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Animal Models of Negative Symptoms: M100907 Antagonizes PCP-Induced Immobility in a Forced Swim Test in Mice

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Schizophrenia is characterized by three types of symptoms: positive, disorganized, and negative. The pathophysiology of negative symptoms is less well understood than that of positive symptoms. Consequently, there are more models of positive symptoms than negative symptoms, and the characterization of novel compounds with respect to their potential effects on negative symptoms has been limited to the use of behavioral models with face validity. Behavioral models of negative symptoms that are currently being used in the development of novel antipsychotic agents include: the social withdrawal model in rodents and nonhuman primates; and the forced swim test. In addition, our data suggest that the chronic mild stress model of anhedonia may also be predictive for compounds with efficacy for negative symptoms. In rodents, chronic administration of PCP increases the duration of immobility in the forced swim test and has been used as a model of the negative symptoms of schizophrenia, such as flattening of affect and avolition. An experiment is presented that evaluated the effects of clozapine, haloperidol, and M100907 against PCP-induced immobility in the forced swim test. M100907 is a selective serotonin 5-HT_{2A} receptor antagonist that is currently being evaluated in clinical trials as a treatment for schizophrenia. Clozapine, which has been found to be clinically active against negative symptoms, significantly attenuated PCP-induced immobility, whereas haloperidol, which is clinically inactive against negative symptoms, had no effect. M100907 (0.3 and 1 mg/kg) significantly attenuated PCP-induced immobility, showing a similar profile to clozapine in the forced swim test. Therefore, M100907 may have a unique ability to alleviate the negative symptoms of schizophrenia without the side effects of current antipsychotic medication.

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The characteristic symptoms of schizophrenia have been conceptualized as falling into three broad categories: positive, negative (or deficit), and disorganized (American Psychiatric Association 1997). Positive symptoms include delusions and hallucinations. Disorganized symptoms include disorganized speech, thoughts, and behavior, and poor attention. Negative symptoms include restricted range and intensity of emotional expression (flattened affect), reduced thought and speech productivity (alogia), anhedonia, and decreased initiation of goal-directed behavior (avolition) (American Psychiatric Association 1997).

Negative symptoms recently have been divided further into three components: (1) deficit or primary enduring negative symptoms that may not respond to treatment; (2) primary nonenduring negative symptoms; and (3) secondary negative symptoms (Collaborative Working Group on Clinical Trial Evaluations 1998). Pri-

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mary negative symptoms are thought to be intrinsic to schizophrenia and little is known about their neurobiology or effective treatment. Secondary negative symptoms appear as a consequence of other factors, including positive symptoms, neuroleptic-induced Parkinsonism, depression, or environmental deprivation.

Negative symptoms of schizophrenia, which were once thought to be refractory to treatment, have received renewed attention as a result of the development of newer medications, the "atypical" antipsychotics (Kelley et al. 1999). Atypical antipsychotics have generally been found to be more effective against negative symptoms than conventional antipsychotics, although their effects on specific components of negative symptoms are not known (Collaborative Working Group on Clinical Trial Evaluations 1998). The prototypical atypical antipsychotic, clozapine, is characterized by substantial 5-HT_{2A} antagonism and some D_2 antagonism, and there is growing evidence that 5-HT_{2A} antagonism may be important to its clinical activity (Meltzer 1996; Meltzer et al. 1989).

M100907, a selective 5-HT_{2A} receptor antagonist, is a putative antipsychotic agent that exhibits a promising profile of atypical antipsychotic activity in preclinical models, without producing acute or late neurological side effects. M100907 has been shown to antagonize amphetamine-stimulated locomotion (Hitchcock and Grauffel 1996; Kehne et al. 1996; Moser et al. 1996; Sorensen et al. 1993) and to block amphetamine-induced disruption of latent inhibition (Moser et al. 1996). Moreover, chronic administration of M100907 selectively reduced the number of spontaneously active dopamine neurons in the mesolimbic (A10) but not in the nigrostriatal area (A9) of the brain (Sorensen et al. 1993), suggesting an antipsychotic profile similar to clozapine. M100907 has also shown potent activity in models of the negative symptoms of schizophrenia.

This paper reviews available behavioral models of negative symptoms of schizophrenia, the effects of atypical antipsychotics (including M100907) in these models, and presents the results from a recent study comparing the effects of M100907, clozapine, and haloperidol against PCP-induced immobility in the forced swim test.

PRECLINICAL MODELS OF NEGATIVE SYMPTOMS

Preclinical models of schizophrenia are mainly based on observations in normal humans treated with dopaminergic compounds. For example, chronic use of amphetamines causes a paranoid psychosis similar to that observed in schizophrenia (Lieberman et al. 1987), and excess activity in the mesolimbic dopamine system is postulated to underlie the positive symptoms of schizophrenia. Accordingly, antagonism of the behavioral effects of amphetamine, such as amphetamine-induced locomotor behavior and amphetamine-induced disruptions in latent inhibition, are widely used to characterize compounds with potential antipsychotic efficacy. However, these models have predictive validity for positive symptomatology only.

There is increasing evidence that alterations in dopaminergic and glutamatergic function in the prefrontal cortex (PFC) may contribute to the negative symptoms of schizophrenia (Carlsson 1995; Moghaddam 1994). This theory is partially based on observations that the glutamatergic N-methyl-D-aspartate (NMDA) receptor antagonists, phencyclidine (PCP) and ketamine, produce effects in healthy subjects that are similar to the spectrum of symptoms associated with schizophrenia (Breier et al. 1997; Javitt and Zukin 1991; Krystal et al. 1994; Luby et al. 1959; Pearlson 1981) and worsen symptoms in schizophrenic patients (Lahti et al. 1995a,b; Malhotra et al. 1997). PCP psychosis, unlike amphetamine psychosis, incorporates both positive and negative symptoms of schizophrenia. In addition, the fact that high doses of NMDA antagonists produce neurodegenerative changes in corticolimbic regions (Olney and Farber 1995) has been cited as evidence that alterations in the glutamatergic system, particularly NMDA receptor function, might contribute to the negative symptoms of schizophrenia. Furthermore, lesions to the PFC in humans and monkeys and chronic PCP abuse in humans can induce symptoms resembling negative symptoms of schizophrenia (Hertzman et al. 1990).

The neurochemical or pharmacological basis of negative symptoms is less well-understood than that of positive symptoms. Consequently, the characterization of novel compounds with respect to their potential effects on negative symptoms has been limited to the use of behavioral models with face validity. These models, reviewed below, include social withdrawal models in rodents (Corbett et al. 1995; Sams-Dodd 1998) and monkeys (Ellenbroek et al. 1989; Shapiro et al. 1995, 1996), a model of anhedonia produced by chronic mild stressors (Monleon et al. 1995; Willner et al. 1987), and PCP-induced immobility in the forced swim test (Noda et al. 1995, 1997).

Social Withdrawal Models

Rodents. The social withdrawal model of negative symptoms has been modified from an anxiolytic paradigm, and consists of placing unfamiliar pairs of rats in an "open-field" test area and observing their social behavior for five minutes. The social withdrawal model is sensitive to the locomotor-depressant effects of drugs. Clozapine (5 and 10 mg/kg) dose dependently increases social interaction in pairs of unfamiliar rats, but has no effect on social behavior in familiar rats. In con-

trast, haloperidol (0.25 and 0.5 mg/kg) produces a dose-dependent decrease in social interaction in both unfamiliar and familiar pairs of rats, suggesting a locomotor depressant effect in rats (Corbett et al. 1993). The effects of diazepam are distinguishable from the effects of clozapine in this paradigm; diazepam (5 mg/kg) increases social interaction in both unfamiliar and familiar pairs of rats, whereas clozapine increases social interaction in only unfamiliar pairs of rats. However, this result suggests that clozapine may have some anxiolytic properties.

Acute or chronic administration of PCP (2 and 4 mg/kg), but not amphetamine, can selectively induce social withdrawal in rats that were housed in pairs (familiar rats) for several days prior to testing (Corbett et al. 1995; Sams-Dodd 1998). Social withdrawal is observed at PCP doses that do not disrupt other types of behavior. This PCP-induced social withdrawal in rats has been used as a model of the social withdrawal commonly observed as one of the negative symptoms in schizophrenia. We have found that SCH 23390 (dopamine D_1-receptor antagonist), raclopride (selective dopamine D_2-receptor antagonist), haloperidol, and chlorpromazine failed to reverse the social withdrawal induced by PCP in rats, even at doses that produced significant impairment of motor function. In contrast, clozapine (2.5 and 5 mg/kg) and olanzapine (0.25 and 0.5 mg/kg) significantly ($p < .05$) reversed the disruptive effects of PCP on social interaction; risperidone failed to produce a significant reversal at doses that did not affect normal spontaneous locomotor activity (Corbett et al. 1995).

Nonhuman Primates. Administration of the psychotomimetic compounds amphetamine or (±)-4-iodo 2,5-dimethoxyamphetamine (DOI) to selected members of primate social colonies produces behavioral changes that model the positive and negative symptoms of schizophrenia (Shapiro et al. 1995). Amphetamine and DOI produce increased distancing from other colony members and decreased initiated social grooming, and these behaviors are thought to model the social withdrawal observed in schizophrenic patients (Shapiro et al. 1996). Two studies by Shapiro et al. (1995, 1996) have evaluated the effects of M100907 on social withdrawal behaviors produced by amphetamine and DOI. Administration of d-amphetamine (1 mg/kg, IM) to four of five stumptail macaques significantly increased ($p < .01$) the distance of treated monkeys from other colony members. Pretreatment with M100907 (1 or 3 mg/kg, NG) restored distance scores of d-amphetamine-treated monkeys back to baseline levels ($p < .05$ vs. d-amphetamine alone); M100907 alone had no effect on distance to other colony members. In amphetamine-induced behaviors that are thought to model positive symptoms of schizophrenia, M100907 significantly ($p < .05$) antagonized increased submissiveness (paranoia) and checking (hypervigilance). M100907 did not antagonize amphetamine-induced stereotypies or induce movement disturbances in the monkeys, suggesting that M100907 has a low potential to produce extrapyramidal symptoms (Shapiro et al. 1996).

In the other study by Shapiro et al. (1995), administration of DOI induced behavioral changes similar to those produced by d-amphetamine and most hallucinogens, including myoclonus limb jerks, decreased food chewing, decreased social grooming, and increased visual scanning. M100907 significantly antagonized DOI-induced limb jerks ($p < .01$), decreased scanning/checking ($p < .01$), increased food chewing ($p < .05$), and restored social grooming ($p < .05$) (Shapiro et al. 1995). Together, the results of these 2 studies suggest that M100907 will be clinically active against both the positive and negative symptoms of schizophrenia.

Stress-Induced Anhedonia

Studies by Willner and colleagues (Willner et al. 1987) have shown that chronic exposure (5 to 9 weeks) to a succession of mild unpredictable stress reduces the consumption of, and preference for saccharin or sucrose solutions over water in rats, which is thought to model an inability to experience pleasure or anhedonia. The chronic mild stress (CMS) model was initially developed as an animal model for depression as preference for sucrose can be reestablished after administration of most antidepressant agents for 2 to 4 weeks (Monleon et al.1995; Papp et al. 1996). Because anhedonia is also a core feature of the negative symptoms of schizophrenia, we hypothesized that the CMS model may also predict compounds with efficacy for the negative symptoms of schizophrenia. Therefore, we tested clozapine and haloperidol in this model.

We now report that the atypical antipsychotic agent clozapine is effective in reversing the CMS-induced decrease in sucrose preference, whereas haloperidol was without effect. In addition, M100907 had a similar profile as clozapine in this model (Mondadori et al., unpublished observations, The effects of M100907 in the chronic mild stress model). This is the first report to show that atypical antispychotic agents are active in this model and to suggest that the CMS model may have utility in predicting compounds with efficacy for the negative symptoms of schizophrenia.

The Forced Swim Test

The forced swim test consists of placing rodents in a water-filled glass cylinder from which they cannot escape. Rodents become immobile in this situation. This immobility appears to be sensitive to several antidepressants and is reversed by acute antidepressant treatment, suggesting that this task may be a useful model of depression or despair (Porsolt et al. 1977a,b, 1978).

Repeated treatment with PCP enhances immobility in a forced swim test in mice, and this effect is reduced by atypical antipsychotics (Noda et al. 1995). Hence, the effects of PCP in the forced swim test may also be useful as an animal model of the negative symptoms of schizophrenia, particularly as a model of flattening of affect or avolition (Noda et al. 1995, 1997).

Noda et al. (1995) first studied the effects of PCP on the immobility induced by forced swimming. The investigators reported that treatment with PCP (10 mg/kg daily) for 14 successive days produced a significant increase in immobility in the forced swim test; this immobility persisted for at least 21 days after PCP administration was stopped. The enhancing effect of PCP on immobility was found to be attenuated by ritanserin (3 and 10 mg/kg, PO), risperidone (0.3 mg/kg, PO), and clozapine (0.3 and 1 mg/kg, PO), whereas haloperidol (0.3 and 1 mg/kg, PO) was without effect (Noda et al. 1995). We performed a study to partially replicate the results of Noda et al. (1995) and compare the effects of M100907 to those of clozapine and haloperidol on PCP-induced immobility in the forced swim test in mice. The results of this study are reported below.

METHODS

Animals

Male CD-1 mice weighing from 25 to 30 grams (Charles River) were used. The animals were housed under standard laboratory conditions as outlined in the 'NIH Guide for the Care and Use of Laboratory Animals' (National Institute of Health Publications, No. 85–23, revised 1983), maintained on a 12-hour light/12-hour dark cycle, and allowed free access to food and water until the beginning of the experimental procedure.

Drugs

Clozapine, PCP, haloperidol (McNeil Pharmaceuticals, Inc.), and M100907 (R(+)-α-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidine-methanol, synthesized at Hoechst Marion Roussel) were either dissolved or suspended in distilled water with a drop of Tween 80 and administered in an injection volume of 1 mL/100 grams per mouse. The final volume was prepared to account for salt content and the dosage was expressed as 100% base.

Procedure

On the first day, mice were individually placed in a transparent glass cylinder (20 cm high, 8 cm in diameter), which contained water at 25°C to a depth of 10 cm, and were forced to swim for 3 minutes (Noda et al. 1995). The duration of immobility (immobility time in seconds) was measured by an observer unaware of treatment condition. The mice were then randomly assigned to one of four treatment groups. On the second day, chronic PCP treatment was started, and thereafter, saline or PCP (1, 3, and 10 mg/kg, SC) was administered once daily for 14 days. On Day 16, each mouse was placed in the water again for 3 minutes, and immobility time was recorded. Clozapine (1, 3, or 10 mg/kg, PO)

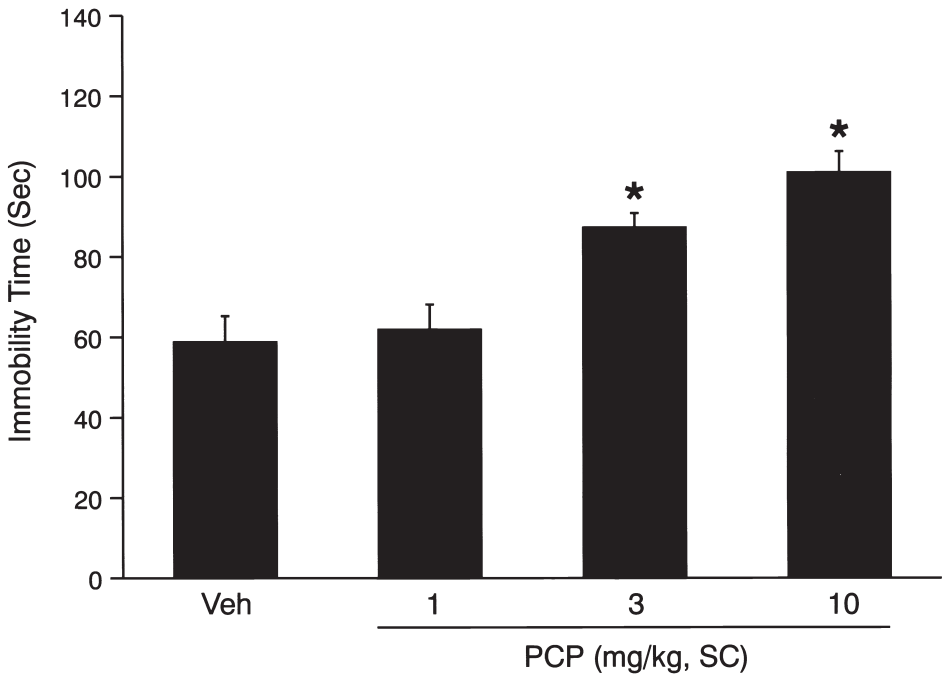

Figure 1. Effects of repeated PCP (1, 3, and 10 mg/kg daily, SC) treatment on forced swimming induced immobility in mice. $N = 8$ per group. *$p < .05$ vs. control group (Dunnett's multiple comparison test).

and haloperidol (3 or 1 mg/kg, PO) were administered 1 hour before measurement of the second immobility time, and M100907 (0.1, 0.3, 1 mg/kg, IP) was administered 30 minutes before measurement of the second immobility time. Control animals received vehicle only.

RESULTS

The effects of chronic PCP administration on immobility in the forced swim test are shown in Figure 1. The figure shows that chronic PCP administration significantly ($p < .05$) and dose dependently prolonged immobility time compared with the vehicle control group in the second measurement of immobility; PCP at 3 and 10 mg/kg SC significantly increased immobility time by 50% and 72%, respectively. The effects of haloperidol and clozapine on PCP-induced immobility are shown in Figures 2a and 2b, respectively.

Haloperidol (0.3 and 1 mg/kg, PO) administered 1 hour before the second measurement of immobility failed to attenuate the enhancing effect of PCP on immobility (Figure 2a), whereas clozapine (3 and 10 mg/kg, PO) significantly ($p < .05$) attenuated the effect of PCP (Figure 2b). M100907 (0.3 and 1 mg/kg, IP) showed a similar profile as clozapine and significantly ($p < .05$) antagonized PCP-induced immobility in the forced swim test (Figure 3).

DISCUSSION

The results with haloperidol and clozapine in the present study are consistent with the findings of Noda et al. (1995), who showed that clozapine, risperidone, and ritanserin were effective in reducing PCP-induced immobility, whereas haloperidol was without effect. In the light of the hypothesis that the PCP forced swim test might represent a model for negative symptoms, there is a striking similarity to clinical observations that clozapine, risperidone, and ritanserin are more effective in treating the negative symptoms of schizophrenia than haloperidol (Duinkerke et al. 1993; Iskedjian and Remington 1998; Kane et al. 1988). Antagonism of PCP-induced enhancement of immobility in the forced swim test appears to be best correlated with antagonism of the serotonin 5-HT_{2A} receptor subtype (Noda et al. 1997). This would explain the effects of M100907, a highly selective 5-HT_{2A} antagonist, in this model and predicts that M100907 will have clinical activity against negative symptoms.

The clinical efficacy of clozapine against negative symptoms has been observed at doses at which 5-HT_{2A} receptors are saturated (Nordström et al. 1995). Consistent with this finding, the effects of M100907 in the forced swim test in the present experiment were observed at doses (0.3–1 mg/kg) at which 5-HT_{2A} receptors are saturated (unpublished findings). The possible importance of 5-HT_{2A} receptors in the treatment of neg-

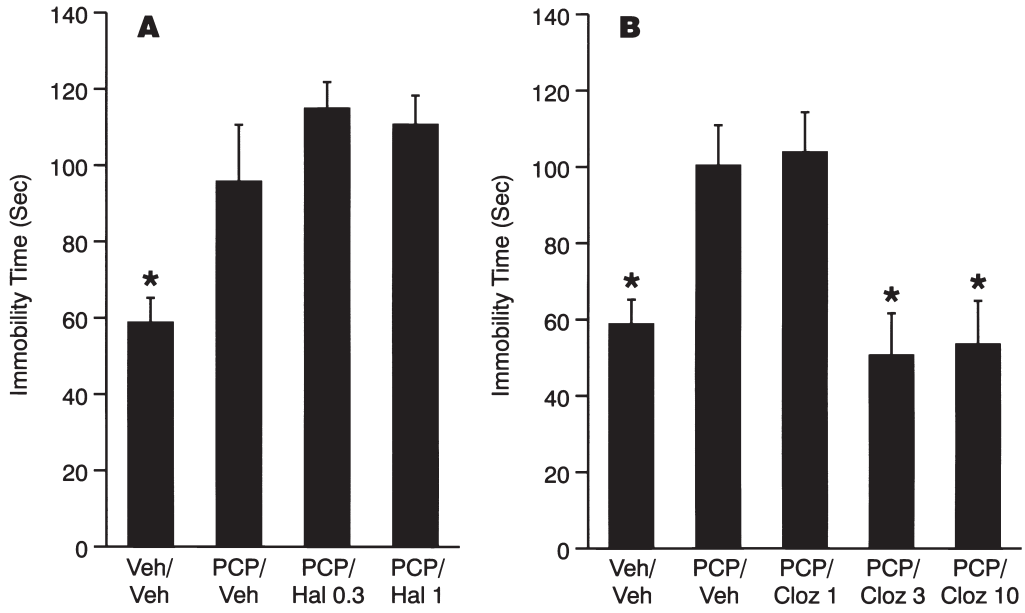

Figure 2. Effects of: (a) haloperidol (Hal 0.3 and 1 mg/kg, PO); and (b) clozapine (Cloz 1, 3, and 10 mg/kg, PO) on the PCP-induced (10 mg/kg, SC) enhancement of immobility in mice. $N = 8$ per group. *$p < .05$ vs. repeated PCP-vehicle treated group (Dunnett's multiple comparisons test).

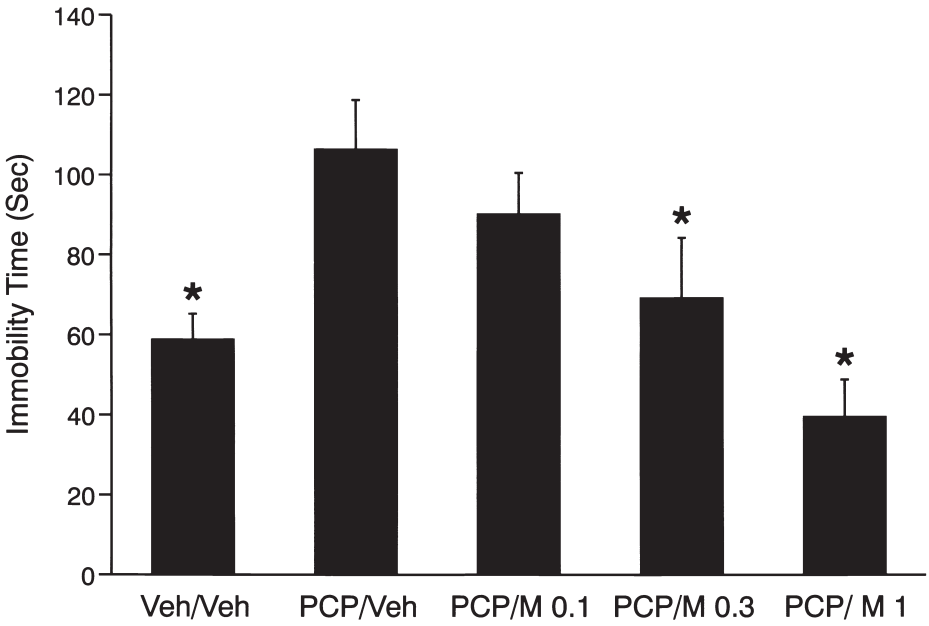

Figure 3. The effects of M100907 (M 0.1, 0.3, 1 mg/kg, IP) on the PCP-induced (10 mg/kg, SC) enhancement of immobility in mice. $N = 8$ per group. $^*p < .05$ vs. repeated PCP-vehicle treated group (Dunnett's multiple comparisons test).

ative symptoms is also highlighted by the fact that ritanserin, a nonselective 5-HT_{2A}/5-HT_{2C} antagonist used in combination with typical antipsychotics (neuroleptics), can ameliorate negative symptoms (Duinkerke et al. 1993). In addition, the atypical antidepressant mianserin, which has 5-HT_{2A} antagonistic properties, was effective in treating affective flattening and blunting negative symptoms as an adjunct therapy in schizophrenics (Hayashi et al. 1997).

The known biochemical correlates of PCP-induced enhancement of immobility in the forced swim test are mainly dopaminergic: a decrease in the turnover of dopamine, an increase in the content of 5-hydroxyindole acetic acid (5-HIAA), and an increase in the 5-HIAA/5-HT ratio in the PFC of mice have been observed (Noda et al. 1997). Clozapine has been found not only to counteract PCP-induced prolongation of immobility in the forced swim test but also to increase dopamine activity in the PFC. In contrast, the typical antipsychotic agent haloperidol not only failed to decrease the chronic PCP-induced immobility in this paradigm but also failed to increase PFC dopamine (Noda et al. 1995). M100907, similar to clozapine, has been found to increase dopamine content in the PFC (Schmidt and Fadayel 1995), and in the present experiment, to counteract PCP-induced immobility.

CONCLUSIONS

The characterization of novel compounds with respect to their potential effects on negative symptoms has been limited to the use of behavioral models with face validity because the pathophysiology of negative symptoms is less well-understood than that of positive symptoms. However, there is emerging evidence for a role of glutamate in the negative symptoms of schizophrenia. One piece of this evidence comes from the fact that NMDA antagonists produce positive and negative schizophrenic-like symptoms in healthy subjects (Javitt and Zukin 1991). Acute administration of the noncompetitive NMDA antagonist ketamine has been found not only to induce acute psychosis in healthy human volunteers, but also was shown to worsen psychotic symptoms in schizophrenic patients (Lahti et al. 1995a,b). Accordingly, within the context of the pronounced effects of M100907 in glutamatergic animal models of schizophrenia, potential interactions between serotonergic and glutamatergic neurons are of major interest in studies of the pathophysiology of schizophrenia and the development of novel antipsychotics.

During the past few years, evidence has accumulated that glutamatergic and serotonergic neurotransmitter systems are closely interlinked in the PFC. For example, serotonergic 5-HT_{2A} receptors have been found to be located on the apical dendrites of layer V pyramidal cells, which are glutamatergic neurons (Hamada et al. 1998; Jakab and Goldman-Rakic 1998; Willins et al. 1997). These 5-HT_{2A} receptors might presynaptically modulate excitatory neurotransmission by increasing the release of glutamate through an "asynchronous" mechanism, not associated with the arrival of an action potential (Aghajanian and Marek 1997; Marek and Aghajanian 1998). This asynchronous glutamate re-

lease by the activation of 5-HT_{2A} receptors may be pathologically increased in schizophrenia, leading to the manifestations of negative symptoms.

In line with this hypothesis, recent findings have also shown that acute treatment of rodents with NMDA receptor antagonists can selectively increase glutamate release in the PFC (Moghaddam and Adams 1998). Accordingly, the therapeutic importance of the $5HT_{2A}$ receptor blockade might lie in the fact that it provides a mechanism to normalize excessive glutamate release, which is essential for normal higher-order functions (Jakab and Goldman-Rakic 1998). Moreover, the capacity of selective 5-HT_{2A} antagonists such as M100907 to facilitate dopamine neurotransmission in the prefrontal cortex, without blocking dopamine receptors, may provide a mechanism for reducing primary negative symptoms, while simultaneously minimizing the risk of inducing secondary negative symptoms.

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