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# M100907 and Clozapine, but not Haloperidol or Raclopride, Prevent Phencyclidine-Induced Blockade of NMDA Responses in Pyramidal Neurons of the Rat Medial Prefrontal Cortical Slice

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*In the present study, we demonstrate that, in a concentration-dependent manner, M100907 (formerly MDL 100907, a highly selective 5-$HT_{2A}$ receptor antagonist and a purported atypical antipsychotic drug [APD]), but not its much less active stereoisomer M100009, completely prevents or markedly reverses the phencyclidine (PCP)-induced blockade of N-methyl-D-aspartate (NMDA) responses in pyramidal neurons of the medial prefrontal cortex (mPFC). Furthermore, the atypical APD clozapine, but not the typical APD haloperidol or raclopride (a selective dopamine $D_{2,3}$ receptor antagonist), mimicked the action of M100907, preventing the PCP-induced effect. These results suggest that M100907 might be an antidote for treating the PCP-induced psychotomimetic state that closely resembles schizophrenia; they could also account for the antipsychotic potential of M100907. Furthermore, our results suggest that the prototype (clozapine) and a candidate (M100907) atypical APDs might be effective in ameliorating schizophrenic symptoms including cognitive and neuropsychological deficits, which are induced in humans who abuse PCP. We hypothesize that the ability of M100907 and clozapine to prevent or reverse the PCP-induced blockade of the NMDA receptor channel is attributed to their 5-$HT_{2A}$ receptors antagonizing property. Therefore, with further systematic studies, the ability of compounds to prevent or reverse PCP's blockade of NMDA responses may prove to be an effective electrophysiological model for screening potential atypical APDs and predicting their therapeutic efficacy in cognitive deficits.*
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KEY WORDS: *Antipsychotic drugs; Phencyclidine; 5-$HT_{2A}$ receptors; NMDA receptors; Pyramidal cells; Medial prefrontal cortex*

The psychotomimetic state induced by the noncompetitive N-methl-D-aspartate (NMDA) receptor channel blockers, such as PCP and ketamine, in normal human subjects is thought to be a better model for schizophrenia than that produced by amphetamine. In humans, not only does PCP cause hallucinations and delusions, but it also causes an associated apathetic state and a type of formal thought disorder that are more distinctive features of schizophrenia (Allen and Young 1978; Javitt and Zukin 1991; Kristensen et al. 1992; Krystal et al. 1994; Malhotra et al. 1996, 1997a,b; Pearlson 1981).

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Furthermore, in schizophrenics, NMDA receptor antagonists produce an exacerbation of psychotic symptoms and cognitive impairment (Javitt and Zukin 1991; Lahti et al. 1995; Malhotra et al. 1996, 1997a,b). Cognitive deficits have also been observed in PCP- or ketamine-treated rats (Alessandri et al. 1989; Danysz et al. 1988; Jentsch et al. 1997a; Verma and Moghaddam 1996) and monkeys (Boyce et al. 1991; Jentsch et al. 1997b). In addition, unlike normal subjects, both schizophrenics (Ingvar and Franzen 1974; Weinberger et al. 1986, 1988; Weinberger and Berman 1996) and PCP-abusing humans (Hertzman et al. 1990; Wu et al. 1991) failed to activate frontal cortical regions during performance of frontal-dependent tasks. These observations form the foundation for the glutamate hypothesis of schizophrenia in which it is postulated that an aberrant glutamatergic neurotransmission, particularly NMDA receptor hypofunction, results in both the cognitive and the psychiatric manifestation of the disorder (Carlsson and Carlsson 1990; Deutsch et al. 1989; Kim et al. 1980; Moghaddam 1994; Olney and Farber 1995; Wachtel and Turski 1990).

Although typical APDs, which not only alleviate schizophrenic symptoms but also cause extrapyramidal side effects (EPS), are in general not very effective in treating PCP-induced psychoses (Allen and Young 1978; Pearlson 1981), evidence has been accumulating in animal studies to suggest that some APDs, particularly those atypical ones (which possess antipsychotic activity but lack EPS), are capable of reversing the PCP-induced effect. For example, the potency of a series of neuroleptics in blocking PCP-induced hyperlocomotion in rodents correlated with their affinity for 5-hydroxytryptamine$_{2A}$ (5-HT$_{2A}$) receptors (Gleason and Shannon 1997; Maurel-Remy et al. 1995). Moreover, the atypical APDs clozapine and olanzapine have been shown to reverse noncompetitive NMDA antagonist-induced social withdrawal in rats (Corbett et al. 1995) and prevent MK-801 neurotoxicity (Farber et al. 1996). Clozapine also ameliorated a long-lasting cognitive deficit induced by repeated administration of PCP in monkeys (Jentsch et al. 1997b). In addition, clozapine, but not haloperidol, has been shown to improve PCP-induced impairment of performance in a water maze (Okuyama et al. 1997). Similarly, it has been demonstrated that clozapine and seroquel, but not haloperidol or risperidone, antagonize PCP-induced deficits in sensorimotor gating of the startle response (Bakshi et al. 1994; Keith et al. 1991; Swerdlow et al. 1996). In contrast, it has been reported that haloperidol reduces significantly both MK-801-induced popping and hyperactivity in mice (Rosse et al. 1995); haloperidol and raclopride, but not SCH 23390, reverse the disruptive effect of ketamine on spatial delayed alternation performance (Verma and Moghaddam 1996); both haloperidol and clozapine reverse PCP-induced increases in striatal neuron firing in free-moving rats (White et al. 1995). At present, the underlying mechanisms by which the aforementioned APDs reverse the PCP/ketamine-induced effect are not clear.

We have previously demonstrated that both clozapine and M100907 [R-(+)-α-(2,3-dimethoxyphenil)-1-[4-fluorophenylethyl)]-4-piperidinemethanol (Kehne et al. 1996; Sorensen et al. 1993); but not raclopride, markedly potentiate NMDA receptor-mediated neurotransmission in pyramidal cells of the mPFC and this effect is antagonized by the selective NMDA receptor antagonist D(−)-2-amino-5-phosphonopentanoic acid (d-AP5) (Arvanov and Wang 1998; Arvanov et al. 1997). Haloperidol was less effective than clozapine and M100907 in potentiating NMDA responses. Furthermore, M100907 and clozapine markedly potentiate; whereas, haloperidol depresses, glutamate neurotransmission elicited by electrical stimulation of the forceps minor (white matter) in the mPFC. The latter finding might be related to the fact that haloperidol, but not M100907 or clozapine, depresses the (±)-α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)-induced response in a concentration dependent manner (Arvanov and Wang 1998; Arvanov et al. 1997). M100907 enhances the release of excitatory amino acids (EAAs) induced by NMDA or electrical stimulation of the forceps minor; EAAs, in turn, activate both NMDA and non-NMDA receptors, depolarize membrane potential, and remove the $Mg^{2+}$ block of the NMDA receptor–ionophore complex, and thereby dramatically increasing NMDA-induced inward current by 350 to 550% in pyramidal cells (Arvanov and Wang 1998).

Based on our findings, we predict that M100907 is capable of preventing or reversing PCP-induced blockade of NMDA receptor–ionophore complex because: (1) the block of NMDA-induced inward current by ketamine/PCP is highly voltage-dependent; and (2) the onset/offset of ketamine/PCP's blockade of the NMDA receptor channel is a function of repeated presentations of the agonist (Honey et al. 1985; MacDonald et al. 1987). Therefore, experiments were designed to examine this possibility. For comparison, the ability of clozapine, haloperidol, raclopride, and M100009 to prevent/reverse PCP's effect was also investigated.

## MATERIALS AND METHODS

### Preparation of mPFC Slices

The techniques and procedures for preparation of rat mPFC slices and for standard intracellular recording of presumed pyramidal neurons have been described previously (Arvanov and Wang 1998; Arvanov et al. 1997). Briefly, male Sprague–Dawley rats were decapitated under halothane anesthesia, and their brains were removed and cooled in ice-cold artificial cerebrospinal fluid (ACSF). The coronal (transverse) slices of mPFC (450-μm thick) were cut in ice-cold ACSF containing (in

mM: NaCl 117, KCl 4.7, $CaCl_2$ 2.5, $MgCl_2$ 1.2, $NaHCO_3$ 25, $NaH_2PO_4$ 1.2 and D-glucose 11, aerated with 95% $O_2$/5% $CO_2$ (pH 7.4) and kept submerged at room temperature for at least 1 h to allow for recovery. A single slice was then transferred to a recording chamber (32°C). The chamber was continuously superfused with ACSF at a constant rate of 2 ml/min.

### Intracellular Recording and Single-Electrode Voltage Clamp

The procedures for intracellular recording and single-electrode voltage clamp using an Axoclamp 2B amplifier have been described elsewhere (Arvanov and Wang 1998; Arvanov et al. 1997). Sharp electrodes were pulled on a horizontal puller (Model P-87, Sutter Instruments, San Rafael, CA) and filled with 4 M K-acetate or 3 M KCl (tip resistances 55–80 MΩ). In current-clamp mode, the bridge balance was continually monitored and adjusted as necessary. Single-electrode voltage clamp was achieved under discontinuous mode at a sampling rate of 5–6.2 KHz (30% duty cycle), gain of 2.5–5 nA/mV. The efficacy of voltage clamp, electrode "settling time," and input capacitance neutralization at the head stage were continuously monitored on an oscilloscope. Current and voltage records were acquired using a D/A sampling and acquisition software (pClamp 6, Axon Instruments, Foster City, CA), filtered at 1 KHz, and analyzed off-line. Voltage and current signals were recorded on a Gould Easy Graph Thermal Recorder (TA 240) and two-channel video tape recorder (VR-10B Digital Data Recorder, Instrutech, Elmont, NY). During voltage clamp recordings, tetrodotoxin (TTX, 0.5 μM), glycine (1 μM), and bicuculline (5 μM) were routinely included in the ACSF. All cells were held at −60 mV to minimize activating $I_M$ and $I_h$ (Halliwell and Adams 1982). The problems (e.g., space clamping) associated with this method in neurons with extended processes have been discussed elsewhere (Finkel and Redman 1985). As has been pointed out, these problems faced during single-electrode voltage clamp may be less acute when dealing with the relative changes following drug application (Madison et al. 1987; Schweitzer et al. 1993).

Except where noted, drugs were administered via the superfusion medium. PCP was administered in the ACSF for 5 min before repeated application of NMDA (see below). When the ability of M100907 and APDs to prevent PCP's effect was examined, these compounds were superfused 15 min before PCP and then continuously throughout the experiment. NMDA was applied by placing a microdrop (10 μl) of concentrated solution (1 mM with a dilution factor 1:100) on a marked spot in the inflow channel of the chamber (volume 1 ml) as previously described (Arvanov and Wang 1998; Arvanov et al. 1997). Repeated microdrop application of NMDA to the same pyramidal cell with an interapplication interval of approximately 15 min produced a consistent inward current, although the baseline current caused by NMDA varied from cell to cell (30–200 pA). Typically, two or three stable consecutive control responses to NMDA were obtained, the average of which was counted as the baseline of NMDA, prior to any drug tests.

### Data Analysis

The percent modulation produced by APDs on NMDA-evoked responses was calculated by subtracting the baseline peak amplitude of the responses from that evoked by bath application of APDs. This value was then divided by the baseline response and multiplied by 100. The results were presented as mean ± SE. Paired *t*-tests and Student's *t*-tests were used; 0.05 was selected for testing the level of significance.

In addition, we used SAS' PROC MIXED for our data analyses. The design of our experiments was as follows; within each cell a drug was given, and the effects were measured at multiple times. Each cell received one drug (or combinations of drugs), and the effect was measured at 15-min intervals. In this design, cells constituted one level of analysis, and the individual time measurements within cells constituted another. Such data are often referred to as repeated measures data. Because of the nature of the design, we have unbalanced data (i.e., some cells had more time measurements than others). Recently developed software such as SAS' PROC MIXED for multilevel modeling produces maximum likelihood estimates of the parameters and the variance covariance matrix of residuals (Bryk and Raudenbush 1992; Diggle 1988; Littell et al. 1996), which is superior to analysis of variance (ANOVA) with repeated measurements in handling unbalanced data.

One of the key assumptions of ANOVA is homoskedasticity of variances in the parameters under study. Because of heteroskedastic variances in the parameters studied, the analysis and significance tests were performed after applying transformations, which included log, square root, reciprocal square root, and reciprocal square (Zar 1996).

### Drugs

The compounds raclopride, NMDA, QX 314, and bicuculline methchloride were all purchased from Research Biochemicals International (RBI, Natick, MA). TTX was purchased from Sigma Chemical Co. (St. Louis, MO). M100907 and M100009, clozapine, haloperidol, and PCP were generous gifts from Hoechst Marion Roussel, Inc. (Bridgewater, NJ), Sandoz (Hanover, NJ), McNeil Laboratories (Fort Washington, PA), and National Institute of Drug Abuse (NIDA, Rockville, MD), respectively.

The concentration of stock solution of drugs was prepared 1000-fold higher than that of the final target concentration. As previously described (Arvanov and Wang 1997), drugs were first dissolved in 50 to 100 μl of either 5% lactic acid (e.g., M100907 and haloperidol) or 99% DMSO (e.g., clozapine), and then brought to stock concentration by the addition of purified water. Some compounds were dissolved directly in purified water (e.g., TTX [citrate buffer], (−)-bicuculline methchloride, CNQX-HBC complex, glycine, PCP and raclopride).

## RESULTS

### Presumed Pyramidal Neurons in the mPFC

All experiments were routinely performed on presumed pyramidal neurons in layers V and VI of the mPFC, an area that contains a high density of both 5-$HT_{2A}$ and NMDA receptors (Blue et al. 1988; Dure and Young 1995; Mengod et al. 1990; Willins et al. 1997) and has been suggested to play a key role in the pathogenesis of schizophrenia (Goldman-Rakic and Selemon 1997; Weinberger and Lipska 1995). The mPFC is located medial to the forceps minor and can be easily identified in the slice.

A total of 58 presumed pyramidal cells has been recorded; the electrophysiological criteria for distinguishing presumed pyramidal versus nonpyramidal cells have been previously published (Arvanov et al. 1997; Cauli et al. 1997; Connors and Gutnick 1990; Kawaguchi and Kubota 1996; McCormick et al. 1985; Yang et al. 1996). Briefly, the interneurons were characterized by a brief spike duration (<1 ms at half-maximum spike amplitude) and a lack of pronounced spike-frequency ad-

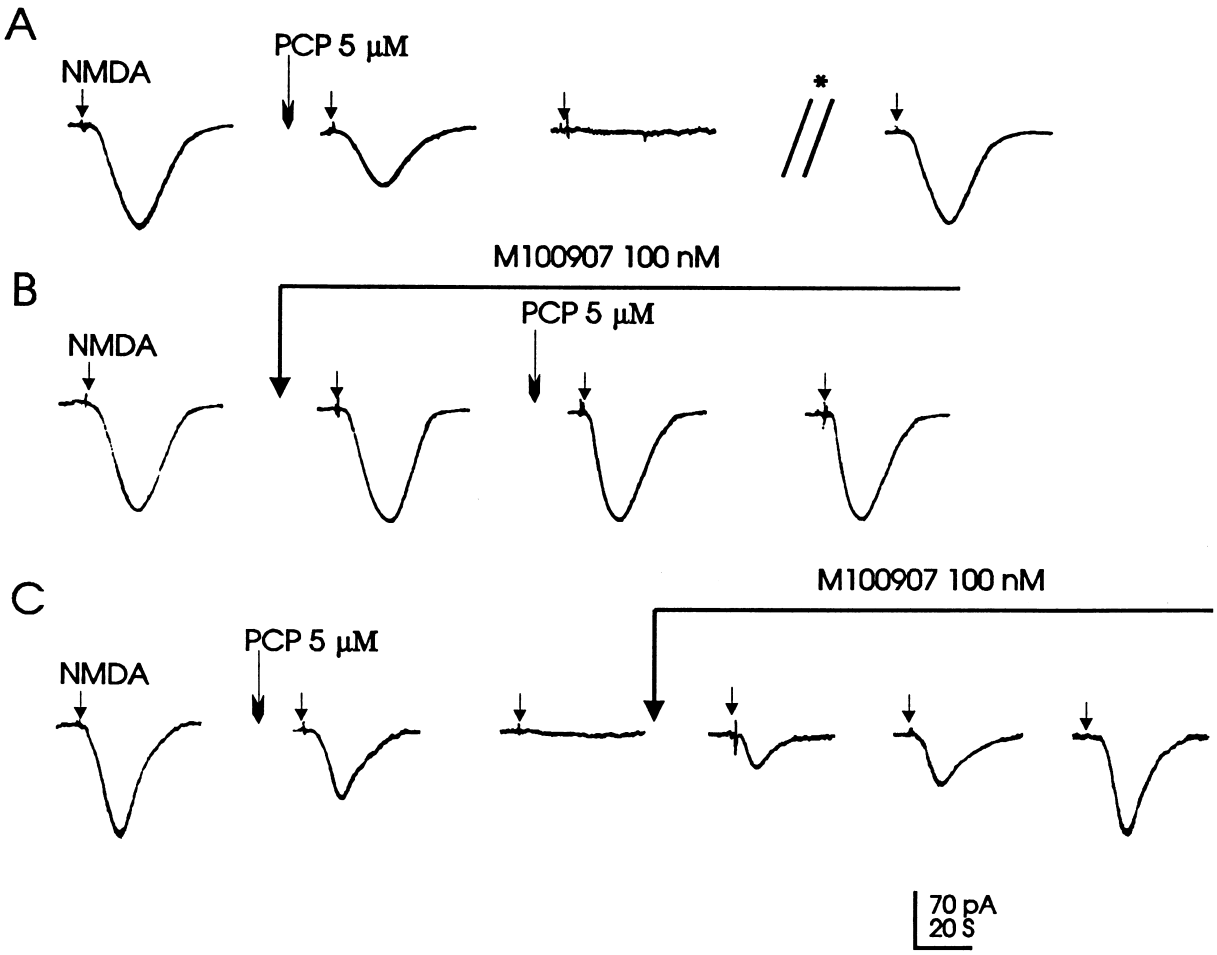


**Figure 1.** Representative current traces to illustrate that 100 nM M100907 effectively prevents and reverses PCP's blockade of NMDA responses. **A**: Administration of PCP 5 μM into the ACSF for 5 min partially blocked the first NMDA response and completely prevented the second NMDA responses, reflecting the use-dependent blockade of NMDA receptor-ionophore by PCP. The asterisk indicates that NMDA was applied repeatedly with an interapplication interval of 15 min. It took approximately 2 h for this neuron to recover from PCP's depressant effect. **B**: Perfusion of M100907 5 min before the administration of PCP and continuously throughout the experiment completely prevented PCP's effect. **C**: Administration of M100907 following PCP strikingly shortened the duration of the blockade of NMDA receptor channel by PCP.

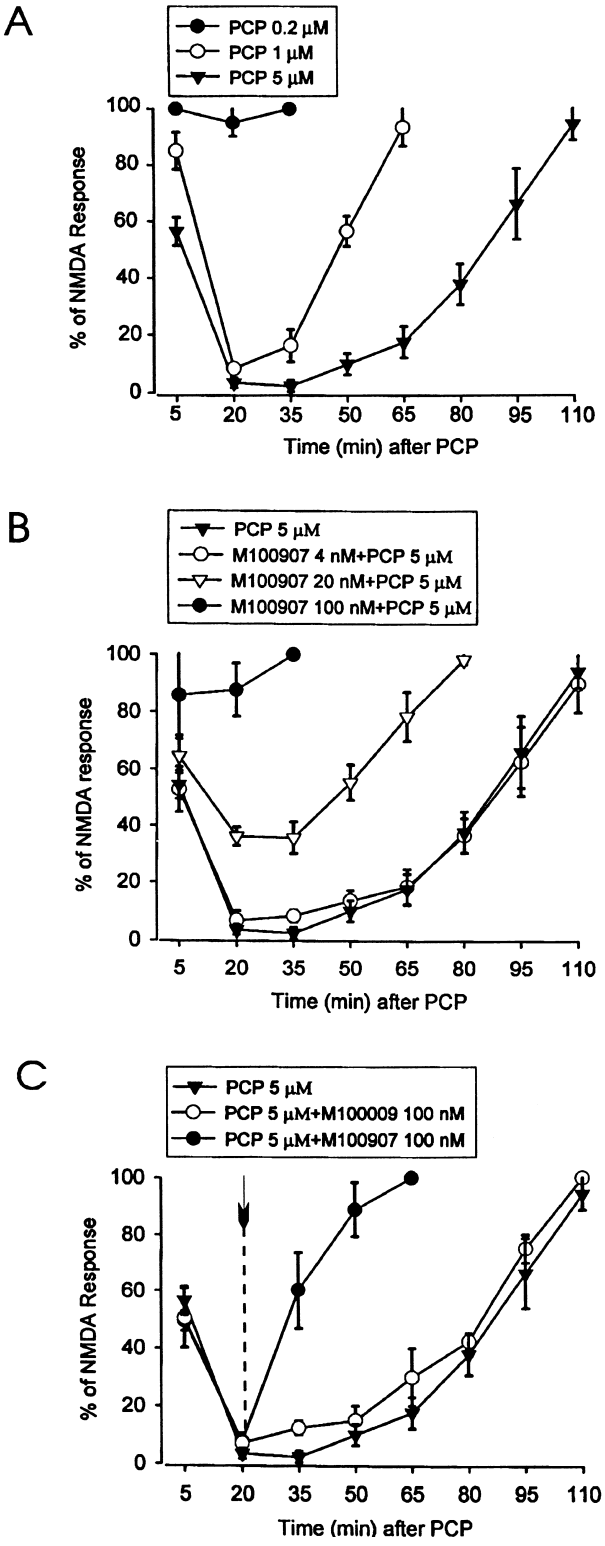


**Figure 2.** Diagrams illustrating that M100907, but not M100009, prevents and reverses the PCP-induced blockade of NMDA responses. **A**: PCP reduced and blocked NMDA-induced inward current in a concentration-dependent manner. **B**: In a concentration-dependent fashion, M100907 either prevented totally or reduced markedly the ability of PCP to block NMDA responses. **C**: M100907, but not M100009, was capable of reversing the PCP-induced blockade of NMDA responses, when it was administered (arrow) immediately following the onset of PCP's blockade. M100907 markedly reduced the duration of the blockade of NMDA responses by PCP.

aptation in response to constant-current depolarizing pulses. In contrast, the pyramidal cells had a longer spike duration, particularly the second spike (1–3 ms at half-maximum spike amplitude), and showed a pronounced spike-frequency adaptation.

### Effect of NMDA in Presumed Pyramidal Cells of the mPFC

As previously reported (Arvanov and Wang 1997; Arvanov et al. 1997), NMDA (10 μM) elicited excitatory postsynaptic potentials (EPSPs) followed by a membrane depolarization (amplitude, 12.6 ± 1.5 mV, range, 8–18 mV) and bursts of action potentials. In the voltage clamp mode, at the holding potential (Vh) of −60 mV, NMDA 10 μM produced an inward current of 30–200 pA (68 ± 8 pA, $n = 57$).

### Effect of PCP on NMDA-Induced Response

We have found that bath application of PCP invariably produced a significant hyperpolarization (4 ± 2.1 mV, $n = 17$; $p < .001$, paired $t$-test) of membrane potential. Accordingly, to avoid interference of voltage-related alteration of ion channels, we have routinely used the techniques of a single-electrode voltage clamp. When the presumed pyramidal neuron was held at −60 mV, bath application of PCP for 5 min produced a dramatic blockade of NMDA responses in a concentration-dependent fashion (Figures 1 and 2). PCP at 0.2 μM produced a marginal blockade of NMDA responses; whereas, at a concentration of either 1 or 5 μM, PCP completely blocked NMDA-induced inward current (Figure 2A). The blockade produced by 1 μM PCP was use-dependent; i.e., requiring depolarization and current flow (open channels) for block to occur. Thus, 1 μM PCP produced little effect on the initial inward current induced by NMDA (NMDA response was reduced by 15 ± 6.5%, $n = 4$, which was not significantly different from that of controls, $p = .1$, paired $t$-test), but dramatically reduced the second NMDA response by 91.5 ± 1.4% ($n = 4$, Figure 1A). The blocking effect of 5 μM PCP was less use-dependent, because the blockade of the first and second NMDA-induced inward current by 5 μM PCP reached 56 ± 5% and 98 ± 1.9% ($n = 5$), respectively. Both NMDA responses were significantly smaller than that of controls ($p < .001$, paired $t$-tests). The blockade lasted for 60 ± 15 ($n = 4$) and 110 ± 15 min. ($n = 5$) for 1 and 5 μM

PCP, respectively, during repeated application of NMDA with an interapplication interval of 15 min (Figure 2A). Overall, there is a significant difference between the effect produced by 5 vs. 1 μM PCP (SAS Proc Mixed multilevel modeling, chi square = 50, df = 3, $p < .0001$) and between the effect produced by 1 vs. 0.2 μM PCP (SAS Proc Mixed multilevel modeling, chi square = 48.5, df = 5, $p < .0001$) on the time course of NMDA responses.

As reported Previously (Honey et al. 1985; MacDonald et al. 1987), PCP-induced blockade of the NMDA receptor ion channel is voltage dependent. Thus, when the holding potential was at −40 and −20 mV, PCP produced little or no blockade of the NMDA-induced inward current ($n = 3$, not shown).

### Comparison of Effects of M100907 and M100009 on PCP-Induced Blockade of NMDA Responses

When M100907 was administered 15 min before 5 μM PCP and then continuously throughout the experiment, it markedly reduced or completely prevented the PCP-induced blockade of the NMDA receptor-ionophore complex in a concentration-dependent manner (Figure 1B). Thus, at concentrations of 20 and 100 nM M100907 significantly reduced and completely abolished PCP's effect, respectively (SAS Proc Mixed multilevel modeling, chi square = 44.2 and 83.9, df = 6 and 3 for 20 and 100 nM M100907, respectively; $p < .0001$ for both concentrations); whereas 4 nM M100907 was without effect (SAS Proc Mixed multilevel modeling, chi square = 5.8, df = 8, $p = .695$; Figure 2B). Moreover, when M100907 (100 nM), but not the same concentration of M100009, was administered after PCP, it significantly shortened the duration of PCP's blockade of NMDA responses, reversing the PCP effect (50 ± 8 vs. 113 ± 7 min, *t*-test, $p < .001$). The recovery time course of PCP with the addition of M100907 is significantly different from that of PCP alone (SAS Proc Mixed multilevel modeling, chi square = 45, df = 2, $p < .0001$). In contrast, addition of M100009 did not significantly alter the recovery time course of PCP (SAS Proc Mixed multilevel modeling, chi square = 0.64, df = 2, $p < .728$; Figure 2C).

### Comparison of Effects of M100009, M100907, Clozapine, Haloperidol, and Raclopride on PCP-Induced Blockade of NMDA Responses

We have examined and compared the ability of M100907, M100009, clozapine, haloperidol, and raclopride to prevent 1 μM PCP-induced blockade of NMDA responses. The concentration of 1 μM PCP was selected because it closely related to the serum and CSF PCP concentrations detected in humans (Donaldson and Baselt 1979; Pearlson 1981; Walberg et al. 1983). Moreover, 100 nM clozapine was only partially effective (50 ± 13%, $n = 4$) in preventing the blockade of NMDA responses by 5 μM PCP. The duration of the blockade of NMDA responses by 1 μM PCP lasted less than 65 min, which was too short to examine reliably the ability of the aforementioned compounds to reverse PCP's effect, using our paradigm of repeated application of NMDA at an interapplication interval of 15 min (see Figure 2A). We, therefore, compared the ability of these compounds to prevent PCP's action. The concentration of 100 nM was selected, because we have previously shown that the potentiation of NMDA-induced inward current in pyramidal cells of the mPFC produced by M100907 and clozapine has reached a plateau at this concentration.

Figures 3 and 4 show that at the concentration of 100 nM, both M100907 (SAS Proc Mixed multilevel modeling, chi square = 65.4, df = 3, $p < .0001$) and clozapine (SAS Proc Mixed multilevel modeling, chi square = 63.6, df = 4, $p < .0001$), but not M100009, haloperidol, or raclopride, effectively prevented the PCP-induced blockade of NMDA responses (SAS Proc Mixed multilevel modeling and chi square tests, $p > .05$; Figure 4).

## DISCUSSION

It has been previously reported that the blockade of the NMDA receptor channel by PCP and ketamine is highly voltage dependent, and the onset/offset of the blockade is dependent upon the exposure to agonists (Honey et al. 1985; MacDonald et al. 1987). Therefore, it is no surprise that M100907 is able to effectively antagonize the PCP-induced effect, because we have shown that M100907 enhances NMDA-induced release of EAAs, which activate both NMDA and non-NMDA receptors and depolarize membrane potential and remove $Mg^{2+}$ blockade of the NMDA receptor channel, thereby potentiating strikingly NMDA responses (Arvanov and Wang 1998). Reminiscent of the action of M100907, the atypical APD clozapine, but not the typical APD haloperidol or raclopride, effectively potentiates the glutamatergic neurotransmission (Arvanov et al. 1997) and prevents the PCP-induced blockade of NMDA responses in pyramid cells of the mPFC. The application of either M100907 or clozapine alone did not alter resting membrane potential and input resistance of presumed pyramidal cells (Arvanov and Wang 1998; Arvanov et al. 1997). However, both clozapine and M100907 markedly potentiated NMDA-induced release of EAAs, which in turn acted upon primarily non-NMDA receptors and caused membrane depolarization, because the potentiating effect produced by M100907 and clozapine could be blocked by CNQX (Arvanov and Wang 1998; Arvanov et al. 1997). This action could account for the ability of these compounds to prevent PCP's blockade of the NMDA receptor channel, analogous to the removal of the $Mg^{2+}$ blockade of the NMDA receptor channel by depolarization of the mem-

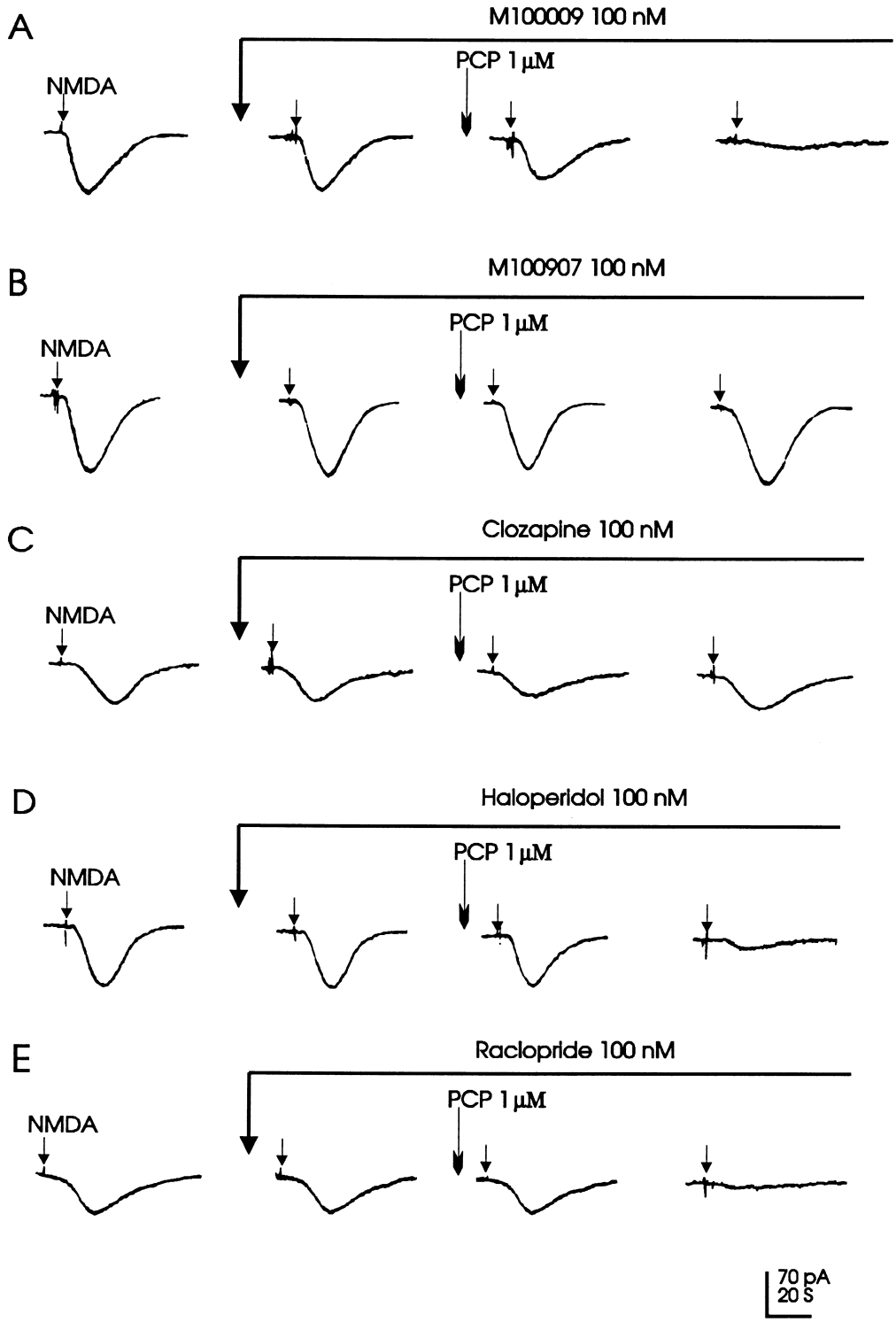


**Figure 3.** Representative current traces to illustrate that at the concentration of 100 nM, M100907 and clozapine but not M100009, haloperidol, or raclopride, prevented the PCP-induced blockade of the NMDA-induced inward current.

brane potential (Arvanov and Wang 1998). Indeed, we have confirmed the previous finding that the PCP-induced blockade of the NMDA receptor ion channel is voltage dependent (Honey et al. 1985; MacDonald et al. 1987). Thus, when the holding potential was at −40 and −20 mV, PCP produced little or no blockade of the NMDA-induced inward current.

Haloperidol at the concentration of 100 nM also potentiated NMDA-induced inward current. However, haloperidol at concentrations of ⩾100 nM tended to hyper-

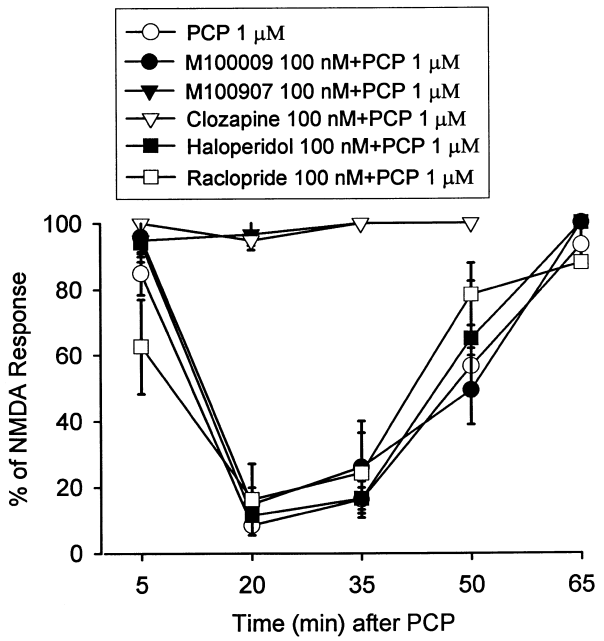


**Figure 4.** Comparison of the ability of M100907, clozapine, haloperidol, raclopride and M100009 to prevent the PCP-induced blockade of NMDA responses. Clozapine and M100907, but not M100009, haloperidol, or raclopride, were capable of preventing PCP-induced blockade of NMDA responses.

polarize the membrane potential (Arvanov et al. 1997), which could contribute to the inability of haloperidol in preventing PCP's action.

At present, it is not clear how M100907 reversed PCP's effect by potentiating NMDA-induced release of EAAs if NMDA receptors have already been blocked. Perhaps at the concentration of PCP used in this study, the blockade of the NMDA receptor channel by PCP was incomplete. Even an initial small amount of EAAs being released by NMDA could gradually relieve PCP's blockade by depolarization of membrane potential (see above) and by further increasing the release of EAAs via activation of the glutamate autoreceptor-mediated positive feedback pathway (Arvanov and Wang, 1997; Berretta and Jones 1996; Connick and Stone 1988; Montague et al. 1994). M100907 might have potentiated NMDA-induced release of EAAs and facilitated the process of recovery. Repeated application of NMDA and enhanced release of EAAs should have helped the recovery process, because offset of the blockade of the NMDA receptor channel by PCP is dependent upon the exposure to agonists (Honey et al. 1985; MacDonald et al. 1987).

In agreement with our results are the recent reports indicating that clozapine, but not haloperidol, blunts NMDA antagonist-induced psychosis (Malhotra et al. 1997b; Lahti et al. 1995). The inability of haloperidol to affect PCP's blockade of NMDA responses is consistent with the observations that typical APDs are in general not very effective in treating PCP-induced psychosis (Allen and Young 1978; Pearlson 1981) and PCP-induced behavioral effects (see introductory paragraphs). In view of the dramatic ability of M100907 to prevent/reverse PCP's effect, it is suggested that M100907 may be used as an antidote for the PCP-induced psychotomimetic state; this may also account for, at least partly, the potential antipsychotic action of this compound (M100907 is currently under phase IIB clinical studies as a potential APD; personal communication, Dr. S. Sorensen, Hoechst Marion Roussel). On the other hand, the use of clozapine to treat the PCP-induced psychotomimetic state should be avoided, because it is less potent than M100907 and may lower seizure threshold and/or precipitate severe hypotension (Haller and Binder 1990; Pearlson 1981) and because of the danger of bone marrow toxicity.

As pointed out earlier, in addition to hallucination and delusion, PCP/ketamine induces schizophrenia-like cognitive and neuropsychological deficits, and causes thought disorder (Krystal et al. 1994; Malhotra et al. 1996, 1997a,b; Witkin 1995). Although it has been proposed that cognitive dysfinction in schizophrenia might result from underlying brain structural damage and cognitive symptoms are associated with the poor outcome of schizophrenia (Kay and Sevy 1990), the ability of PCP to induce reversible neuropsychological abnormalities suggests that a deficiency in NMDA receptor-mediated neurotransmission could be critically linked to cognitive and neuropsychological deficits seen in schizophrenia. The ability of the prototype (clozapine) and a candidate (M100907) atypical APD to prevent and reverse the PCP-induced blockade of NMDA responses strongly suggests that these compounds and perhaps other putative atypical APDs might be effective in ameliorating schizophrenic negative symptoms and potentially improving cognitive and neuropsychological deficits. Consistent with this view, we have recently demonstrated that M100907, but not M100009, enhances the induction of long-term potentiation (which has been regarded as a cellular basis for certain forms of learning and memory) in the synapses of CA1 cells of the hippocampal slices (Wang and Arvanov 1998). Moreover, there is supporting evidence that clozapine decreases negative symptoms and improves cognitive function (Fujii et al. 1997; Hagger et al. 1993; Lee et al. 1994; Meltzer 1995; Meltzer et al. 1996; but also see Breier et al. 1994; Goldberg and Weinberger 1994); whereas, typical APDs produced little improvement in negative symptoms and cognitive deficits in schizophrenia (Cassens et al. 1990; Lee et al. 1994).

It is likely that the ability of M100907 and clozapine to prevent or reverse the PCP-induced blockade of the NMDA receptor channel is the result of their 5-$HT_{2A}$ receptors antagonizing property because (1) M100907 is a

highly selective 5-$HT_{2A}$ receptor antagonist (Kehne et al. 1996), and (2) clozapine and other putative atypical APDs are known to possess a relatively high affinity to 5-$HT_{2A}$ receptors (Meltzer et al. 1989), and they do not bind directly to the MK-801 site on the NMDA receptor-ionophore complex (Corbett et al. 1995; Lidsky et al. 1993; Lynch and Gallagher 1996; Tarazi et al. 1996). Moreover, neither the typical APD haloperidol nor the dopamine $D_{2,3}$ ligand raclopride was capable of preventing/reversing PCP-induced blockade of NMDA responses, ruling out the possibility of a major role of dopamine $D_{2,3}$ and σ receptors (to which haloperidol possesses a high affinity). In concordance with the present results, we have previously demonstrated that clozapine, but not haloperidol or sulpiride, potently blocks the action of the 5-$HT_{2A,2C}$ receptor agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) in pyramidal cells of the mPFC (Ashby and Wang 1990). Furthermore, M100907, clozapine, and other 5 $HT_{2A}$-related compounds (e.g., ketanserin, ritanserin, metergoline, and LY 53857), but not haloperidol or raclopride, are capable of potentiating, dramatically, NMDA receptor-mediated neurotransmission (Arvanov and Wang 1998; Liang and Wang unpublished observations). Although the mechanisms by which M100907 and 5-$HT_2$ related compounds modulate glutamatergic neurotransmission are not clear, it is possible that the facilitation of release of EAAs by M100907 and 5-$HT_2$ related compounds may play a major role in their modulatory action. Indeed, we have previously demonstrated that M100907 markedly facilitates NMDA-induced release of EAAs (Arvanov and Wang 1998), which is in consonant with the report showing that activation of presynaptic 5-$HT_{2A}$ receptors inhibits the release of glutamate from cerebellar mossy fiber terminals (Maura et al. 1991). Further systematic examination and comparison of the actions of 5-$HT_{2A}$ receptor antagonists on PCP-induced effect are needed to verify our hypothesis that the ability of M100907 and clozapine to prevent or reverse the PCP-induced blockade of the NMDA receptor channel is attributed to their 5-$HT_{2A}$ receptor antagonizing property.

If 5-$HT_{2A}$ receptors do play a predominant role in modulating PCP's blockade of the NMDA receptor channel, it might be speculated that atypical APDs, that are known to possess a relatively high affinity to 5-$HT_{2A}$ receptors (Meltzer et al. 1989), are a lot more effective than typical APDs in preventing/reversing PCP's blockade of the NMDA receptor channel, although further systematic examinations and comparisons of the ability of various typical and atypical APDs to prevent/reverse PCP's blockade of NMDA responses are needed to verify this view. In fact, this may prove to be an effective electrophysiological model for screening potential atypical APDs and predicting their effectiveness in alleviating some schizophrenic negative symptoms and improving neuropsychological and cognitive deficits.

It should be pointed out that controlled clinical studies of a 5-$HT_{2A,2C}$ receptor antagonist ritanserin in schizophrenia suggest only limited efficacy (Bleeker and Versleger 1990; Gelders et al. 1986). However, recent studies did suggest that ritanserin, either alone (Wiesel et al. 1994) or added to stable treatment with neuroleptics (Duinkerke et al. 1993), may have clinically significant efficacy. The poor efficacy of ritanserin as an APD has been attributed to several factors, including the dose restriction of ritanserin and the potentially propsychotic properties of ritanserin (Martin et al. 1997). A more definitive conclusion on whether a pure 5-$HT_{2A}$ antagonist is an effective APD will have to await the results from clinical studies of M100907.

In conclusion, in the present study, we have demonstrated that both M100907 and clozapine, but not M100009, haloperidol or raclopride, effectively prevent the PCP-induced blockade of the NMDA responses in pyramidal cells of the mPFC. Our results support the hypothesis that M100907 might be an effective atypical APD, and it might be an antidote for the PCP-induced psychotomimetic state in humans. It will be of great interest to determine whether our findings can be generalized to other atypical APDs; this may represent a new electrophysiological model for screening potential atypical APDs and predicting the effectiveness of these compounds for treating negative symptoms and neuropsychological and cognitive deficits associated with schizophrenia.

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