.5±1124.5
	25	10	15726.9±1170.4 ##
PCP alone	10	15	10080.0± 666.0 **
+7-Nitro indazole	25	10	9226.3± 614.6

7-Nitro indazole (5 or 25 mg/kg i.p.) was administered 15 min before treatment with PCP (3 or 10 mg/kg s.c.). The locomotor count was recorded over a 30-min period beginning 30 min after PCP treatment. ** $P < 0.01$ vs. control. ## $P < 0.01$ vs. PCP (3 mg/kg) alone (Dunnett's multiple comparisons test).

L-Arginine (1 g/kg i.p.), D-arginine (1 g/kg i.p.), and L-lysine (1 g/kg i.p.) were administered 20 min before PCP (3 mg/kg) treatment.

2.4. Statistics

Statistical differences among values for individual groups were determined by using Dunn's and Dunnett's multiple comparisons tests.

3. Results

3.1. Effects of NO synthase inhibitors on behavioral changes induced by PCP

Mice treated with PCP, at a dose of 1 mg/kg, failed to show behavioral changes compared with saline-treated mice. At a PCP dose of 3 mg/kg, the mice showed intense sniffing and hyperlocomotion, slight head movement, ataxia, and motor coordination deficits. At the high dose of 10 mg/kg, the mice showed more marked sniffing, head movement, ataxia (maximum individual scores being 2–3), and lack of motor coordination; the extent of hyperlocomotion, however, was similar to that obtained with a PCP dose of 3 mg/kg (Figs. 1 and 2).

Treatment with L-NAME (50 mg/kg), D-NAME (50 mg/kg) or 7-nitro indazole (25 mg/kg) alone had no effect on the behaviors in mice. Treatment with both L-NAME (50 mg/kg) and PCP (3 mg/kg) resulted in a significant enhancement of the PCP-induced ataxia. The hyperlocomotion induced by PCP (3 mg/kg) was significantly enhanced by L-NAME (5 and 50 mg/kg) in a dose-related manner. Such effects were not obtained by combined treatment with PCP and D-NAME (50 mg/kg). The behavioral changes induced by PCP at doses of 1 or 10 mg/kg were not modified by L-NAME (Figs. 1 and 2).

7-Nitro indazole at the dose of 25 mg/kg, at which dose the drug itself failed to affect behaviors, also significantly enhanced PCP (3 mg/kg)-induced hyperlocomotion in mice, while it failed to affect PCP (10 mg/kg)-induced hyperlocomotion (Table 1).

3.2. Effects of L-arginine, D-arginine and L-lysine on the enhancement of PCP (3 mg/kg)-induced ataxia and locomotion by L-NAME

L-Arginine (1 g/kg i.p.), D-arginine (1 g/kg i.p.), and L-lysine (1 g/kg i.p.) alone did not produce ataxia or affect locomotor activity in mice. The enhancing

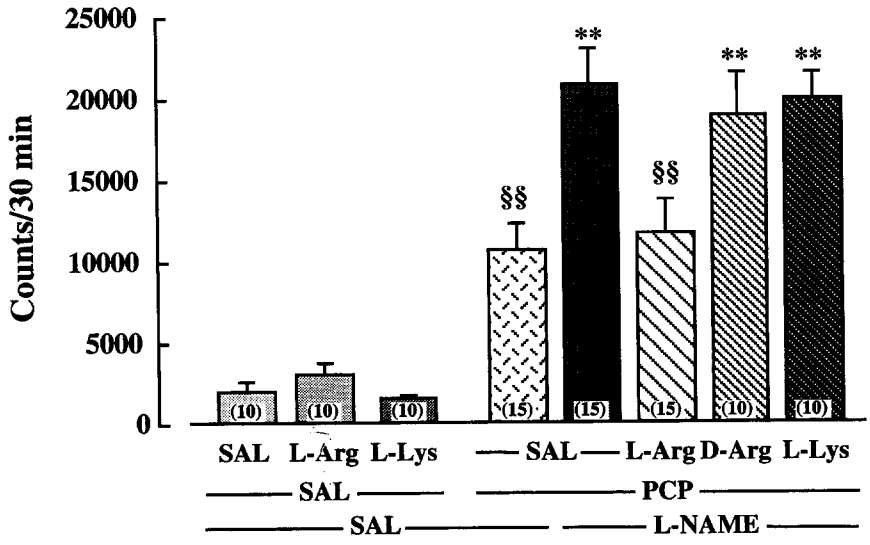

Fig. 4. Effects of L-arginine, D-arginine and L-lysine on the enhancement of PCP-induced locomotion by L-NAME in mice. L-Arginine (1 g/kg i.p.), D-arginine (1 g/kg i.p.), and L-lysine (1 g/kg i.p.) were administered 20 min before PCP (3 mg/kg) treatment. SAL, saline; L-Arg, L-arginine; D-Arg, D-arginine; and L-Lys, L-lysine. Numbers in parentheses show the number of animals used. ** $P < 0.01$ vs. saline + PCP. §§ $P < 0.01$ vs. L-NAME + PCP (Dunnett's multiple comparisons test).

effect of L-NAME (50 mg/kg) on the PCP (3 mg/kg)-induced ataxia was not prevented by L-arginine, D-arginine and L-lysine, at the dose of 1 g/kg i.p., a dose at which the agents did not affect the behaviors themselves (Fig. 3). In contrast, the significant enhancement of the PCP-induced hyperlocomotion induced by L-NAME was significantly prevented by L-arginine (Fig. 4). However, D-arginine (1 g/kg i.p.) and L-lysine (1 g/kg i.p.) had no effect in this regard (Fig. 4).

4. Discussion

The central mechanisms of action of PCP have been widely investigated in past years. The results of these studies indicate a wide spectrum of interactions with various neuronal systems, such as the glutamatergic, dopaminergic, serotonergic, adrenergic, and GABAergic systems (Anis et al., 1983; Castellani and Adams, 1980; Javitt and Zukin, 1991; Menon et al., 1980; Nabeshima et al., 1982, 1983, 1984, 1985; Sturgeon et al., 1979; Tonge and Leonard, 1971). PCP shows the most potent effects on glutamatergic systems (Javitt and Zukin, 1991), in which it acts at a site within the ion channel (Lehmann, 1989; Lodge and Johnson, 1990). Previous studies have demonstrated that PCP induces a characteristic behavioral syndrome consisting of ataxia, hyperactivity, lack of motor coordination, and stereotyped behaviors (Castellani and Adams, 1981; Sturgeon et al., 1979). In agreement with the results reported by previous investigators, we observed that PCP induced stereotyped sniffing, head movement, ataxia, lack of motor coordination, and hyperlocomotion in a dose-dependent manner in mice. Similar behaviors were seen after treatment with the competitive NMDA receptor antagonists, 2-amino-5-phosphovaleric acid (AP-5) and 3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonoic acid (CPP) (Koek and Ornstein, 1987; O'Neill and Liebman, 1987; Schmidt, 1986; Schmidt et al., 1987), and following the systemic administration of ketamine and MK-801 (Hiramatsu et al., 1989; Bennett et al., 1988), suggesting that the effects of PCP are produced by blockade of the NMDA/PCP receptor ion channel complex.

Recently, the activation of NMDA receptors has been shown to induce NO synthesis (Garthwaite et al., 1988), which then activates soluble guanylate cyclase (Knowles et al., 1989) and leads to the formation of cyclic GMP in the brain (Bredt and Snyder, 1989; East and Garthwaite, 1991; Garthwaite et al., 1988). It is possible that NMDA antagonists inhibit NO synthesis, since these agents inhibit increases in the levels of cyclic GMP. Further, NMDA receptor antagonists such as MK-801 and PCP have an effect similar to that of NO synthase inhibitors in the CNS. For example, hippocampal long-term potentiation is inhibited by NMDA antagonists and by NO synthase inhibitors such as L-NAME and *N*-monoethyl-L-arginine (O'Dell et al., 1991; Schuman and Madison, 1991), and these antagonists protect against NMDA-induced neurotoxicity (Dawson et al., 1993; Haberny et al., 1992). Further, it has very recently been reported, by Nakamura et al. (1995), that NO synthase inhibitors, as well as NMDA receptor antagonists, protect against NMDA receptor-mediated convulsions in animals. In addition, it has been shown that NO synthase inhibitors and NMDA receptor antagonists impair learning and memory in animals (Böhme et al., 1993; Chapman et al., 1992; Hölscher and Rose, 1993). However, there is evidence that inhibition of NO synthase does not impair learning or prevent the induction of long-term potentiation and NMDA-induced convulsions in animals (Bannerman et al., 1994a,b; Buisson et al., 1993). In the present study, we found that L-NAME (5 and 50 mg/kg), at doses which, per se, did not cause any behavioral changes, enhanced the PCP (3 mg/kg s.c.)-induced hyperlocomotion and ataxia in a dose-related manner, while D-NAME, a less active enantiomer of L-NAME, administered at the same dose, had no effect, suggesting a stereospecific mechanism. The dose (50 mg/kg) of L-NAME used in the present study seems to be rather high. However, several investigators have used higher doses than the dose used here and have suggested the involvement of NO in morphine- or cocaine-induced behavioral changes in animals (Calignano et al., 1993; Itzhak, 1994; Pudiak and Bozarth, 1993). Further, we found that the enhancing effect on PCP-induced hyperlocomotion was also observed after pretreatment with 7-nitro indazole, which is a selective inhibitor for brain NO synthase, without effects on blood pressure and endothelial NO synthase (Moore et al., 1993; Cappendijk et al., 1995). Thus, the behavioral effects of L-NAME in the present study might be due to the inhibition of NO synthase, but not the alternation of blood pressure or cerebral blood flow, suggesting that NO synthase inhibitors enhance NMDA receptor antagonist-mediated responses. Interestingly, this enhancing effect of L-NAME on PCP-induced hyperlocomotion was completely prevented by L-arginine, but not by D-arginine, at a dose which, per se, had no effect on mouse behaviors, whereas the hyperlocomotion induced by PCP (3 mg/kg) alone was not altered by L-arginine (1 g/kg i.p.) (data not shown). It has been reported that NO synthase inhibitors, such as L-NAME and N^G-nitro-L-arginine, at concentrations up to 100 μM, have no effect on [^{3}H]MK-801 binding to PCP receptors and [^{3}H]CGP 39653 binding to NMDA receptors (Itzhak, 1994). Taken together with these findings, our findings suggest that the enhancing effect of L-NAME is due to the blockade of NO synthase, and that L-arginine is involved in the mechanisms linked to NO production. We also found that L-lysine, an amino acid not involved in the L-

arginine/NO pathway, did not interfere with the effects induced by the combination of L-NAME (50 mg/kg) with PCP (3 mg/kg). NO synthase has been found in the nucleus caudatum and striatum, areas related to PCP-induced behavioral changes, including hyperlocomotion (Nabeshima et al., 1983). A conceivable explanation of our results is that L-arginine attenuates the L-NAME-induced enhancing effects by increasing the generation of endogenous NO. Thus, this finding suggests that the mediation of PCP-induced hyperlocomotion may occur via modulation of the L-arginine/NO pathway. L-NAME and 7-nitro indazole failed to enhance the behavioral changes induced by PCP at the high dose of 10 mg/kg. These findings suggest that the enhancing effects of both compounds on locomotion may be masked by motor dysfunction, such as ataxia and the lack of motor coordination induced by these doses of PCP. This hypothesis is supported by the finding that at a dose of 10 mg/kg PCP was more effective in inducing ataxia and lack of motor coordination than it was at a dose of 3 mg/kg, whereas the hyperlocomotion induced by PCP (10 mg/kg) was almost equivalent to that induced by a dose of 3 mg/kg.

The enhancing effect of L-NAME on hyperlocomotion was clearer than its effect on other behaviors. This difference may depend on the different neuronal systems involved in the hyperlocomotion and the other behaviors induced by PCP, since there is some evidence that PCP exerts its behavioral effects not only through the reduction of neurotransmission at NMDA receptors and the interactions between glutamatergic and dopaminergic systems, but also through other neuronal systems. For example, serotonergic systems in discrete rat brain regions have been shown to play a significant role in the head movement induced by this drug (Nabeshima et al., 1987). However, this point must be considered with caution, as the neuropharmacology of PCP remains to be further clarified.

In conclusion, our present results show that the behavioral changes, particularly hyperlocomotion, induced by PCP were modified by the NO synthase inhibitor, L-NAME, and further, that this effect was attenuated by the NO precursor, L-arginine, suggesting that NO may play an important role in the inhibition of the NMDA/PCP receptor ion channel complex elicited by PCP, indicating a role for NO in the CNS.

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