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NMDA receptor antagonists acting at the glycine$_B$ site in rat models for antipsychotic-like activity

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Summary. Several partial agonist and full antagonists acting at the glycine site of the NMDA receptors were tested for potential antipsychotic-like properties in rats. As models, amphetamine- and phencyclidine (PCP)-induced locomotor activation in the open field and PCP-induced impairment of prepulse inhibition of the acoustic startle response were employed. In the open field test, partial agonists, D-cycloserine failed to show any effect, aminocyclopropane carboxylic acid (ACPC) enhanced the action of PCP (but not that of amphetamine) and R(+)HA-966 attenuated the locomotor activation produced by both amphetamine and PCP. Both full glycine$_B$ antagonists, L-701,324 and MRZ 2/576 attenuated the action of amphetamine and PCP but at the doses that also produce transient behavioural inhibition in naive animals. A competitive NMDA receptor antagonist CGP 39551 was ineffective. In the prepulse inhibition test neither L-701,324 nor MRZ 2/576 changed sensorimotor gating in naive animals nor attenuated the disrupting effects of PCP. The present data do not support antipsychotic profile of glycine$_B$ full antagonists. However, psychotomimetic potential of glycine$_B$ antagonists seems to be low.

Keywords: Amphetamine, phencyclidine, NMDA antagonists, prepulse inhibition, antipsychotics, glycine$_B$ antagonists, L-701,324, MRZ 2/576.

Introduction

Psychotomimetic activity is one of the most common side-effects observed in humans treated with N-methyl-D-aspartate (NMDA) receptor antagonists (Muir et al., 1994; Sveinbjornsdottir et al., 1993). In case of NMDA channel blocker phencyclidine (PCP), both negative and positive psychotic symptoms have been observed (Luby et al., 1959; Javitt and Zukin, 1991). Moreover, recently a decrease in the NMDA receptor subunit NR1 was found in

schizophrenic patients suggesting that in fact hypofunction of NMDA receptors may evoke psychotomimetics-like alteration (Humphries et al., 1996). It is note worthy that this subunit contains glycine recognition site. Also density of glutamate uptake sites assessed with [^{3}H]-D-aspartate binding is decreased in the caudate nucleus, putamen and nucleus accumbens of schizophrenics indicating impaired glutamatergic innervation of these subcortical regions (AparicioLegarza et al., 1997).

These, and other observations gave the basis for the hypothesis of glutamatergic hypofunction as an underlying mechanism of schizophrenia (Carlsson and Carlsson, 1990; Deutsch et al., 1989; Ishimaru and Toru, 1997; Javitt and Zukin, 1991; Kim et al., 1980). As a result, treatment strategies aimed at positive modulation of NMDA receptors have been proposed. The initial clinical studies used agonists or partial agonists of the glycine site (glycine$_B$) present at the NMDA receptor complex and playing a positive modulatory role (Danysz and Parsons, 1998). Some of these clinical trials indicate that glycine improves primarily negative symptoms in schizophrenic patients (Javitt, 1996; Waziri, 1988). Similarly, a partial agonist at the glycine$_B$ site, D-cycloserine, produced an improvement at a low dose (50 mg) but worsening at higher dose (250 mg) which probably reflects its different intrinsic activity at various NMDA receptor subtypes (Cascella et al., 1994; Goff et al., 1995; Krueger et al., 1997).

In rodents, glycine itself or other agonists of glycine$_B$ site such as D-serine or D-alanine inhibit hyperactivity and stereotypy produced by PCP or another NMDA channel blocker (+)-5-methyl-10,11-dihydro-5H-dibenzocyclohepten-5,10-imine maleate ((+)MK-801) (Contreras, 1990; Gandolfi and Dallolio, 1993; Tanii et al., 1994). Also a systematically active glycine uptake inhibitor, glycyldodecylamide (GDA), was found to be very potent in reversing PCP-induced hyperactivity in rodents (Javitt and Frusciante, 1997).

Somewhat in contradiction to these observations it has been recently postulated that full antagonists acting at the glycine$_B$ site such as L-701,324 (7-chloro-4-hydroxy-3-(3-phenoxy)-phenyl-2(H)quinolone) might have features of atypical neuroleptics. Namely, L-701,324 attenuates PCP-induced increase in dopamine turnover in the mesolimbic system (Hutson et al., 1995) and inhibits hyperlocomotion produced by amphetamine injection into the nucleus accumbens but not stereotypy following striatal injection of amphetamine or systemic administration of apomorphine (Bristow et al., 1996). Moreover, L-701,324 attenuates impairment of sensorimotor gating – following isolation in rats as evidenced by disruption of prepulse-induced inhibition of the acoustic startle (Bristow et al., 1995; Swerdllow et al., 1994; Wan et al., 1995).

We have recently developed a series of systemically active selective antagonists acting at the glycine$_B$ site belonging to pyrido-phthalazinediones (Parsons et al., 1997) which were shown in preliminary studies to attenuate the locomotor effects of amphetamine (AMPH) – resembling in this respect L-701,324 (Danysz et al., 1996).

Thus, the aim of the present study was to verify the potential antipsychotic-like potential of glycine$_B$ antagonists and partial agonists in two animal models: amphetamine- or PCP-induced locomotor activation and

PCP-induced impairment of prepulse inhibition in rats. For comparison, a competitive NMDA receptor antagonist was used.

Materials and methods

Antagonism of amphetamine- and PCP-induced hyperactivity

Animals

Naive male Sprague Dawley rats (220–250 g) were housed 5 per cage with water and food ad libitum, in a 12 h light-dark cycle (light on at 6 a.m.), and controlled temperature (23°C). All tests were performed 11.00 a.m. and 6.00 p.m.

Apparatus

Locomotor activity was measured in four perspex boxes (45 × 45 × 35 cm) in a noise proof chamber equipped with red light of 40 W, placed 45 cm above the floor, ventilation and a video camera. The Opto-Varimex system (Omnitech, Columbus Instruments, Ohio) was used for the measurement of activity in each cage. Two sets of 48 infrared photobeams placed 3 cm above the floor measured horizontal activity. The minimal number of photobeams interrupted resulting in the registration of horizontal activity, was set at 3 so that locomotion, but not head waving or sniffing was counted. The output from the counters was integrated and analysed on line by an IBM computer with use of Auto-Tracking software.

Experimental procedure

In the first set of experiments rats were injected with tested agents or corresponding vehicles and placed in the open field boxes. After 5 min of habituation the locomotor activity was measured for 30 min in 5 min intervals. Doses having no effects or very modest effects on locomotor activity were then chosen for the interaction experiments (see below). In the second set of experiments rats were injected with AMPH or PCP (at the doses based on the previous study from the same laboratory, Danysz et al., 1994) and NMDA receptor antagonist or vehicle and locomotor activity was measured for 120 min in 20 min intervals.

Substances

The following substances have been used, stimulants: amphetamine sulphate (RBI, USA) and PCP hydrochloride (RBI, USA), glycine$_B$ partial agonists: aminocyclopropane carboxylic acid (ACPC, Tocris, UK), D-cycloserine (D-CS, Sigma, USA), and R(+)-3-amino-1-hydroxy-2-pyrrolidone (R(+)-HA-966, Tocris, UK), glycine$_B$ antagonists: L-701,324 (Tocris, UK); MRZ 2/570, MRZ 2/571 and MRZ 2/576 (choline salts of pyrido-phthalazine-diones having Br, F or Cl in position 8 respectively, Merz + Co., Germany, Parsons et al., 1997) and a competitive NMDA receptor antagonist DL-(E)-2-amino-4-methyl-5-phosphono-3-pentanoic acid methyl ester (CGP 39551, Ciba Geigy, Switzerland).

All agents were injected i.p. at a volume of 2 ml/kg of body weight. Substances were dissolved in physiological saline except for CGP 39551 and MRZ agents that were dissolved in distilled water and L-701,324 was dissolved in 25% polyethylenglycol with few drops of NaOH. PCP and amphetamine were given 5 min, CGP 39551 120, partial agonists and L-701,324 30 and other agents 15 min before the test.

Statistical analysis

Open field activity results are expressed as means ± S.E.M. and dose dependency studies were analysed by one-way ANOVA separately for each interval and if significant,

followed by the Dunnett's test for comparison with the control – vehicle treated group. In interaction experiments (combination with amphetamine or PCP) the results are analysed by two-way ANOVA separately for each interval and for the sum of counts for the whole observation period. For simplification only significant interaction is further indicated in the results section as this was central to the aim of the study.

Prepulse-induced inhibition of the acoustic startle response

Animals

This experiment was carried out on Wistar male rats weighing 250–300 g. After delivery, the animals were habituated to the experimental room for 1 week. Rats were kept in plastic cages (58 × 37 × 19 cm) in groups of 6 rats per cage, under controlled light-dark cycle (light on: 7.00–19.00) with water and food available ad libitum.

Apparatus

The startle apparatus (Columbus Instruments, Ohio) consisted of three plastic transparent cages placed in a sound-proof cabinet and equipped with a movable platform floor attached to a sensor recording vertical movements of the platform. Startle reaction was evoked by acoustic stimuli delivered by a loudspeaker suspended above the cage and connected to an acoustic generator (Columbus Instruments, Ohio). The transient force resulting from the movements of the platform evoked by the startle reaction was recorded with a PC computer during a recording window of 200 ms measured from the onset of the acoustic stimulus, digitalized and stored in the computer for further evaluation.

Experimental procedure

This experiment was performed in order to evaluate the effect of the compound MRZ 2/576 given either alone or in combination with PCP, on sensorimotor gating measured by prepulse-induced inhibition of the acoustic startle response in rats. PCP was used as a reference drug with strong psychotomimetic properties, and producing consistent inhibition of the prepulse inhibition.

After 1 week of adaptation, pre-test was performed in order to select experimental groups and after next 3 days the test was carried out. The rats were injected with vehicle or drug and after an appropriate time placed into the testing cages. After 5 min of habituation (background white noise, 65 dB), two types of acoustic stimuli were used: acoustic stimulus alone (120 dB, 40 ms, 4,000 Hz) or the stimulus preceded by a pre-pulse (75 dB, 20 ms, 4,000 Hz) applied 100 ms before the stimulus. During each experimental session 20 trials of each type were presented with interstimulus interval of 20 s.

Substances

MRZ 2/576 and L-701,324 were injected i.p., 15 or 30 min before the test respectively, while PCP was injected at the dose of 10 mg/kg, s.c., 5 min before the start of the session. PCP was dissolved in the physiological saline, MRZ 2/576 in water and L-701,324 in 25% polyethylenglycol with added few drops of NaOH. All agents were administered in a volume of 2 ml/kg of body weight.

Statistical analysis

The amplitude of the startle response was measured during the whole recording window (200 ms) and an average value of amplitude was taken for further evaluation. The amplitudes were averaged for each individual animal, separately for both types of trials (stimulus alone or stimulus preceded by the prepulse). In order to evaluate the drugs effects on

the startle response by itself and on the prepulse inhibition, a two-way analysis of variance (drug treatments as factors) and for individual post-hoc comparisons between groups, Newman-Keuls test was used. The results are expressed as mean ± S.E.M.

Results

Open field test

A partial glycine$_B$ agonist D-CS alone did not change locomotor activity up to 300 mg/kg (Fig. 1A), but enhanced AMPH effect in the last observation period (ANOVA – significant interaction, Fig. 1B) and failed to affect PCP-induced hyperactivity (Fig. 1C). Similarly after ACPC treatment spontaneous activity was not changed (up to 600 mg/kg, Fig. 2A) although at this dose it enhanced clearly hyperlocomotion produced by PCP but not that induced by AMPH (Fig. 2B). Another glycine$_B$ partial agonist R(+)-HA-966 at 30 mg/kg attenuated significantly the effect of AMPH (Fig. 3A) and also that of PCP, but during the first testing period only (Fig. 3B). At 10 mg/kg R(+)-HA-966 failed to change the effect of PCP (not shown). Although in the present study we have not tested the effect of R(+)-HA-966 on locomotion in naive animals, previous work from this laboratory indicates that it is inactive up to 30 mg/kg (Danysz et al., 1994).

Glycine$_B$ full antagonist, L-701,324 alone inhibited locomotion at 3 and 10 mg/kg during the first 5 min of the test (Fig. 4A). At 10 mg/kg L-701,324 attenuated activation produced by AMPH in the 2nd observation interval and the total sum of counts (Fig. 4B). L-701,324 also diminished the action of PCP but the effect was modest since significant only at 80 min time point (Fig. 4C). Similarly, MRZ 2/576 alone produced initially modest sedation at 3 and 10 mg/kg (Fig. 5A) and attenuated significantly (also for the sum of scores) the effect of AMPH and PCP at 10 mg/kg (Fig. 5B and C).

On the other hand CGP 39551 produced sedation at 10 and 30 mg/kg (Fig. 6A) and at the dose of 10 mg/kg it tended to attenuate the effect of AMPH, but this failed to reach statistical significance (Fig. 6B). Moreover, CGP 39551 did not change the locomotor effect of PCP (Fig. 6C).

Prepulse inhibition

PCP, as expected produced impairment of prepulse inhibition at the dose of 10 mg but did not change startle respone amplitude (Figs. 7 and 8). L-701,324 alone did not affect the prepulse inhibition of the acoustic startle or the startle amplitude (Fig. 7A and B) and also failed to affect impairment of prepulse inhibition induced by PCP (Fig. 7A and B). Similarly, MRZ 2/576 alone changed neither the prepulse inhibition on its own nor modified the action of PCP (Fig. 8A and B).

Discussion

The present data show that glycine$_B$ partial agonist with low intrinsic activity i.e. R(+)-HA-966 and full antagonists (L-701,324 and MRZ 2/576) inhibit hyperlocomotion produced by amphetamine and PCP. However, none of the

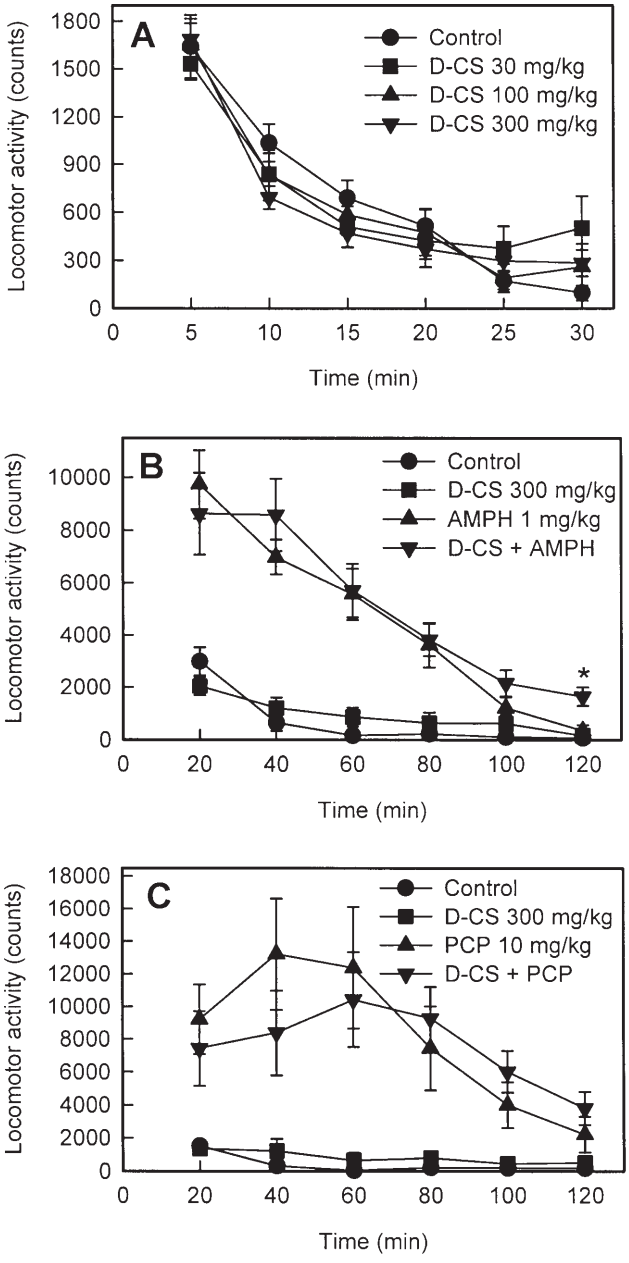

Fig. 1. Effect of D-CS on locomotor activity in the open field in naive (**A**), amphetamine treated (**B**) and PCP treated (**C**) rats. Results are mean ± S.E.M. of 7–9 animals. * − $p <$ 0.05 significant interaction between stimulant and NMDA receptor antagonist (ANOVA) at indicated time interval

glycine$_B$ full antagonists affected either prepulse inhibition of the acoustic startle on its own or changed impairment evoked by PCP.

It has been suggested that antagonism of amphetamine- and/or PCP-induced locomotor activation is indicative of antipsychotic-like activity. Thus, using this "model" it was shown by Bristow and colleagues that in mice a full

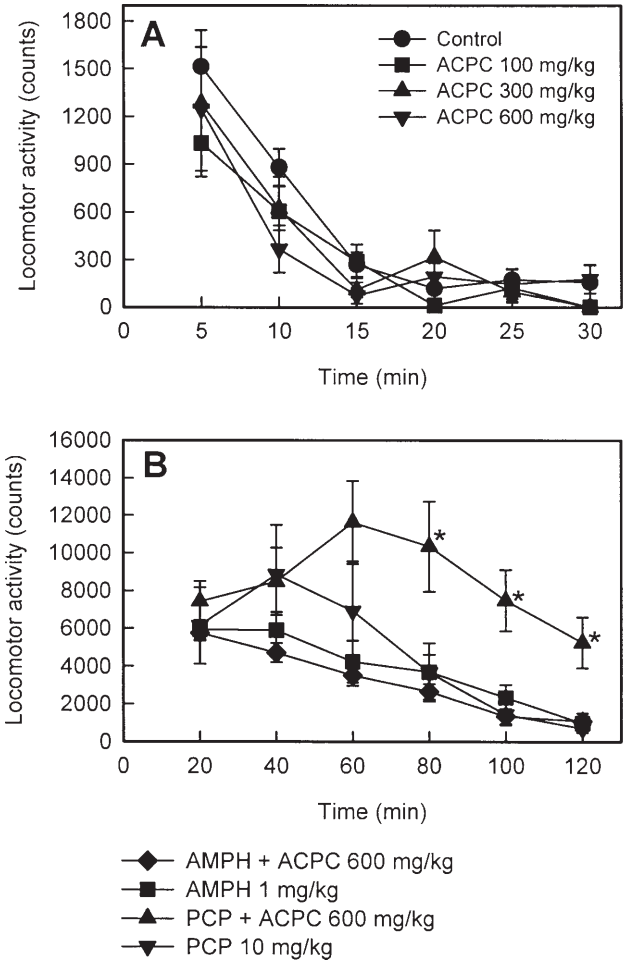

Fig. 2. Effect of ACPC on locomotor activity in the open field in naive (**A**) and amphetamine or PCP treated (**B**) rats. Results are mean ± S.E.M. of 7–9 animals. * − $p < 0.05$ vs. stimulant alone (Student t test)

glycine$_B$ antagonist L-701,324 attenuates locomotion following amphetamine treatment (Bristow et al., 1996). In rats, also locomotor activation produced by a direct administration of amphetamine into the nucleus accumbens was attenuated (ibid.) while stereotyped behaviour (believed to involve striatum mainly) evoked by systemic administration of apomorphine or striatal injection of amphetamine was not changed (Bristow et al., 1996). Moreover, L-701,324 inhibited an increase in dopamine turnover in the mesolimbic system but did not produce catalepsy, in contrast to typical neuroleptics (ibid). Thus, on the basis of these findings an atypical neuroleptic profile of L-701,324 was proposed. Similar effects were obtained with a partial agonist of the glycine$_B$ site, R(+)-HA-966 (Hutson et al., 1991). Also in the present study L-701,324 and additionally MRZ 2/576 attenuated both amphetamine and PCP stimulation in the open field. Also none of these agents produced catalepsy, but in the contrary both attenuated haloperidol-induced catalepsy in the previous study

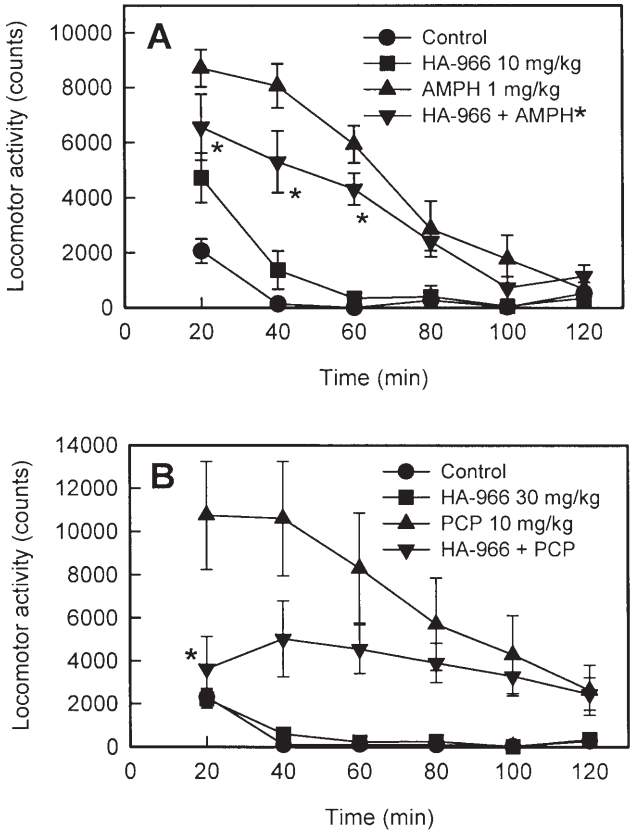

Fig. 3. Effect of R(+)HA-966 on locomotor activity in the open field in amphetamine (**A**) or PCP treated (**B**) rats. Results are mean ± S.E.M. of 7–9 animals. * – $p < 0.05$ significant interaction between stimulant and NMDA receptor antagonist (ANOVA). Star by the legend indicates that the interaction was also significant when the sum of scores for the whole observation period was analysed

(Karcz-Kubicha et al., 1999). Concerning the open field test results, even though the apparent "specificity" of the effect is indicated by the significant interaction revealed by ANOVA analysis, it should be taken into account that the effect observed might be a consequence of general nonselective action such as interaction with the execution of locomotion or other effect. Significant interaction in ANOVA analysis is by no means a definitive prove of the overadditive interaction between two substances. It could only be proven by showing that e.g. PCP dose response curve is shifted parallely (without slope change) to the right after treatment with $glycine_B$ antagonists (Tallarida, 1992).

Prepulse inhibition of the acoustic startle response which is a model sensorimotor gating has been used for predicting psychotomimetic potential (Swerdllow et al., 1994; Wan et al., 1995; Wedzony et al., 1994). In fact, it is disrupted both in schizophrenic patients and in healthy volunteers administered PCP (Swerdllow et al., 1994). Since, PCP in men mimics quite well both

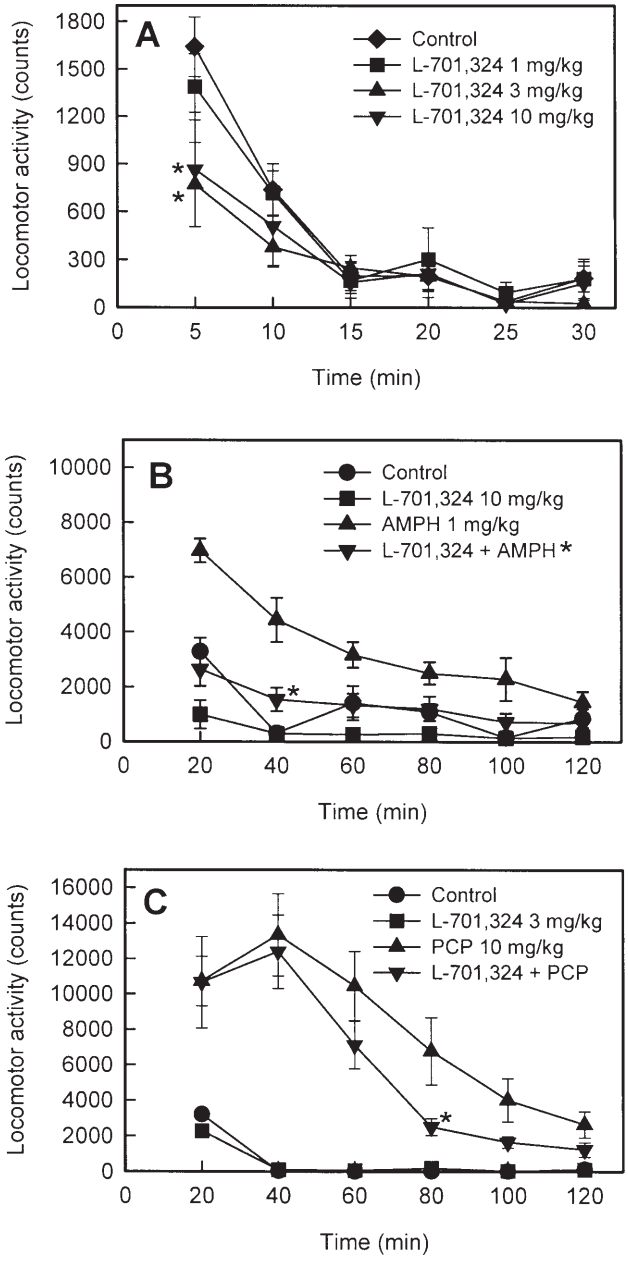

Fig. 4. Effect of L-701,324 on locomotor activity in the open field in naive (**A**) amphetamine (**B**) or PCP treated (**C**) rats. Results are mean ± S.E.M. of 7–9 animals. **A** * − $p < 0.05$ vs. control; **B,C** * − $p < 0.05$ significant interaction between stimulant and NMDA receptor antagonist (ANOVA). Star by the legend indicates that the interaction was also significant when the sum of scores for the whole observation period was analysed

negative and positive symptoms of schizophrenia (Javitt and Zukin, 1991; Luby et al., 1959), it has been proposed that PCP-induced behavioural alterations in animals might provide a good screening model for potential therapies.

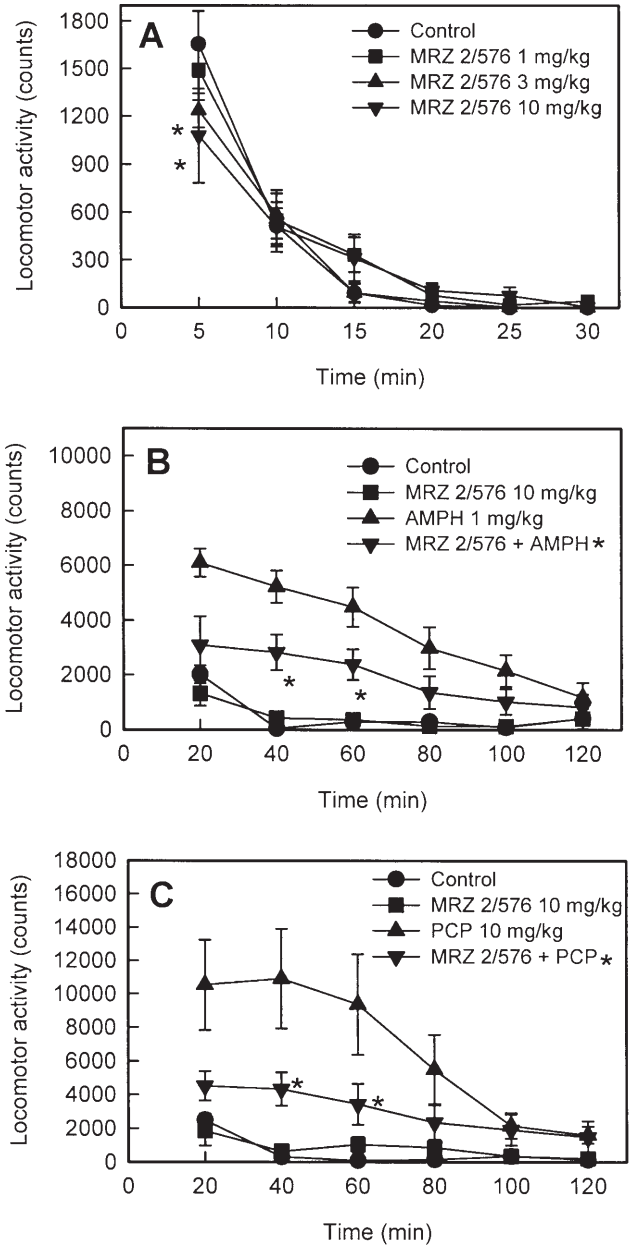

Fig. 5. Effect of MRZ 2/576 on locomotor activity in the open field in naive (**A**) amphetamine (**B**) or PCP treated (**C**) rats. Results are mean ± S.E.M. of 7–9 animals. **A** * – $p < 0.05$ vs. control; **B,C** * – $p < 0.05$ significant interaction between stimulant and NMDA receptor antagonist (ANOVA). Star by the legend indicates that the interaction was also significant when the sum of scores for the whole observation period was analysed

In the present study we failed to observe any negative effect of glycine$_B$ antagonist, L-701,324 and MRZ 2/576 on prepulse inhibition. The doses used were apparently sufficient to assure a blockade of the NMDA receptor in the CNS as evidenced by indirect pharmacodynamic experiment i.e. blockade of

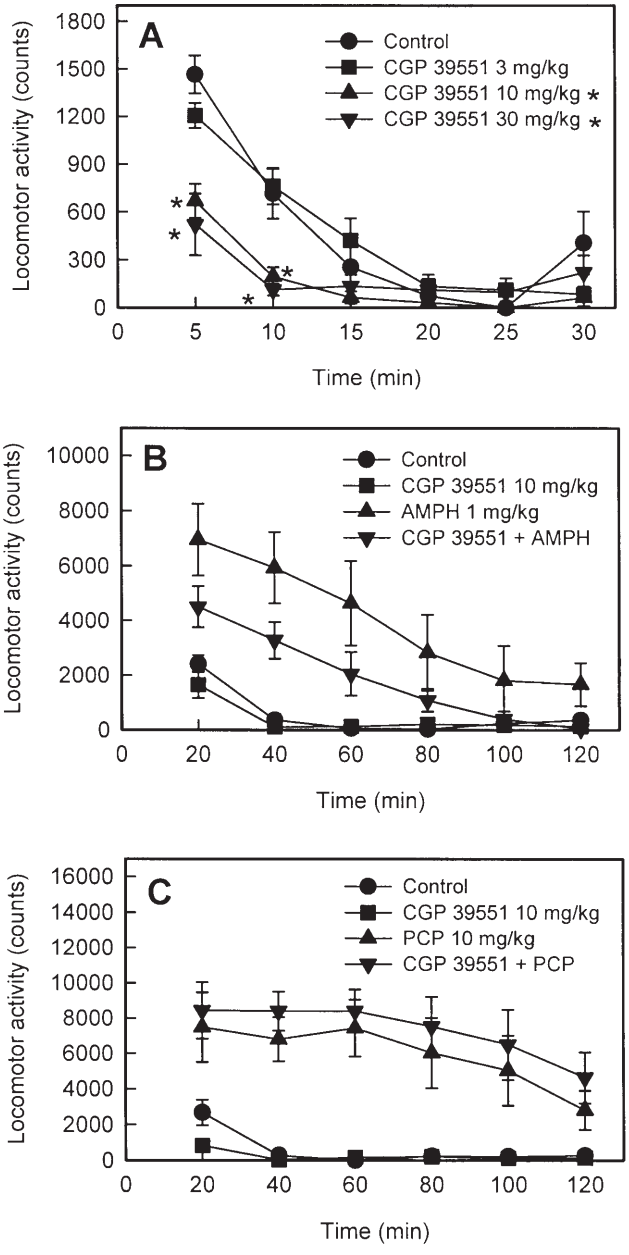

Fig. 6. Effect of CGP-39551 on locomotor activity in the open field in naive (**A**) amphetamine (**B**) or PCP treated (**C**) rats. Results are mean ± S.E.M. of 7–9 animals. * − $p < 0.05$ vs. control (one way ANOVA)

the maximal electroshock-induced convulsions in mice which is seen with both agents below 10 mg/kg, and pharmacokinetic studies assessing brain concentration after systemic administration (Bristow et al., 1996; Hesselink et al., 1999). The lack of negative effect of these glycine$_B$ antagonist on sensorimotor gating is in line with previous findings of Balster and colleagues who showed that ACEA-1021 and ACEA-1011 failed to disrupt prepulse inhibition even

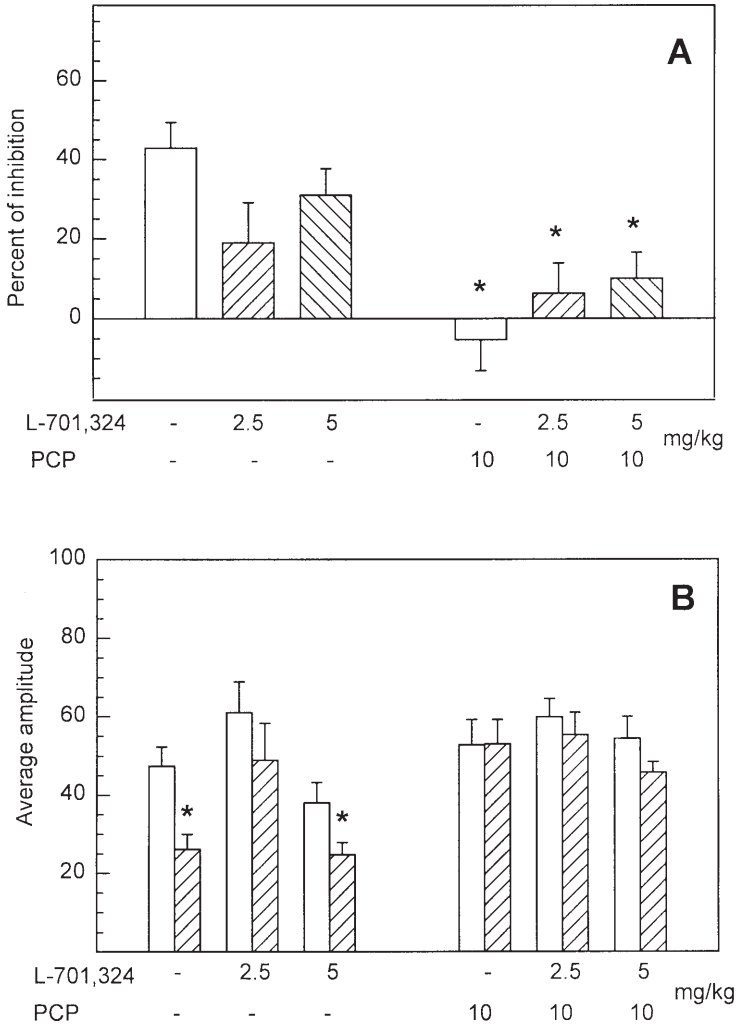

Fig. 7. Effect of L-701,324 on PCP-induced impairment of prepulse inhibition of the acoustic startle response. Results are mean ± S.E.M. of 12 animals of percent inhibition (**A**) or average amplitude of startle response with or without prepulse (**B**). **A** * $p < 0.05$ vs. control group (the first column) **B** * $p < 0.05$ vs. trials without prepulse (two way ANOVA followed by Newman-Keuls test)

at the doses that decreased the amplitude of the startle response itself (Balster et al., 1995). Similar observations were made with ACEA 1021 by Kretschmer and co-workers (Kretschmer et al., 1997). Also another glycine$_B$ antagonist, MDL 105,519 was inactive in this test up to the dose of 200 mg/kg which already inhibited startle response (Baron et al., 1997). In contrast, Furuya and Ogura (1997) detected disruption of prepulse inhibition following central (i.c.v.) administration of 5,7-dichloro-kynurenic acid – which does not penetrate to the brain after systemic administration. Nevertheless, it can be probably summed up that after systemic administration at the doses not producing overall behavioural disturbances glycine$_B$ antagonists lack psy-

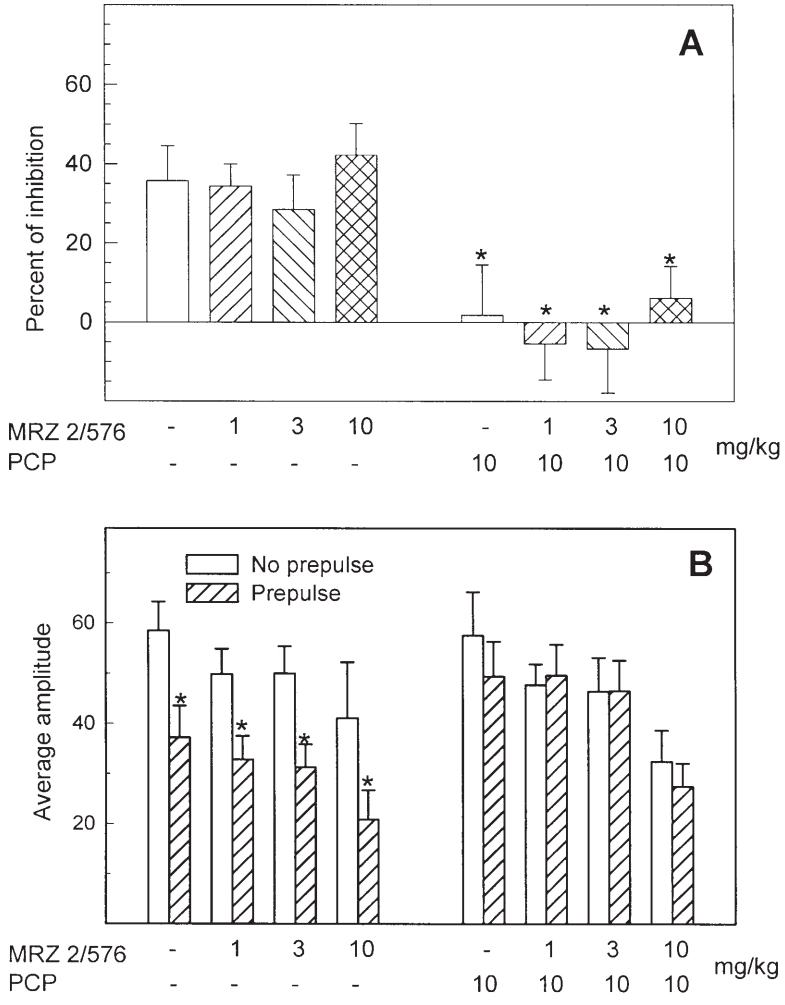

Fig. 8. Effect of MRZ 2/576 on PCP-induced impairment of prepulse inhibition of the acoustic startle. Results are mean ± S.E.M. of 12 animals of percent inhibition (**A**) or average amplitude of startle response with or without prepulse (**B**). **A** * $p < 0.05$ vs. control group (the first column) **B** * $p < 0.05$ vs. trials without prepulse (two way ANOVA followed by Newman-Keuls test)

chotomimetic potential, in contrast to some of the NMDA channel blockers. It is also noteworthy in this respect that a profile similar to glycine$_B$ antagonists was seen with a competitive antagonist CGP 37849 (Wedzony et al., 1994).

Another issue that can be addressed using prepulse inhibition model is whether glycine$_B$ antagonist have antipsychotic potential, as suggested by Bristow and co-workers (Bristow et al., 1995, 1996). The indication that it might be the case was provided by the study showing that isolation-induced disruption of prepulse inhibition was attenuated by treatment with L-701,324 (Bristow et al., 1995). However, in the current study no positive effect of glycine$_B$ antagonists, L-701,324 or MRZ 2/576 was observed following

PCP-induced disruption of sensorimotor gating. Previously, it was reported that also R-(+)-HA-966 is ineffective against prepulse inhibition impairment produced by PCP (Furuya et al., 1996). Thus, probably glycine$_B$ antagonists are able to attenuate a deficit in sensorimotor gating if produced by environmental manipulation (isolation, Bristow et al., 1995), but not pharmacologically by PCP. Some authors suggested that prepulse inhibition produced by PCP (or other NMDA channel blockers) is attenuated by atypical neuroleptics like clozapine but not by classical once such as haloperidol (Bakshi et al., 1994; Keith et al., 1991). Hence, from this point of view both glycine$_B$ full antagonists tested do not fulfill the criteria of atypical neuroleptics. However, it has been suggested that isolation-induced deficit shows better predictive validity for antipsychotics than impairment produced by NMDA receptor antagonists (Varty and Higgins, 1995).

In conclusion, present data only partially support the hypothesis that glycine$_B$ antagonists might have neuroleptic-like properties. While positive effect were obtained in the open field test, prepulse inhibition model based on PCP-induced impairment failed to provide such confirming evidence. Nevertheless, it seems that psychotomimetic potential of glycine$_B$ antagonists given at moderate doses is fairly minimal.

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