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Repeated Phencyclidine Treatment Induces Negative Symptom-like Behavior in Forced Swimming Test in Mice: Imbalance of Prefrontal Serotonergic and Dopaminergic Functions

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Repeated treatment with phencyclidine (PCP) prolonged the immobility time in a forced swimming test, compared with saline treatment, this behavioral change being regarded as avolition which is one of the negative symptoms of schizophrenia. In the present study, we investigated an involvement of serotonergic (5-HTergic) and dopaminergic systems in PCP-induced enhancement of immobility in mice, since an alteration in 5-HTergic and dopaminergic systems has been hypothesized in schizophrenia. The enhancing effect of PCP on the immobility in a forced swimming test was attenuated by clozapine, risperidone and olanzapine, which have serotonin (5-HT) and dopamine receptor antagonistic properties. These attenuating effects were significantly antagonized by a 5-HT$_2$ receptor agonist, (±)-2,5-dimethoxy-4-iodamphetamine (DOI) without affecting the immobility itself. (−)Sulpiride at a low dose and methylphenidate reversed the PCP-induced enhancement of immobility whereas pimozide, chlorpromazine and levomepromazine had no effect. There was no difference in the frequency of DOI-induced head twitches, which are mediated via 5-HT$_2$ receptors, between PCP- and saline-treated mice following the forced swimming test, indicating no functional changes in post-synaptic 5-HT$_2$ receptors. 5-HT utilization in the prefrontal cortex was increased, but dopamine utilization was decreased in mice showing PCP-induced enhancement of immobility. These results suggest that the enhanced effect of PCP on the immobility is mediated by imbalance of 5-HTergic and dopaminergic systems in the prefrontal cortex and could be used as a model of the negative symptoms of schizophrenia.
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An increasing number of investigations have centered on the role of monoamines in the pathogenesis of negative symptoms. There is evidence that serotonergic (5-HTergic) dysfunction is associated with negative symptoms in schizophrenia (Bleich et al. 1988; Meltzer 1989; Kapur and Remington 1996). It is well established that novel-type antipsychotics, such as clozapine and ris-

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peridone, which are potent serotonin (5-HT) receptor antagonists, improve negative symptoms in schizophrenia (Castelao et al. 1989; Gelenberg and Doller 1979; Lieberman et al. 1989). Thus, it appears that 5-HTergic functions are overactive in negative symptoms of schizophrenia. A direct approach which might reveal an under or overactivity of 5-HTergic systems in schizophrenia is the analysis of levels of 5-HT and its metabolite 5-hydroxyindolacetic acid (5-HIAA) in post mortem brain samples (Beskow et al. 1976; Cochran et al. 1976; van Praag 1977). On the other hand, several lines of research suggest that negative symptoms in schizophrenia are also due to dysfunction of the prefrontal cortex, possibly, its dopaminergic innervation (Carlsson 1988; Goldman-Rakic 1991; Kahn and Davis 1995). The prefrontal cortex receives a prominent dopaminergic projection (Thierry et al. 1973; Williams and Goldman-Rakic 1993), and the cortical dopaminergic hypoactivity may be involved in this disorder and be underlying cognitive deficits and some other negative symptoms of schizophrenia. Thus, these findings suggest that the impaired function of cortical 5-HTergic and/or dopaminergic neuronal systems could be associated with negative symptoms of schizophrenia.

Phencyclidine (PCP) induces schizophrenic-like symptomatology in humans (Luby et al. 1959) and precipitates psychosis in schizophrenia (Ital et al. 1967). This compound can induce and stimulate both positive and negative symptoms of schizophrenia (Javitt and Zukin 1991). As such, PCP administration has been suggested to represent a drug-induced model of schizophrenia (Javitt and Zukin 1991; Steinpreis 1996). In animals, PCP causes hyperlocomotion and stereotyped behaviors (Castellani and Adams 1981; Nabeshima et al. 1987). The effects of PCP on brain 5-HTergic and dopaminergic systems have received particular attention since alterations in 5-HTergic and dopaminergic systems have been hypothesized in schizophrenia.

Recent studies have shown that the immobility in a forced swimming test (Porsolt et al. 1977a, 1977b, 1978) was enhanced in repeated PCP-treated mice (Noda et al. 1995, 1997). This effect of PCP on the immobility appears to be sensitive to atypical antipsychotic (clozapine and risperidone) treatment, but not to haloperidol and tricyclic antidepressant treatments (Noda et al. 1995, 1997). Since these findings were consistent with the clinical findings that risperidone and clozapine, but not haloperidol and tricyclic antidepressants, improve negative symptoms in schizophrenia, the enhancement of immobility in mice pretreated with PCP repeatedly could be used as a model of the negative symptoms. However, the mechanisms of the enhanced effect of PCP on the immobility still remain unclear.

In the present study, we describe the results of experiments designed to test the hypothesis that repeated treatment with PCP results in the cortical dysfunction of 5-HTergic and/or dopaminergic systems. We investigated the effects of various antipsychotics, which act at 5-HTergic and dopaminergic systems, on the PCP-induced enhancement of immobility in the forced swimming test in mice. Further, we determined the functional and neurochemical changes in pre- and/or post-synaptic 5-HTergic and dopaminergic systems by using behavioral and biochemical techniques.

MATERIALS AND METHODS

Animals

Male mice of the ddY strain (Japan SLC Inc., Shizuoka, Japan), weighing 25–27 g at the beginning of the experiments were used. The animals were housed in plastic cages and were kept in a regulated environment (23 ± 1°C, 50 ± 5% humidity), with a 12/12 h light-dark cycle (lights on at 7:30 A.M.). Food (CE2, Clea Japan Inc. Tokyo, Japan) and tap water were available ad libitum.

All experiments were performed in accordance with the Guidelines for Animal Experiments of the Nagoya University School of Medicine. The procedures involving animals and their care conformed with the international guidelines set out in "Principles of Laboratory Animal Care" (NIH publication no. 85-23, revised 1985).

Drugs

Clozapine, chlorpromazine hydrochloride, pimozide, (±)-2,5-dimethoxy-4-iodamphetamine hydrochloride (DOI) and 5,7-dihydroxytryptamine creatinine sulfate (5,7-DHT) were purchased from Research Biochemicals International (Natick, MA, USA). Levomepromazine was purchased from Sigma (St. Louis, MO, USA). Risperidone, olanzapine and methylphenidate hydrochloride were supplied by Janssen Kyowa (Tokyo, Japan), Eli Lilly Co. (Indianapolis, IN, USA) and Novartis Pharmaceuticals Co. (Tokyo, Japan), respectively. Phencyclidine hydrochloride (PCP) was synthesized by the authors according to the method of Maddox et al. (1965) and was checked for purity.

PCP, chlorpromazine, DOI and methylphenidate were dissolved in 0.9% NaCl solution. 5,7-DHT was dissolved in 0.9% NaCl solution containing 0.1% ascorbic acid. Pimozide, levomepromazine, and risperidone were dissolved in water containing 1% tartaric acid. Clozapine and olanzapine were suspended in saline containing 0.1% (w/v) carboxymethyl cellulose sodium salt (CMC). All compounds were administered in a volume of 0.1 ml/10 g body weight.

Forced Swimming Test and Locomotion

The experimental schedule is indicated in Table 1. On day 1, each mouse was placed in a transparent glass

cylinder (20 cm high, 8 cm in diameter), that contained water at 22–23°C to a depth of 15 cm, and was forced to swim for 180 s. The duration of swimming was measured by using a SCANET MV-10 AQ apparatus (Toyo Sangyo Co. Ltd., Toyama, Japan). The immobility time was calculated as follows: 180 (s) − swimming time (s) = immobility time (s) (the first measurement of immobility). The mice were matched according to the results of immobility time in the first measurement of immobility, and were divided into various treatment groups.

On day 2, drug treatment was commenced. Saline or PCP (10 mg/kg s.c.) was administered once a day for 14 days (day 2 to day 15).

On day 16, each mouse (under the condition of PCP free) was placed in water again for 180 s, and the immobility time was calculated (the second measurement of immobility: swimming group). Drugs were administered before the second measurement of immobility as described in each figure legend. Control animals received the vehicle only and the same procedure was performed. Further, the non-swimming group, which did not perform the forced swimming test on day 1 and day 16 (the first and second measurement of immobility), was prepared.

The effects of drugs on the spontaneous activity were examined before the second measurement of immobility: the saline-pretreated mice were administered the tested drugs and then the spontaneous activity of each mouse was measured for 3 min by using behavioral analysis systems (SCANET SV-10: Toyo Sangyo Co. Ltd.).

Head Twitch Behavior

The experimental schedule is indicated in Table 1. Immediately after the second measurement of immobility, each mouse was given DOI (1 and 3 mg/kg i.p.), and then placed in an observation cage (17 × 24 × 13 cm). The number of head twitches was counted for 5 min from 5 to 10 min after DOI injection. The same treatment was performed in saline- and PCP-pretreated, non-swimming mice one day after the final injection of saline and PCP.

Monoamines and Their Metabolites

The experimental schedule is indicated in Table 1. Immediately after the second measurement of immobility, each mouse was sacrificed. Brains were rapidly removed and the prefrontal cortex and striatum were dissected out on an ice-cold plate. Each tissue sample was quickly frozen with dry ice and stored in a deep freezer at −80°C until assayed. Further, the tissue samples in saline- and PCP-pretreated, non-swimming mice were also prepared one day after the final injection of saline and PCP.

The contents of monoamines were determined by using a HPLC system with an electrochemical detector (Eicom,

Table 1. Experimental Schedule

Experiments	Day 1	Days 2–15	Day 16			Immediately after Test	Tables and Figures
	The First Measurement of Immobility	Repeated Treatment	Pretreatment Time	Locomotion	The Second Measurement of Immobility		
Tested drug efficacy	3 min	PCP 10 mg/kg/day (14 days)	30 or 60 min	–	3 min	–	Figures 1, 2 and 3
Tested drug efficacy and spontaneous activity	3 min	Saline (14 days)	30 or 60 min	3 min	3 min	–	Table 2
Antagonism by DOI	3 min	PCP 10 mg/kg/day (14 days)	5 or 60 min	–	3 min	–	Figure 4
DOI efficacy	3 min	Saline (14 days) PCP 10 mg/kg/day (14 days)	5 min	–	3 min	–	Table 3A Table 3B
5,7-DHT efficacy	3 min	PCP 10 mg/kg/day (14 days)	7 days	–	3 min	–	Table 4
Head-twitch test	3 min	PCP 10 mg/kg/day (14 days)	–	–	3 min	DOI treatment	Figure 5
Monoamine metabolism	3 min	PCP 10 mg/kg/day (14 days)	–	–	3 min	Sacrifice	Table 5 Figures 6 and 7

Kyoto, Japan) as described by Noda et al. (1997, 1998). Briefly, each frozen tissue sample was weighed, then homogenized with an ultrasonic processor (475 W, Model XL2020, Heat Systems Inc., New York, USA) in 350 μl of 0.2 M perchloric acid containing isoproterenol (internal standard). The homogenate was placed in ice for 30 min and then centrifuged at 20,000 ×*g* for 15 min at 4°C. The supernatant was mixed with 1 M sodium acetate to adjust the pH to 3.0 and then injected into a liquid chromatography system equipped with a reversed-phase ODS-column [4.6 × 150 mm, Eicompak MA-5 ODS (diameter of stationary phase grains; 5 μm), Eicom, Kyoto, Japan] and an electrochemical detector (Model ECD-100, Eicom). The column temperature was maintained at 25°C and the detector potential was set at +750 mV. The mobile phase consists of 0.1 M citric acid and 0.1 M sodium acetate, pH 3.9, containing 14% methanol, 160 mg/l sodium-l-octanesulfonate and 5 mg/l EDTA; the flow rate was 1 ml/min.

Statistical Analysis

Statistical significance was determined with analysis of variance (one-way ANOVA, behavioral experiments; two-way ANOVA, biochemical experiments) followed by the Dunnett (behavioral experiments) and Student-Newman-Keuls (biochemical experiments) multiple comparisons tests. *P* values less than 0.05 were taken to indicate statistically significant differences.

RESULTS

Effects of Serotonin- and Dopamine-related Compounds on the PCP-induced Enhancement of Immobility in the Forced Swimming Test in Mice

We have confirmed our previous results (Noda et al. 1995) that atypical antipsychotics attenuate the PCP-induced enhancement of immobility in the second measurement of immobility in mice, but not whether the typical antipsychotic, haloperidol, does. In the repeated PCP-treated mice, a significant prolonged immobility time was observed in the second measurement of immobility, compared with the saline-treated mice (Figure 1). When such mice received clozapine (3 mg/kg p.o.), risperidone (0.3 mg/kg p.o.) and olanzapine (3 mg/kg p.o.) administered 1 h before the second measurement of immobility, the enhanced effects of PCP on the immobility were significantly attenuated (Figure 1), consistent with our previous report (Noda et al. 1995). However, typical antipsychotics such as chlorprom-

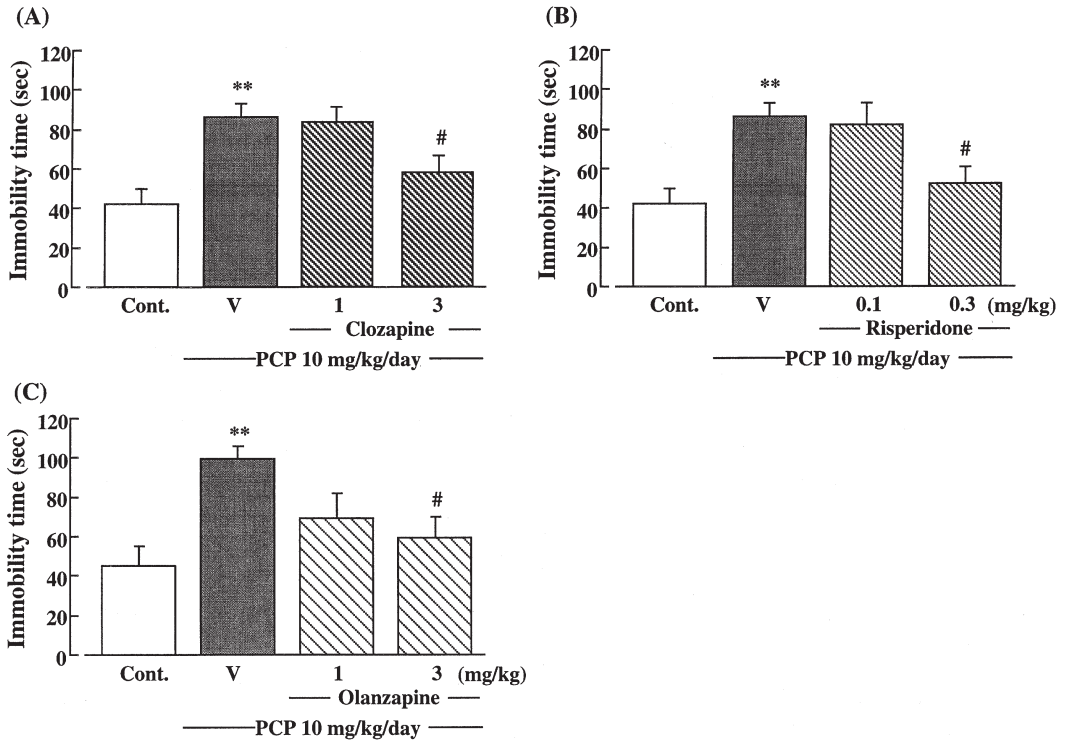

Figure 1. Effects of clozapine **(A)**, risperidone **(B)** and olanzapine **(C)** on the PCP-induced enhancement of immobility in mice. The repeated PCP-treated mice were administered clozapine (1 and 3 mg/kg p.o.), risperidone (0.1 and 0.3 mg/kg p.o.) and olanzapine (1 and 3 mg/kg p.o.) 1 h before the second measurement of immobility. Values are the mean ± S.E.M. for 10 mice. Results with one-way ANOVA were: (A); $F(3,36) = 7.6560$ ($p < .01$), (B) $F(3,36) = 7.1422$ ($p < .01$), (C) $F(3,36) = 5.2907$ ($p < .01$). Cont., control; V, vehicle. $^{**}p < .01$ compared to the control group. $\#p < .05$ compared to the repeated PCP-treated group.

Table 2. Effects of Various Compounds on the Immobility in Mice Pretreated with Saline Repeatedly

Treatment	Dose (mg/kg)	*n*	Immobility Time (Sec)	Locomotion (Counts/3 Min)
Control		8	55.9 ± 8.5	1356.4 ± 146.3
Olanzapine	3	8	61.7 ± 12.3	783.4 ± 144.9
Chlorpromazine	30	8	48.8 ± 13.0	210.1 ± 72.7 **
Levomepromazine	10	8	70.5 ± 20.8	291.6 ± 128.4 **
Pimozide	1	8	60.6 ± 11.9	281.6 ± 106.1 **
Sulpiride	30	8	57.7 ± 9.8	1087.8 ± 226.3
Methylphenidate	0.3	8	69.4 ± 11.6	1556.0 ± 227.8
	1.	8	38.7 ± 7.4	1772.9 ± 125.7

The repeated saline-treated mice were administered olanzapine, chlorpromazine, levomepromazine, pimozide, sulpiride and methylphenidate 60, 60, 60, 60, 60, and 30 min before the second measurement of immobility.

Values are the mean ± S.E.M. for 8 mice.

Results with one-way ANOVA on the immobility time and locomotion were as follows: F (8, 63) = 0.6284 ($p > .05$) and 16.735 ($p < .01$), respectively. **$p < .01$ compared to control group.

azine (10 and 30 mg/kg p.o.), pimozide (1 and 3 mg/kg p.o.), and levomepromazine (3 and 10 mg/kg p.o.) had no affect the exploratory behaviors and immobility in saline- or PCP-pretreated mice (Table 2 and Figure 2).

(−)Sulpiride, a selective dopamine$_2$ receptor antagonist, at low doses and methylphenidate, a dopamine uptake inhibitor, have been demonstrated to stimulate dopaminergic systems. When (−)sulpiride at 30 mg/kg p.o. and methylphenidate at 0.3 and 1 mg/kg i.p. were administered, the enhancement of immobility induced by PCP was significantly attenuated (Figure 3). (−)Sulpiride (30 mg/kg) and methylphenidate (0.3 and 1 mg/kg) had no effect on the exploratory behaviors or the immobility in saline-pretreated mice (Table 2).

Effects of DOI on the Attenuation of PCP-induced Enhancement of Immobility by Serotonin-dopamine Antagonists

To clarify whether the attenuating effects of compounds having 5-HT$_2$ receptor antagonistic properties on PCP-induced enhancement of immobility were mediated via 5-HT$_2$ receptors, we investigated the antagonistic effects of a 5-HT$_2$ receptor agonist, DOI, on the effects of clozapine, risperidone and olanzapine.

As shown in Figure 4, DOI (3 mg/kg) significantly antagonized the attenuating effects of these drugs on the PCP-induced enhancement of immobility in a dose-related manner. DOI itself had no effect on the immobility in the saline- and PCP-treated mice (Table 3).

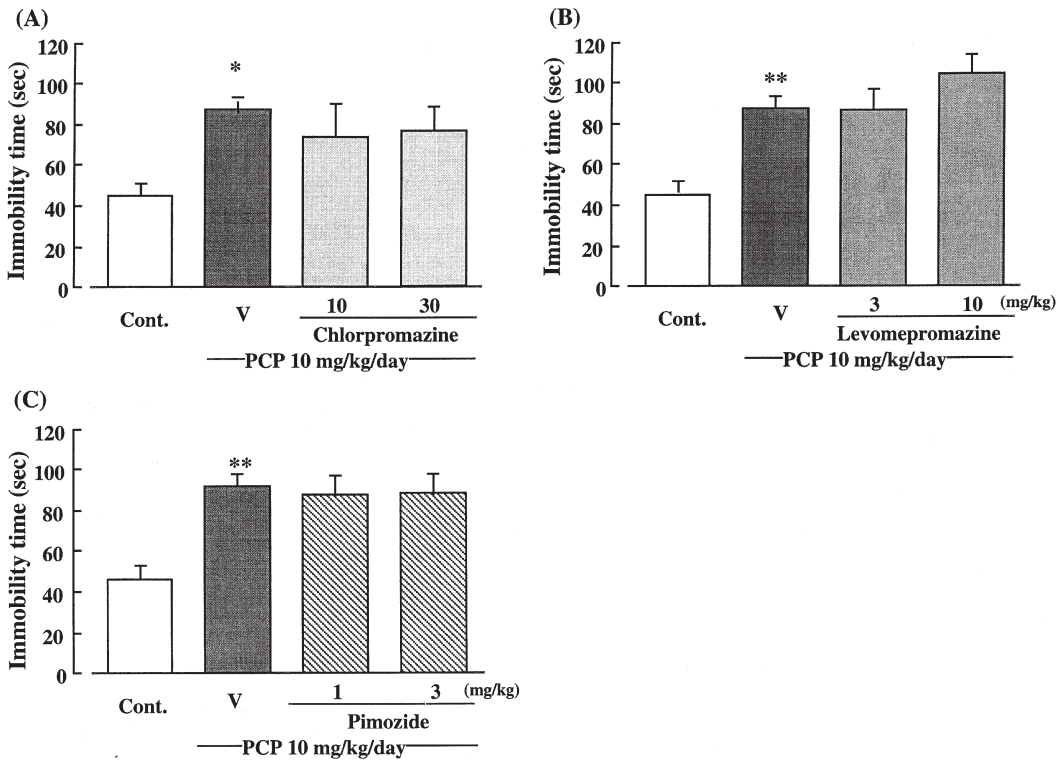

Figure 2. Effects of chlorpromazine **(A)**, levomepromazine **(B)** and pimozide **(C)** on the PCP-induced enhancement of immobility in mice. The repeated PCP-treated mice were administered chlorpromazine (10 and 30 mg/kg p.o.), levomepromazine (3 and 10 mg/kg p.o.) and pimozide (1 and 3 mg/kg p.o.) 1 h before the second measurement of immobility. Values are the mean ± S.E.M. for 10–20 mice. Results with one-way ANOVA were: (A) F(3,36) = 2.9683 ($p < .05$), (B) F(3,36) = 11.778 ($p < .01$), (C) F(3,56) = 10.906 ($p < .01$). Cont., control; V, vehicle. *$p < .05$, **$p < .01$ compared to the control group.

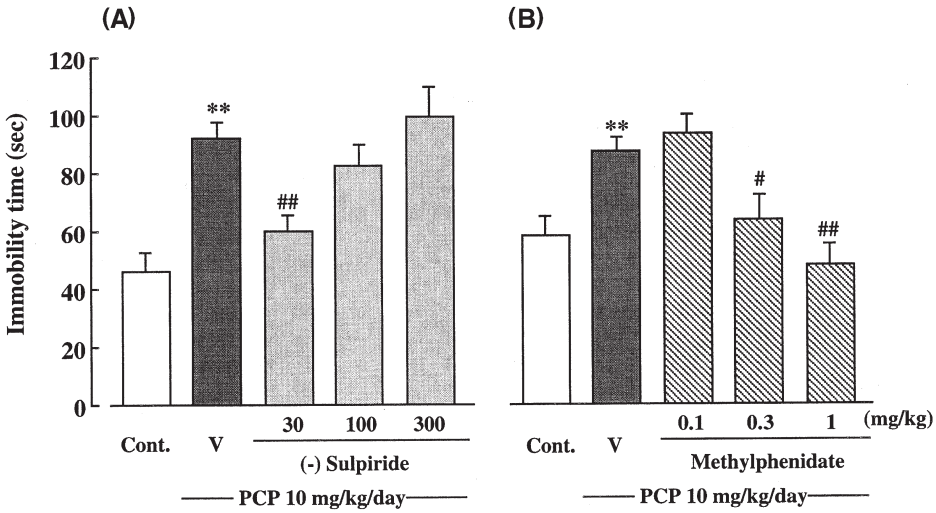

Figure 3. Effects of (−)sulpiride **(A)** and methylphenidate **(B)** on the PCP-induced enhancement of immobility in mice. The repeated PCP-treated mice were administered (−)sulpiride (30–300 mg/kg p.o.) and methylphenidate (0.1–1 mg/kg i.p.) 1 h and 30 min, respectively, before the second measurement of immobility. Values are the mean ± S.E.M. for 10–20 mice. Results with one-way ANOVA were: **(A)** $F(4,65) = 11.921$ ($p < .01$), **(B)** $F(4,69) = 8.3572$ ($p < .01$). Cont., control; V, vehicle. $^{**}p < .01$ compared to the control group. $\#p < .05$, $\#\#p < .01$ compared to the repeated PCP-treated group.

Effect of 5,7-DHT on the PCP-induced Enhancement of Immobility in the Forced Swimming Test in Mice

5,7-DHT (100 μg/mouse i.c.v.) was administered 7 days before the second measurement of immobility. With this schedule, a preliminary experiment showed that 7 days after the treatment, the 5-HT content in the prefrontal cortex of mice was decrease by 38.1% of that of the vehicle-treated control (vehicle-treatment mice:

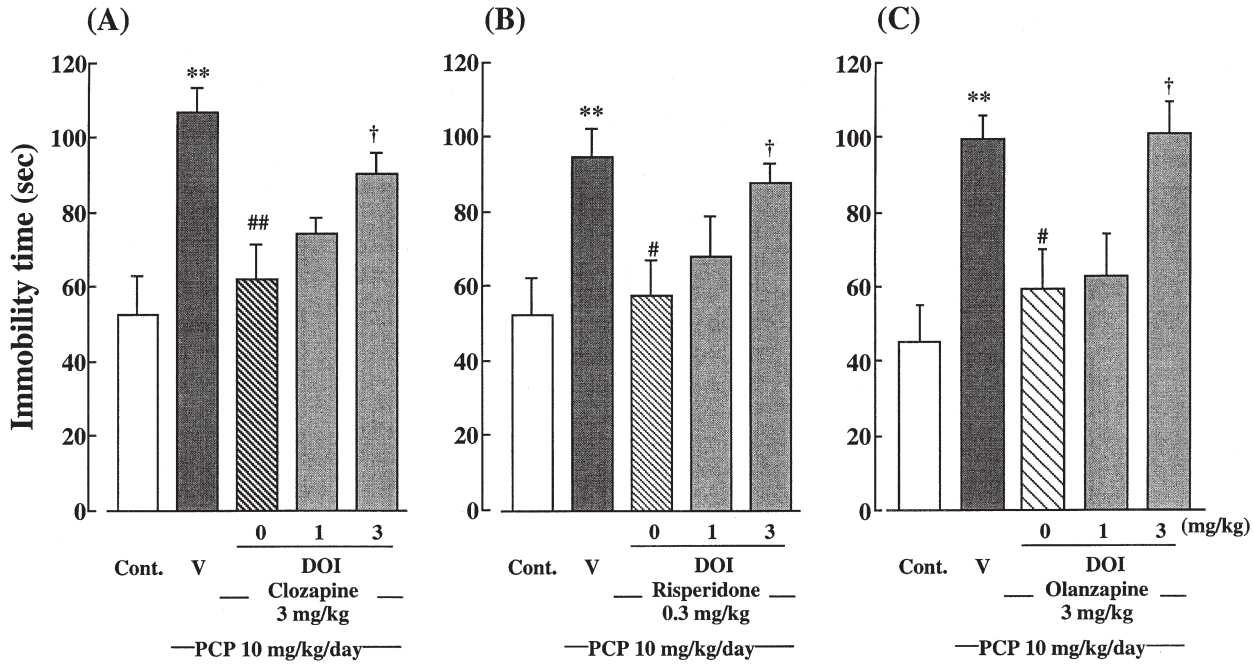

Figure 4. Effects of DOI on the attenuation of PCP-induced enhancement of immobility by clozapine **(A)**, risperidone **(B)** and olanzapine **(C)**. The repeated PCP-treated mice were administered clozapine (3 mg/kg p.o.), risperidone (0.3 mg/kg p.o.), olanzapine (3 mg/kg p.o.) and DOI (1 and 3 mg/kg i.p.) 1 h, 1 h, 1 h and 5 min, respectively, before the second measurement of immobility. Cont., control; V, vehicle. Values are the mean ± S.E.M. for 10–15 mice. Results with one-way ANOVA were: **(A)** $F(4,55) = 7.4051$ ($p < .01$), **(B)** $F(4,55) = 4.3920$ ($p < .01$), **(C)** $F(4,45) = 7.2636$ ($p < .01$). $^{**}p < .01$ compared to the corresponding control group. $\#p < .05$, $\#\#p < .01$ compared to the repeated PCP-treated group. $^{\dagger}p < .05$ compared to the corresponding drug-treated group.

Table 3. Effects of DOI on the Immobility in Mice Pretreated with Saline (A) and PCP (B) Repeatedly

Treatment	Dose (mg/kg)	n	Immobility Time (sec)
(A)			
Saline		12	57.1 ± 8.5
DOI	1	8	65.9 ± 7.6
	3	8	69.3 ± 11.8
(B)			
Saline		10	51.5 ± 8.3
PCP		10	87.0 ± 7.1*
+DOI	1	10	85.2 ± 10.5*
+DOI	3	10	82.7 ± 9.0*

The repeated saline- and PCP-treated mice were administered DOI (1 and 3 mg/kg i.p.) 5 min before the second measurement of immobility.

Values are the mean ± S.E.M. for 8 –12 mice.

Results with one-way ANOVA were (A): $F(2, 25)=0.4879$ ($p > 0.05$), (B): $F(3,36)=3.6484$ ($p < .05$). *$p < .05$ compared to control group.

317.2 ± 28.7 ng/g wet weight, 5,7-DHT-treated mice: 196.3 ± 27.7 ng/g wet weight).

As shown in Table 4, the microinjection of 5,7-DHT (100 μg/mouse i.c.v.) had no effect on the immobility time in repeatedly saline-pretreated mice, compared with microinjection of vehicle. However, the enhancement of immobility in repeatedly PCP-pretreated mice was attenuated by 5,7-DHT (Table 4).

DOI-induced Head Twitches in the Mice Showing PCP-induced Enhancement of Immobility

We investigated whether the DOI-induced head twitches, which are mediated via the stimulation of 5-HT_2 receptors, are modified following the second measurement of immobility in the repeated PCP-treated mice, compared to saline-treated mice. As shown in Figure 5, DOI (1 and 3 mg/kg i.p.) induced head twitches dose dependently in the non-swimming (N: naive) and the saline-treated, swimming groups, and there was no difference in the frequency of head twitches between the two groups. The number of DOI-induced head twitches in the repeated PCP-treated, swimming group did not differ from that in the saline-treated, swimming group.

Table 4. Effects of 5,7-DHT on the Immobility in Mice Pretreated with PCP Repeatedly

Treatment	Dose (μg/Mouse)	*n*	Immobility Time (sec)
Vehicle	–	10	45.0 ± 9.7
5,7-DHT	100	10	57.9 ± 8.6
PCP	–	12	94.7 ± 13.0**
+5,7-DHT	100	14	56.3 ± 7.6 #

The repeated saline- and PCP-treated mice were administered 5,7-DHT (100 μg/mouse i.c.v.) 7 days before the second measurement of immobility.

Values are the mean ± S.E.M. for 10–14 mice.

Result with one-way ANOVA was $F(3,43)=4.7147$ ($p < .01$) **$p < .01$ compared to vehicle group. #$p < .05$ compared to PCP alone group.

Serotonin and Dopamine Metabolism in the Brain Regions of Mice Showing PCP-induced Enhancement of Immobility

The contents of 5-HT, dopamine and their metabolites in the prefrontal cortex and striatum of mice repeatedly treated with saline or PCP and subjected to the second measurement of immobility are shown in Table 5. The ratios of 5-HIAA/5-HT, DOPAC/dopamine and HVA/dopamine (which are used as indices of 5-HT and dopamine turnover rates) in the prefrontal cortex and striatum in the saline- and PCP-treated mice, and non-swimming and swimming groups are shown in Figures 6 and 7, respectively. Significant increases in the DOPAC, DOPAC/dopamine ratio and HVA/dopamine ratio in the prefrontal cortex (Table 5 and Figure 6, respectively) and decreases in the 5-HIAA/5-HT ratio in the striatum (Figure 7) were observed in the saline-treated, swimming group, compared with those in the saline-treated, non-swimming group. However, there were no significant changes in dopamine metabolism in the striatum when the saline-treated, non-swimming and swimming groups were compared (Table 5 and Figure 7).

In the prefrontal cortex, the 5-HIAA content and the 5-HIAA/5-HT ratio were significantly increased by the forced swimming in the PCP-pretreated mice, compared with in the PCP-treated, non-swimming and the saline-treated, swimming group (Table 5 and Figure 6). By contrast, a significant increase in the HVA/dopamine ratio which was observed in the saline-treated swimming group was significantly decreased in the PCP-treated swimming group, compared with in the saline-treated, swimming group (Figure 6).

In the striatum, the 5-HIAA/5-HT ratio were significantly increased by the forced swimming in the PCP-pretreated mice, compared with in the PCP-treated, non-swimming. Significant increases of HVA content, the 5-HIAA/5-HT ration and HVA/dopamine ratio were observed in the PCP-treated swimming group, compared with in the saline-treated swimming group (Table 5 and Figure 7). In the non-swimming group, PCP induced a significant decrease and increase in 5-HT and dopamine metabolisms, respectively; the 5-HIAA content and 5-HIAA/5-HT ratio were decreased (Table 5 and Figure 7) and HVA content and HVA/dopamine ratio were increased (Table 5 and Figure 7).

DISCUSSION

PCP induces a psychotomimetic state that closely resembles schizophrenia; PCP psychosis incorporates

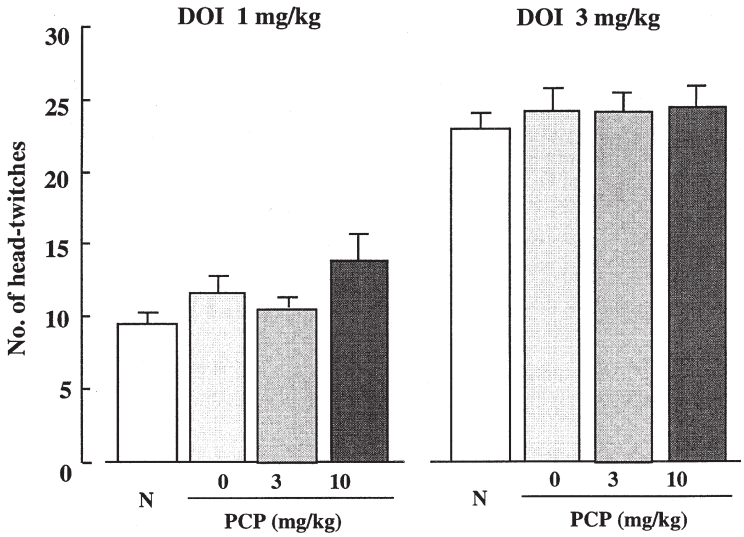

Figure 5. Changes in DOI-induced head twitches following the forced swimming in mice pretreated with PCP repeatedly. The experimental protocol is described in the text. N, naive mice, which did not perform the forced swimming test (non-swimming group). Values are the mean ± S.E.M. for 10–15 mice. Results with one-way ANOVA were: DOI 1 mg/kg group; $F(3,36) = 2.8602$ ($p > .05$), DOI 3 mg/kg group; $F(3,35) = 0.3170$ ($p > .05$).

both positive and negative symptoms of schizophrenia (Javitt and Zukin 1991). PCP-induced behavioral changes such as hyperactivity and stereotyped behavior in animals have been extensively employed as indices of schizophrenia. There are number of studies describing PCP-induced social interaction deficit in rats and monkeys that may serve as a model of the negative symptoms of schizophrenia (Sams-Dodd 1996; Schlemmer and Davis 1983). In addition, we have proposed enhancement of immobility induced by repeated PCP treatment in the forced swimming test as model for negative symptoms of schizophrenia (Noda et al. 1995, 1997). In the present study, forced swimming-induced immobility was enhanced following repeated PCP treatment (indicating the enhancement of avolition) in agreement with previous reports (Noda et al. 1995, 1997). Repeated PCP treatment has been well known to induce the addictive behaviors. It is unlikely that the enhancing effect of PCP on the immobility in the forced swimming test was due to the addictive behaviors, since we have already found that repeated methamphetamine (1 mg/kg/day) treatment, which also induces the addictive behaviors, failed to modify the immobility in the forced swimming test under the same treatment conditions as that used for PCP (Noda et al. 1995). Thus, this result suggests that the repeated PCP

Table 5. Changes in the Amounts of Serotonin (5-HT), Dopamine and their Metabolites in the Prefrontal Cortex (PFC) and Striatum (STR) of Mice Pretreated with Saline and PCP Repeatedly

Region	Treatment	5-HT	5-HIAA	Dopamine	DOPAC	HVA
PFC	*Non-swimming*					
	Repeated saline	333.8 ± 18.5	446.8 ± 6.7	81.8 ± 3.6	28.0 ± 4.3	71.7 ± 5.5
	Repeated PCP	288.0 ± 32.7	334.1 ± 36.8	78.1 ± 9.1	37.2 ± 11.2	63.8 ± 12.6
	Swimming					
	Repeated saline	311.4 ± 33.5	371.3 ± 53.7	84.4 ± 8.3	66.0 ± 10.3*	101.4 ± 19.1
	Repeated PCP	286.6 ± 18.7	530.6 ± 44.7 #,†	111.4 ± 17.0	60.6 ± 5.7	86.1 ± 8.7
STR	*Non-swimming*					
	Repeated saline	509.9 ± 61.4	478.0 ± 48.5	9637.7 ± 1137.8	2602.6 ± 234.0	1097.0 ± 31.3
	Repeated PCP	407.9 ± 40.0	313.5 ± 32.6*	8704.6 ± 727.6	2638.7 ± 235.2	1360.0 ± 50.5*
	Swimming					
	Repeated saline	467.7 ± 25.9	391.6 ± 21.9	9674.3 ± 534.4	2544.8 ± 209.7	1069.9 ± 54.5#
	Repeated PCP	400.2 ± 21.3	373.1 ± 24.5	8244.8 ± 317.6	2434.9 ± 75.1	1332.5 ± 69.7##

Values are expressed as ng/g wet weight and are the means ± S.E.M. for 6–7 animals. The mice were decapitated immediately after the measurement of immobility time for 3 min, and the amounts of 5-HT, dopamine and their metabolites (5-HIAA, DOPAC, and HVA) in the discrete brain regions were determined.

Results with two-way ANOVA on the monoamines and their metabolites of the PFC and striatum were as follows: PFC: 5-HT and DA; all variations among groups are not significant. 5-HIAA; $F(1,21) = 11.379$, $p < .01$ (drug-treatment vs. non-swimming/swimming). DOPAC; $F(1,21) = 13.895$, $p < .01$ (non-swimming vs. swimming). HVA; $F(1,21) = 4.479$, $p < .05$ (non-swimming vs. swimming). STR: 5-HT; $F(1,24) = 4.419$, $p < .05$ (saline vs. PCP). 5-HIAA; $F(1,24) = 7.440$, $p < .05$ (saline vs. PCP) and 4.742, $p < .05$ (drug-treatment vs. non-swimming/swimming). DA and DOPAC; all variations among groups are not significant. HVA; $F(1,24) = 24.360$, $p < .01$ (saline vs. PCP). *$p < .05$ compared to the saline-treated, non-swimming group. †$p < .05$ compared to the PCP-treated, non-swimming group. #$p < .05$, ##$p < .01$ compared to the saline-treated, swimming group.

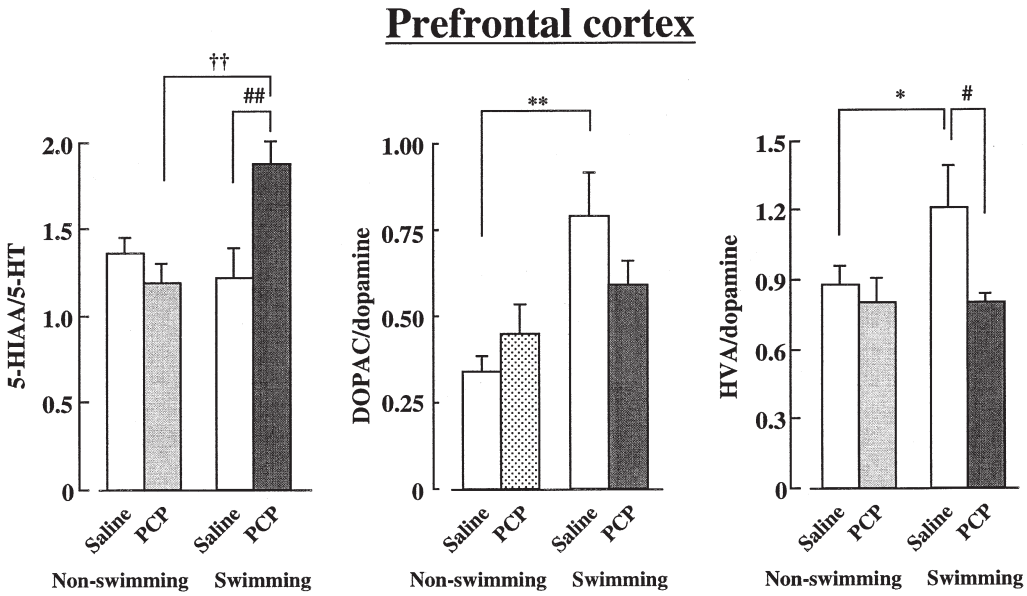

Figure 6. Changes in serotonin and dopamine utilization in the prefrontal cortex of mice pretreated with PCP repeatedly following the forced swimming test. Values are the mean ± S.E.M. Other details are shown in Table 5. Results with two-way ANOVA in 5-HIAA/5-HT, DOPAC/dopamine and HVA/dopamine were as follows: 5-HIAA/5-HT; $F(1,21) = 9.368$, $p < .01$ (drug-treatment vs. non-swimming/swimming). DOPAC/dopamine; $F(1,21) = 12.249$, $p < .01$ (non-swimming vs swimming). HVA/dopamine; $F(1,21) = 5.101$, $p < .05$ (saline vs PCP). $^{*}p < .05$, $^{**}p < .01$ compared to the saline-treated, non-swimming group. $^{\dagger\dagger}p < .01$ compared to the PCP-treated, non-swimming group. $\#p < .05$, $\#\#p < .01$ compared to the saline-treated, swimming group.

treatment produces negative symptom-like behavioral changes in mice, since avolition is one of the negative symptoms of schizophrenia (Barnes et al. 1989).

The mechanisms of negative symptom-like behavioral changes induced by PCP have yet to be elucidated. It has been suggested that a disturbance in the balance of 5-HT- and dopamine-mediated neurotransmission underlies schizophrenia (Meltzer 1989); an increased 5-HTergic activity relative to dopaminergic activity might lead to negative symptoms. This hypothesis is based on the evidence that 5-HT-dopamine antagonists such as risperidone and clozapine improve negative symptoms. Commonly used antipsychotics that potently block dopamine receptors such as haloperidol and chlorpromazine are more effective in treating positive symptoms manifested in chronic schizophrenic patients (Angrist et al. 1980), whereas negative symptoms such as the flattening of affect and avolition are less responsive. Risperidone, clozapine and olanzapine are thought to be efficacious in treating negative symptoms of schizophrenia (Castelao et al. 1989; Gelenberg and Doller 1979; Lieberman et al. 1989; Tollefson and Sanger 1997). In the present study, the enhanced effect of PCP on the immobility was attenuated by risperidone, clozapine and olanzapine, all of which show 5-HT_2 receptor antagonistic properties (Janssen et al. 1988; Wilmot and Szczepanik 1989; Fuller and Snoddy 1992; Meltzer 1999) in agreement with clinical and our previous findings (Noda et al. 1995). Further, these attenuating effects are completely antagonized by DOI, a 5-HT_2 receptor agonist, without affecting the immobility itself in the saline- and PCP-pretreated mice. Thus, this effect of PCP appeared to be mediated, at least in part, via 5-HT_2 receptors.

One possible mechanism is the induction of sensitization of post-synaptic 5-HT_2 receptors by the forced swimming and the repeated pretreatment with PCP. To test our hypothesis, we investigated whether the DOI-induced head twitches, which are mediated via the stimulation of 5-HT_2 receptors, are modified following the forced swimming in the repeated PCP-treated mice, compared to saline-treated mice. However, there was no difference in the frequency of DOI-induced head twitches between the PCP- and saline-treated mice. Thus, it is unlikely that the enhancing effect of PCP on the immobility is due to functional changes in the post-synaptic 5-HT_2 receptors.

Another possible explanation is that there is an interaction between 5-HTergic and dopaminergic systems in the prefrontal cortex. The present biochemical experiment showed that the 5-HIAA/5-HT ratio, a parameter of the turnover rate, in the prefrontal cortex was increased following the forced swimming in mice repeatedly treated with PCP, compared with that in the saline-treated, swimming group. Further, we examined whether newly released 5-HT plays a role in the expression of PCP-induced enhancement of immobility by using 5,7-DHT, a neurotoxin of pre-synaptic 5-HTergic neurons. We found that 5,7-DHT inhibited the PCP-induced enhancement of

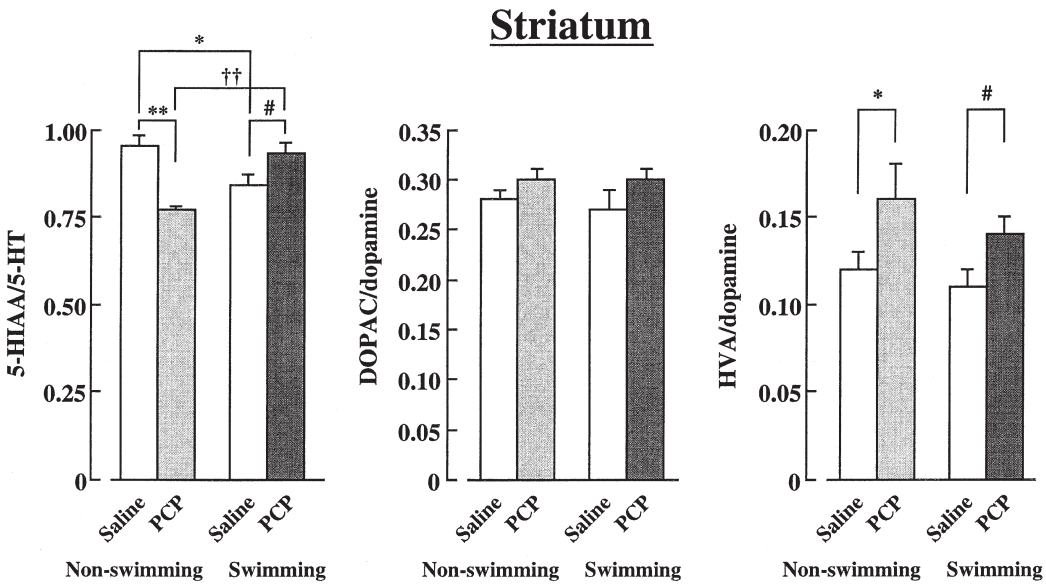

Figure 7. Changes in serotonin and dopamine utilization in the striatum of mice pretreated with PCP repeatedly following the forced swimming test. Values are the mean ± S.E.M. Other details are shown in Table 5. Results with two-way ANOVA in 5-HIAA/5-HT, DOPAC/dopamine and HVA/dopamine were as follows: 5-HIAA/5-HT; $F(1,24) = 26.940$, $p < .01$ (drug-treatment vs. non-swimming/swimming). DOPAC/dopamine; $F(1,24) = 14.597$, $p < .01$ (saline vs. PCP). HVA/dopamine; $F(1,24) = 4.268$, $p < .05$ (saline vs. PCP). $^{*}p < .05$, $^{**}p < .01$ compared to the saline-treated, non-swimming group. $^{\dagger\dagger}p < .01$ compared to the PCP-treated, non-swimming group. $\#p < .05$ compared to the saline-treated, swimming group.

immobility. Thus, the overactivity of pre-synaptic 5-HTergic systems in the prefrontal cortex may be responsible for the expression of the enhancement of immobility in mice pretreated with PCP repeatedly.

Although there were no functional changes in the 5-HTergic system, the DOPAC/dopamine ratio in the prefrontal cortex in mice repeatedly treated with saline increased following the forced swimming. Interestingly, increase in the utilization of dopamine in the prefrontal cortex was not observed following swimming in mice repeatedly treated with PCP. A similar change in dopamine utilization has been reported by other investigators (Jentsch et al. 1997); rats pretreated with saline repeatedly responded to stress (electric foot shock) with an increase in dopamine utilization whereas PCP-pretreated rats exhibited a significant decrease in the stress-induced activation of frontal cortical dopamine metabolism. Several investigators have demonstrated that dysfunction of cortical dopamine efflux is involved in negative symptoms and cognitive deficits of schizophrenia (Knable and Weinberger 1997). Further, this hypothesis has been recently revisited with regard to the PCP model of schizophrenia (Jentsch and Roth 1999). However, no reports have mentioned an imbalance of 5-HTergic and dopaminergic systems in the prefrontal cortex of mice showing negative symptom-like behavioral change. Thus, our PCP model could be used as a new model of the negative symptoms.

Haase et al. (1974) reported that chronic schizophrenic patients given sulpiride, a selective dopamine$_2$ receptor antagonist, showed an elation of mood and clearing of negative signs. Elizur and Davidson (1975) also found sulpiride is effective in improving the autistic state of schizophrenic patients. In agreement with these clinical findings, (−)sulpiride at the low dose of 30 mg/kg, but not at the high doses of 100 and 300 mg/kg, attenuated the PCP-induced enhancement of immobility in the forced swimming test. Low doses of (−)sulpiride are thought to inhibit dopamine autoreceptors, and consequently induce the release of extracellular dopamine. In contrast, high doses of it act at post-synaptic dopamine$_2$ receptors, thereby inhibiting dopaminergic activity. Since the mesocortical dopamine neurons lack impulse-regulating autoreceptors (Chiodo et al. 1984; Galloway et al. 1986), the autoreceptor-mediated effect of sulpiride may be less profound in the prefrontal cortex. However, a significant increase in prefrontal cortical dopamine release could be observed during the local perfusion of sulpiride. Further studies should be carried out to clarify the effects of sulpiride on the activation of dopaminergic systems in the prefrontal cortex. Dopamine agonists such as amphetamine or L-dihydroxyphenylalanine (L-DOPA) alleviate negative symptoms while exacerbating positive symptoms (Angrist et al. 1980). Further, methylphenidate, a dopamine uptake inhibitor, also attenuated the PCP-induced enhancement of immobility in mice whereas typical antipsychotics such as chlorpromazine, levomepromazine, and pimozide had no effect on the immobility in repeated saline- and PCP-pretreated

mice. The positive symptoms of schizophrenia appear to be due to excessive dopaminergic activity, whereas the negative symptoms appear to involve reduced dopaminergic function. Our findings, taken together with these clinical findings, indicate that the effect of PCP on the immobility in the forced swimming test is based, at least in part, on hyperfunctional 5-HTergic and/or hypofunctional dopaminergic systems in the prefrontal cortex and support the hypothesis that increased 5-HTergic activity relative to dopaminergic activity might lead to negative symptoms.

The explanation for this pattern of symptoms may lie in a recent study suggesting that the prefrontal cortex exerts regulatory effects over the subcortical mesolimbic and mesostriatal dopaminergic systems (Deutch 1992). The dopaminergic innervation of the prefrontal cortex appears to have an inhibitory influence on the subcortical dopaminergic neuronal systems. Namely, reductions in prefrontal dopaminergic activity result in increased activity or enhanced sensitivity of the subcortical systems (Pycock et al. 1980; Leccese and Lyness 1987; Haroutunian et al. 1988; Deutch et al. 1990; Rosin et al. 1992). Conversely, increased extracellular dopamine levels in the prefrontal cortex, due to local amphetamine or cocaine application, result in a reduction in dopamine release in the caudate of monkey (Kolachana et al. 1995). Thus, a dopaminergic deficit in the mesocortical would be responsible for the negative symptoms while a consequential increase in activity in the mesolimbic would lead to the manifestation of positive symptoms. In fact, the present study showed that repeated PCP treatment induced a significant decrease of 5-HT, but increase of dopamine utilization in the striatum in the non-swimming group, consistent with a previous report (Nabeshima et al. 1987). Further, a significant increase of dopamine utilization in the striatum was observed in the PCP-treated mice, compared with in the saline-treated mice. Thus, the hypofunctional dopaminergic systems in the prefrontal cortex of repeated PCP-treated mice may be associated with an increased activity of the subcortical structure and such mechanisms may be involved in the development of sensitization of locomotion (a model of positive symptoms).

PCP is known to interact with glutamatergic systems at the PCP binding site within the N-methyl-D-aspartate (NMDA) ionophore receptor complex (Johnson et al. 1987). Javitt and Zukin (1990, 1991) and Javitt et al. (1994) have demonstrated that dysfunction of the NMDA receptor is particularly relevant to the pathogenesis of negative symptoms in schizophrenia. It has been observed that dizocilpine, a noncompetitive NMDA receptor antagonist, increases the metabolism of 5-HT (Löscher et al. 1991) and PCP inhibits 5-HT reuptake (Hiramatsu et al. 1989), suggesting that PCP activates 5-HTergic systems through PCP binding site within the NMDA ionophore receptor complex and/or through the inhibition of 5-HT reuptake. Although the mechanisms of the increases in 5-HT utilization in the prefrontal cortex induced by the forced swimming following repeated PCP treatment have to be elucidated, it is possible that the present biochemical changes may be produced through action on the NMDA ionophore receptor complex. However, this point must be considered with caution, as the neuropharmacology of PCP and association with stress (forced swimming) remain to be clarified.

In conclusion, the most important finding in the present study was that an increased function of the 5-HTergic system, but decreased function of the dopaminergic system, was observed in mice showing an enhancement of immobility induced by repeated PCP treatment. These changes are consistent with those in schizophrenic patients. These results suggest an involvement of imbalance of 5-HTergic and dopaminergic systems in the prefrontal cortex in the enhanced effect of PCP on the immobility, and that the enhancement of immobility in the forced swimming test induced by repeated PCP treatment could be used as a new model of the negative symptoms of schizophrenia.

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