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Enhancement of immobility in a forced swimming test by subacute or repeated treatment with phencyclidine: a new model of schizophrenia

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1 Immobility induced by forced swimming is well known as an animal model of depression. To develop an animal model for the negative symptoms of schizophrenia, in particular the depressive symptoms, the effect of phencyclidine (PCP) on immobility in the forced swimming test was investigated in mice, since PCP produces such negative symptoms in humans.

2 Repeated treatment with PCP (10 mg kg^{-1} day^{-1}, s.c., once a day for 14 days) prolonged the immobility time in the forced swimming test 24 h after the final injection compared with saline treatment; the effect was not obtained by single or 5 treatments with PCP (10 mg kg^{-1}, s.c.), or by repeated treatment with methamphetamine (0.5 and 1 mg kg^{-1} day^{-1}, s.c., once a day for 14 days).

3 The enhancing effect of PCP (10 mg kg^{-1} day^{-1}, s.c.) on the immobility persisted for at least 21 days after the withdrawal of the drug.

4 Haloperidol (0.3 and 1 mg kg^{-1}, p.o.), ritanserin (3 and 10 mg kg^{-1}, p.o.), risperidone (0.1-1 mg kg^{-1}, p.o.), and clozapine (3 and 10 mg kg^{-1}, p.o.) failed to attenuate the immobility induced by the forced swimming in mice repeatedly treated with saline when the drugs were administered 1 h before the forced swimming test. However, ritanserin (30 mg kg^{-1}) and clozapine (30 mg kg^{-1}) did attenuate this immobility.

5 The enhancing effect of PCP on the immobility was attenuated by ritanserin (3 and 10 mg kg^{-1}, p.o.), risperidone (0.3 mg kg^{-1}, p.o.), and clozapine (3 and 10 mg kg^{-1}, p.o.), whereas haloperidol (0.3 and 1 mg kg^{-1}, p.o.) had no effect.

6 These results suggest that the enhancement of immobility in the forced swimming test brought about by repeated PCP treatment could be used as a model of the negative symptoms, particularly the depression, of schizophrenia. This effect of PCP appeared to be mediated, at least in part, via 5-HT_{2A} receptors.

Keywords: Phencyclidine; forced swimming test; immobility; negative symptoms; depression

Introduction

Schizophrenic patients show symptoms that are regarded as positive (e.g. hallucinations, delusions, disordered thinking and paranoia) (Andreasen, 1990; Dickerson *et al.*, 1991; Peralta *et al.*, 1992) and negative (e.g., apathy, manifested as deficits in social interaction, emotional expression and motivation) (Kukla & Gold, 1991; Troisi *et al.*, 1991; Fenton & McGlashan, 1992). Schizophrenic patients also exhibit depression (Barnes *et al.*, 1989), and it is difficult to distinguish between depressive symptoms and the negative symptoms of schizophrenia (Knights & Hirsch, 1981). The association between depressive features and certain negative schizophrenic symptoms (Roth, 1970; Stern *et al.*, 1972; McGlashan & Carpenter, 1976) remains unclear.

The analysis of drug-induced model psychosis has been one of the most effective approaches for investigating the neurochemical dysfunctions involved in schizophrenia. The most extensively examined neurochemical hypothesis of schizophrenia, the dopamine hypothesis, derives, in large part, from the observation that amphetamine induces positive symptoms, that resemble those of acute paranoid schizophrenia by augmenting dopaminergic neurotransmission within the CNS (Sayed & Garrison, 1983). However, many schizophrenic patients, particularly those with negative symptoms, fail to respond adequately to treatment with dopamine antagonists, suggesting that the amphetamine model fails to account for important dimensions of the illness. Thus, a major problem for the evaluation of atypical antipsychotics is the absence of specific animal models for the negative symptoms of schizophrenia.

In humans, phencyclidine (PCP)-induced psychosis manifests with both positive and negative symptoms (Javitt, 1987; Hurlbut, 1991; Javitt & Zukin, 1991; Volkow & Fowler, 1992), as well as depressive symptoms. Thus, PCP may provide a good animal model of schizophrenia that includes the positive and negative symptoms of the condition. However, there is little documentation of PCP-induced depression as a model of these negative symptoms.

Porsolt *et al.* (1977a,b; 1978) found that mice and rats became immobile when they were placed in a glass cylinder containing water from which they could not escape, a phenomenon that reflects an unconditioned behavioural response to stress. This immobility has been called 'behavioural despair' and appears to be selectively sensitive to antidepressant treatment, suggesting that this behavioural change is regarded as depression.

To establish a suitable selective animal model for the depression that is a negative symptom of schizophrenia, we investigated the effect of PCP on forced swimming-induced immobility in mice. When this compound was found to produce the depressive effect, we carried out investigations with a wide variety of atypical antipsychotics that are anticipated to be effective for treating the negative symptoms of chronic schizophrenia, to determine whether the effects of PCP on the immobility were selectivity blocked by these agents after a single administration.

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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 h/12 h light-dark cycle (lights on at 9 h 00 min). Food (CE2, Clea Japan Inc., Tokyo, Japan) and tap water were available *ad libitum*.

Forced swimming test

First measurement of immobility On the 1st day, each mouse was individually placed in a transparent glass cylinder (20 cm high, 8 cm in diameter), which contained water at 25°C to a depth of 8 cm, and was forced to swim for 3 min. The duration of immobility (immobility time) was measured (first measurement of immobility), with a SCANET MV-10 apparatus (Toyo Sangyo Co. Ltd., Toyama, Japan). The mice were matched according to the results of immobility time in the first measurement of immobility, and were divided into various treatment groups.

Drug treatment On the 2nd day, drug treatment was started. Saline, PCP (1–10 mg kg^{-1}, s.c.), or methamphetamine (0.3 and 1 mg kg^{-1}, s.c.) were administered once a day for 13 days. On the 15th day, saline-treated animals were challenged with saline (control group) or with PCP (1–10 mg kg^{-1}, s.c.; single PCP-treated group). PCP- and methamphetamine-treated animals were challenged with PCP (repeated PCP-treated group) and methamphetamine (repeated methamphetamine-treated group), respectively.

Other animals received saline for 9 days, and they were then treated with PCP (10 mg kg^{-1}, s.c.) for 4 days. On the 15th day, such mice were challenged with PCP (10 mg kg^{-1}, s.c.; 5 treatments group).

Second measurement of immobility On the 16th day, each mouse was placed in water again for 3 min, and the immobility time was recorded (second measurement of immobility). Haloperidol (0.3 and 1 mg kg^{-1}), risperidone (0.1–1 mg kg^{-1}), ritanserin (3–30 mg kg^{-1}), and clozapine (1–30 mg kg^{-1}) were administered orally 1 h before the second measurement of immobility.

To examine the immobility time in the repeated PCP-treated mice after the withdrawal of the drug, PCP was withdrawn for 1, 3, 7, 14, or 21 days after the last challenge.

Control animals received the vehicle only and the same procedure was performed.

Locomotor activity

Animals received saline, PCP (10 mg kg^{-1} day^{-1}), or methamphetamine (1 mg kg^{-1} day^{-1}), administered for 14 days. One day after the last injection, they were placed individually in transparent acrylic cages (26 × 44 × 40 cm). Locomotor activity was recorded every 5 min for 30 min by digital counters with infrared cell sensors placed on the walls (SCANET SV-10, Toyo Sangyo Co. Ltd.) (Kitaichi *et al.*, 1994).

Drugs

Methamphetamine hydrochloride (methamphetamine: Philopone) was purchased from Dainippon Pharmaceutical Co. Ltd. (Osaka, Japan) and clozapine was purchased from Funakoshi (Tokyo, Japan). Risperidone and ritanserin were supplied by Janssen Kyowa (Tokyo, Japan). Phencyclidine hydrochloride (PCP) was synthesized by us.

PCP and methamphetamine were dissolved in 0.9% saline solution. Haloperidol, ritanserin and risperidone were dissolved in water containing 1% tartaric acid. Clozapine was 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^{-1} body weight.

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

Statistical analysis

Statistical differences among values for individual groups were determined with Dunnett's multiple comparisons test and Student's *t* test.

Results

Effects of PCP on forced swimming-induced immobility in mice

As shown in Figure 1, a significantly prolonged immobility time was observed in the repeated PCP (10 mg kg^{-1} day^{-1}, s.c.)-treated group in the second measurement of immobility, in comparison with the control group, but this was not observed at the doses of 1 and 3 mg kg^{-1} day^{-1}. Single and 5 treatments with PCP (10 mg kg^{-1}, s.c.) had no effect on the immobility time in the second measurement of immobility, although 14 treatments had an enhancing effect (Figure 2).

After the last administration of repeated PCP (10 mg kg^{-1} day^{-1}, s.c., 14 times), the drug was withdrawn for 1, 3, 7, 14 or 21 days. The enhancing effect of PCP on the immobility was then examined. Figure 3 shows the effects of PCP on the forced swimming-induced immobility time after the withdrawal of PCP for 1, 3, 7, 14 and 21 days. The enhancing effect of PCP did not change after the withdrawal, even after 21 days. The immobility time in the second measurement of immobility was prolonged by PCP in comparison with the time in the control group.

Effects of methamphetamine on forced swimming-induced immobility in mice

Methamphetamine (0.3 and 1 mg kg^{-1} day^{-1}, s.c.), given 14 times, failed to prolong the immobility in mice. The compound (1 mg kg^{-1} day^{-1}, s.c.) reduced the immobility time by about 44% in comparison with the control group, whereas PCP (10 mg kg^{-1} day^{-1}, s.c.) significantly prolonged it (Figure 4).

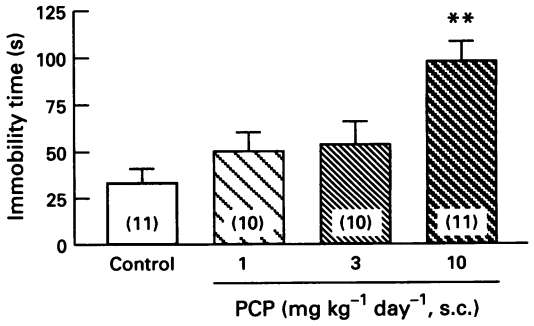

Figure 1 Effects of repeated PCP treatment on forced swimming-induced immobility in mice. One day after the first measurement of immobility (the 2nd day), the administration of PCP (1–10 mg kg^{-1} day^{-1}, s.c.) was started; this continued for a total of 14 days. One day after the last injection (the 16th day), the second measurement of immobility was made. Numbers in parentheses show the number of animals tested. $^{**}P<0.01$ vs control group (Dunnett's multiple comparisons test).

Effects of repeated administration of PCP and methamphetamine on locomotor activity in mice

Figure 5 shows the changes in locomotor activity after 14 repeated administrations of PCP (10 mg kg^{-1} day^{-1}, s.c.) and methamphetamine (1 mg kg^{-1} day^{-1}, s.c.). Repeated administration with PCP and methamphetamine did not produce any change in locomotor activity during the 30 min observation period.

Effects of antipsychotics on forced swimming-induced immobility in the repeated saline-treated mice

When haloperidol (0.3 and 1 mg kg^{-1}, p.o.), risperidone (0.1–1 mg kg^{-1}, p.o.), ritanserin (3 and 10 mg kg^{-1}, p.o.), and clozapine (3 and 10 mg kg^{-1}, p.o.) were administered 1 h before the second measurement of immobility in the repeated saline-treated mice, the immobility time was not affected (Figure 6). However, ritanserin and clozapine, at 30 mg kg^{-1}, p.o., did significantly reduce the immobility time, although they failed to reduce it at the lower doses (Figure 6).

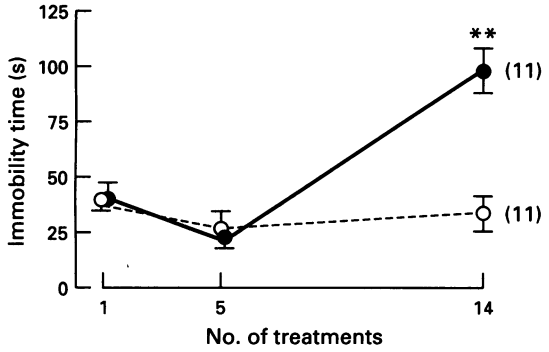

Figure 2 Effects of 1, 5 and 14 treatments with PCP (10 mg kg^{-1}) on forced swimming-induced immobility in mice. One day after the first measurement of immobility, the adminstration of saline was started; this continued for 13 days (single treatment group) or for 9 days (5 treatments group). The single treatment group was challenged with PCP (10 mg kg^{-1}, s.c.) on the last day (the 15th day) of drug treatment. The five treatments group received PCP (10 mg kg^{-1}, s.c.) for 5 days after the saline treatment. On the 16th day, the second measurement of immobility was made for each animal. Numbers in parentheses show the number of animals tested. (○) Control group, (●) PCP-treated group. $^{**}P<0.01$ vs control group (Student's t test).

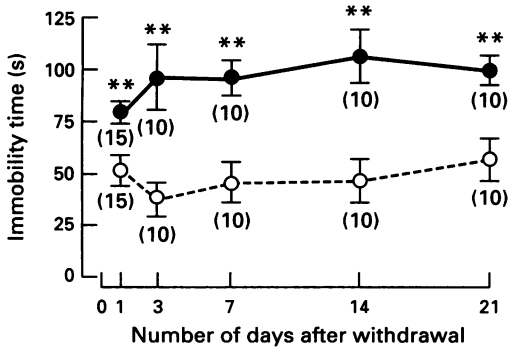

Figure 3 Persistence of enhancing effect of PCP on forced swimming-induced immobility in mice. One day after the first measurement of immobility (the 2nd day), the administration of PCP (10 mg kg^{-1} day^{-1}, s.c.) was started; this continued for 14 days. One, 3, 7, 14 or 21 days after withdrawal of the drug, the second measurement of immobility was made. Numbers in parentheses show the number of animals tested: (○) control group; (●) PCP-treated group. $^{**}P<0.01$ vs control group (Student's t test).

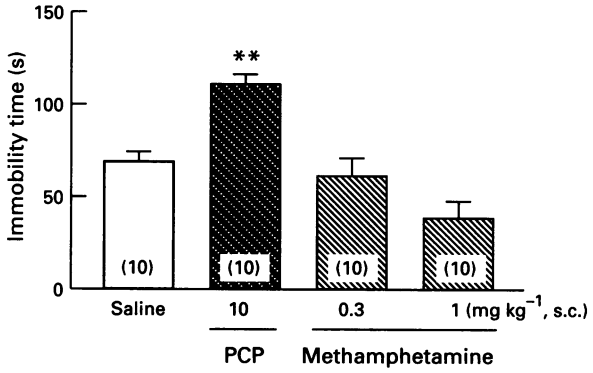

Figure 4 Effects of repeated PCP and methamphetamine treatment on forced swimming-induced immobility in mice. One day after the first measurement of immobility (the 2nd day), the administration of PCP (10 mg kg^{-1} day^{-1}, s.c.) or methamphetamine (0.3 and 1 mg kg^{-1} day^{-1}, s.c.) was started; this continued for 14 days. One day after the last injection (the 16th day), the second measurement of immobility was made. Numbers in parentheses show the number of animals tested. $^{**}P<0.01$ vs control group (Dunnett's multiple comparisons test).

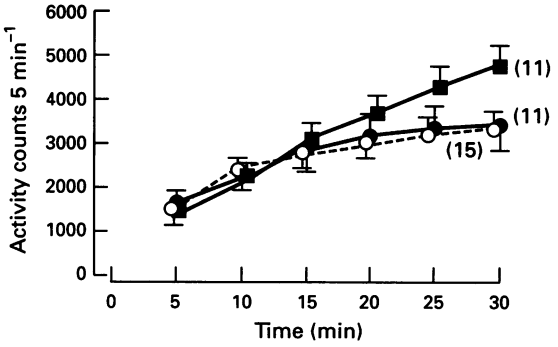

Figure 5 Effect of repeated PCP and methamphetamine treatment on locomotor activity in mice. Animals received PCP (10 mg kg^{-1} day^{-1}, s.c.) or methamphetamine (1 mg kg^{-1} day^{-1}, s.c.), administered for 14 days. One day after the last injection, the locomotor activity was measured. Numbers in parentheses show the number of animals tested: (○) control group; (●) repeated PCP-treated group; (■) repeated methamphetamine-treated group.

Effects of antipsychotics on the PCP-induced enhancement of immobility in forced swimming test in mice

In the repeated PCP-treated mice, a significantly prolonged immobility time was observed in the second measurement of immobility (Figure 7). When such mice received risperidone (0.3 mg kg^{-1}, p.o.), ritanserin (3 and 10 mg kg^{-1}, p.o.), and clozapine (3 and 10 mg kg^{-1}, p.o.), administered 1 h before the second measurement of immobility, the enhancing effect of PCP on the immobility was significantly attenuated, whereas haloperidol (0.3 and 1 mg kg^{-1}, p.o.) failed to attenuate the effect of PCP (Figure 7).

The doses required to attenuate the enhancing effect of PCP on the immobility induced by these drugs in the PCP-treated animals were one-tenth of those required for the saline-treated animals.

Discussion

PCP induces a psychotomimetic state that closely resembles schizophrenia; PCP psychosis, unlike amphetamine psychosis, incorporates both the positive and negative symptoms of

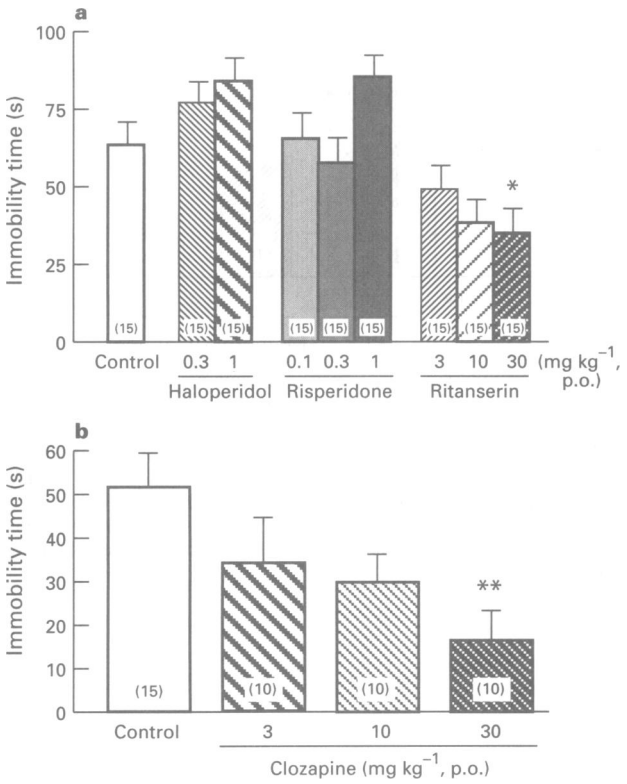

Figure 6 Effects of haloperidol, risperidone, ritanserin, and clozapine on forced swimming-induced immobility in mice. In the repeated saline-treated mice, haloperidol (0.3 and 1 mg kg^{-1}), risperidone (0.1–1 mg kg^{-1}), ritanserin (3–30 mg kg^{-1}), and clozapine (3–30 mg kg^{-1}) were administered orally 1 h before the second measurement of immobility, the animals then performed the measurement of immobility. Numbers in parentheses show the number of animals tested. $^{*}P<0.05$, $^{**}P<0.01$ vs control group (Dunnett's multiple comparisons test).

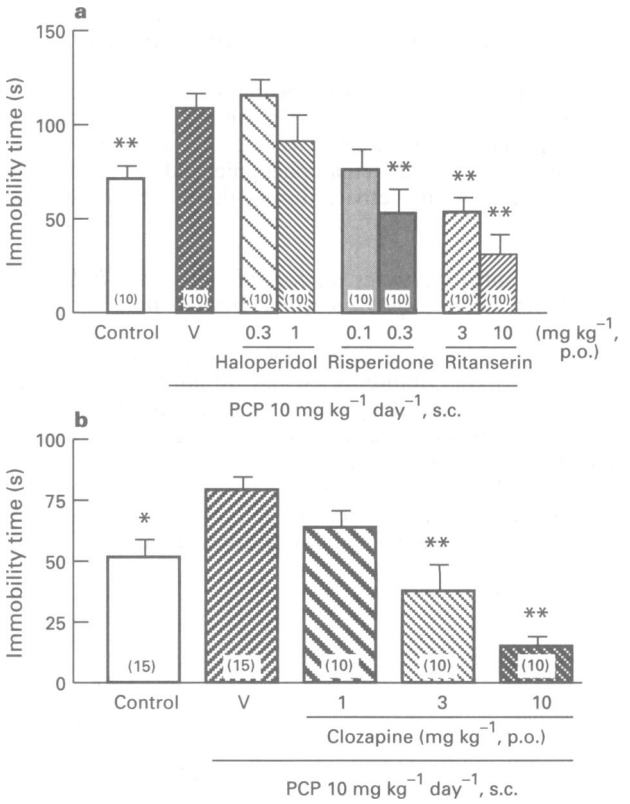

Figure 7 Effects of haloperidol, risperidone, ritanserin, and clozapine on the PCP-induced enhancement of immobility in mice. In the repeated PCP-treated mice, haloperidol (0.3 and 1 mg kg^{-1}), risperidone (0.1 and 0.3 mg kg^{-1}), ritanserin (3 and 10 mg kg^{-1}), and clozapine (1–10 mg kg^{-1}) were administered orally 1 h before the second measurement of immobility, and the animals then performed the measurement of immobility. V: vehicle. Numbers in parentheses show the number of animals tested. $^{*}P<0.05$, $^{**}P<0.01$ vs repeated PCP-treated group (Dunnett's multiple comparisons test).

schizophrenia (Contreras *et al.*, 1986; Yamaguchi *et al.*, 1986; Nabeshima *et al.*, 1989; Sanger & Joly, 1991; Javitt & Zukin, 1991). Although PCP-induced behavioural changes such as hyperactivity and stereotyped behaviours in animals have been extensively employed as indices of schizophrenia, there is little documentation of the PCP-induced behavioural changes in animals that may serve as a model of the negative symptoms of schizophrenia. The most important finding in the present study was that the immobility time in the forced swimming test was prolonged by the repeated PCP treatment. Since forced swimming-induced immobility in animals is regarded as a model of depression (Harlow & Suomi, 1974; Porsolt *et al.*, 1977a,b; 1978) and depression is one of the negative symptoms of schizophrenia (Barnes *et al.*, 1989), this result suggests that the repeated PCP treatment produces a negative symptom-like effect in mice. It is unlikely that the enhancing effect of PCP on the immobility in the forced swimming test was due to motor dysfunction, such as decreased locomotor activity and ataxia, since the repeated PCP treatment did not affect locomotor activity under the same treatment conditions as those used for the forced swimming test. Further, this effect of PCP was observed 24 h after the final injection of PCP, and was well maintained for 21 days after the withdrawal of the drug. These findings therefore indicate that the enhancing effect of PCP on the immobility was not due to an acute effect of PCP, such as the induction of motor dysfunction. In contrast to the effect of PCP, methamphetamine, which also causes psychotomimetic effects in human subjects, failed to modify the forced swimming-induced immobility in mice, suggesting that methamphetamine, unlike PCP, failed to produce a negative symptom-like effect. The present findings are supported by clinical findings that patients with PCP psychosis manifest the negative symptoms of schizophrenia (Contreras *et al.*, 1986; Yamaguchi *et al.*, 1986; Nabeshima *et al.*, 1989; Javitt & Zukin, 1991; Sanger & Joly, 1991), whereas patients with methamphetamine psychosis do not show such symptoms (Javitt & Zurkin, 1991). Similar distinct effects of PCP and methamphetamine have been observed in the social interaction test in rats. Sams-Dodd (1995) has shown that PCP unlike (+)-amphetamine, causes disturbance of social behaviour in rats, suggesting that PCP-induced social isolation may be a possible animal model of negative symptoms.

PCP-induced psychotomimetic effects can be divided into three phases; acute, prolonged, and recurrent (Barnes *et al.*, 1989). The prolonged phase produces psychotic symptoms for up to 4 weeks (Rainey & Crowder, 1975). This clinical finding is consistent with our present findings that the enhancing effect of PCP was well maintained for 21 days after the withdrawal of the drug. PCP is also capable of causing a recurrence of symptoms after being given as a single dose to schizophrenic patients in remission (Ludy *et al.*, 1959), and it has also been shown to cause a recurrence of symptoms after 1 year in nonpsychotic individuals who initially experienced a PCP psychosis (Luisada & Brown, 1976). Further, it is well known that the recurrence phenomenon is also caused by stress. Several studies have shown that previous exposure to stress results in an increased passive behavioural response when the subject is subsequently confronted with a novel stressful situation (Anisman *et al.*, 1978; Katz *et al.*, 1981; Kennett *et al.*, 1985; Cancela *et al.*, 1991; Murua & Molina, 1991; Molina *et al.*, 1994). For instance, following prior exposure to stressors, animals exhibit increased immobility in the forced swimming

test and reduced activity in response to a novel environment (Weiss *et al.*, 1981; Plaznik *et al.*, 1988; Van Dijken *et al.*, 1992). The conditioned emotional response can be measured in terms of inhibition of locomotor activity and the inhibition of lever pressing behaviour for a food or water reward produced by stimuli previously paired with stress (Brady, 1956; Hunt, 1961). Lipska *et al.* (1993) have found that animals with ventral hippocampal lesions showed increased locomotor activity after exposure to a swim stress, and the same effect was also produced by (+)-amphetamine treatment, suggesting an animal model for (+)-amphetamine psychosis. In the present study, when the animals were subjected to a weak stress, forced swimming for 3 min, and then treated repeatedly with PCP and subjected to the same stress again, the forced swimming-induced immobility was enhanced. Thus, the enhancement of immobility seen after PCP treatment could be consistent with the phenomena observed in schizophrenia and with the previous experimental reports, suggesting that this treatment could serve as an animal model for the negative symptoms of PCP psychosis.

Although the classical antipsychotics improve the positive symptoms of schizophrenia (Hirschowitz *et al.*, 1991; Reynolds, 1992; Chouinard *et al.*, 1993), they do not improve the negative symptoms (Boyer *et al.*, 1990; Levinson, 1991). These antipsychotics, of which haloperidol is the most commonly used, are characterized by their action as dopamine-D_2 receptor antagonists. Although haloperidol is efficacious in alleviating positive symptoms of schizophrenia (e.g., delusions, hallucinations, and disordered thinking), its effects on the negative symptoms (e.g., apathy, social withdrawal, and depression) appear to be far from satisfactory (Crow, 1986). A recent advance in this field is the clinical introduction of compounds that have both dopamine-D_2 and 5-HT_{2A} receptor antagonist properties, such as risperidone and clozapine. Such compounds are thought to be efficacious in treating the negative symptoms of chronic schizophrenia (Gelenberg & Doller, 1979; Ceulemans *et al.*, 1985; Castelao *et al.*, 1989; Gelders, 1989; Lieberman *et al.*, 1989; Noda *et al.*, 1993; Oka *et al.*, 1993). In addition, the 5-HT_{2A} antagonist, ritanserin, when combined with typical antipsychotics, has been reported to ameliorate the negative symptoms of schizophrenia (Gelders *et al.*, 1985). In the present study, ritanserin, risperidone, and clozapine, at doses that failed to produce antidepressant effects in the control animals, attenuated the PCP-induced enhancement of immobility in the forced swimming test in mice, whereas haloperidol had no effect. Thus, it would appear that the behavioural change induced by repeated PCP treatment is a useful model for the negative symptoms of schizophrenia, since the ameliorating effects of these antipsychotics in this model would reflect their clinical effectiveness.

The mechanisms by which the negative symptoms are induced in PCP psychosis have yet to be elucidated. Some authors (Ceulemans *et al.*, 1985; Bleich *et al.*, 1988; Janssen *et al.*, 1988; Oka *et al.*, 1993) have indicated that the 5-hydroxytryptaminergic system is involved in the negative symptoms of schizophrenia. It has been reported that PCP interacts with the 5-hydroxytryptaminergic system, since PCP has been shown to inhibit [^{3}H]-spiperone binding to 5-HT_{2A} receptors (Nabeshima *et al.*, 1984a,b; 1985) and since PCP-induced behaviours are inhibited by 5-HT_{2A} receptor antagonists such as ritanserin (Nabeshima *et al.*, 1984c; 1987; Kitaichi *et al.*, 1994). In the present study, the enhancing effect of PCP on immobility was antagonized by ritanserin, risperidone, and clozapine, all of which show 5-HT_{2A} receptor antagonistic properties (Janssen *et al.*, 1988; Wilmot & Szczepanik, 1989; Oka *et al.*, 1993; Kitaichi *et al.*, 1994). Our findings, taken together with these findings, indicate that the effect of PCP on the immobility in the forced swimming test is mediated, at least in part, via 5-HT_{2A} receptors. However, PCP is known to interact with several other binding sites in the brain, including a PCP binding site within the N-methyl-D-aspartate (NMDA) ionophore receptor complex (Johnson *et al.*, 1987) and a sigma binding site that has a high affinity for benzomorphans such as SKF-10,047 (Su, 1982; Tam & Cook, 1984; Largent *et al.*, 1988). Javitt & Zukin (1990; 1991) and Javitt *et al.* (1994) have demonstrated that dysfunction of the NMDA receptor may be particularly relevant to the pathogenesis of negative symptoms in schizophrenia, since PCP psychosis, but not other drug-induced psychoses, mimics both the negative and the positive symptoms of schizophrenia, and these symptoms are induced by blocking the ion channel gated by the NMDA receptor. Further, since PCP interacts with sigma receptors (Nabeshima *et al.*, 1986; Contreras *et al.*, 1987; 1988; Sonders *et al.*, 1988), it is possible that this receptor may be involved in the negative symptoms of schizophrenia (Davidson *et al.*, 1982; Wadworth & Heel, 1990; Meltzer, 1991; Ogawa *et al.*, 1994). Thus, other mechanisms involved in the effects of PCP remain to be elucidated.

This model may provide an explanation for several aspects of the negative symptoms in schizophrenia that have not been accounted for by earlier animal models, although the neuropathologic and neurotransmitter changes after repeated PCP treatment in the present study are not yet clear. The present findings, i.e., that repeated PCP treatment enhanced immobility in the forced swimming test and that this effect of PCP on the immobility was reversed by the atypical antipsychotics, risperidone and clozapine, but not by the typical antipsychotic, haloperidol, are consistent with the clinical findings, and therefore suggest that this model may be useful as an animal model of the negative symptoms of schizophrenia. Further, it appears that PCP may exert its effect, at least in part, via the modulation of 5-HT_{2A} receptors.

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