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NMDA/glutamate mechanism of antidepressant-like action of magnesium in forced swim test in mice

Ewa Poleszak [a,*], Piotr Wlaź [b], Ewa Kędzierska [a], Dorota Nieoczym [b], Andrzej Wróbel [c], Sylwia Fidecka [a], Andrzej Pilc [d,e], Gabriel Nowak [d,f]

[a] Department of Pharmacology and Pharmacodynamics, Skubiszewski Medical University of Lublin, Staszica 4, PL 20-081 Lublin, Poland
[b] Department of Animal Physiology, Institute of Biology, Maria Curie-Skłodowska University, Akademicka 19, PL 20-033 Lublin, Poland
[c] Second Department of Gynecology, Skubiszewski Medical University of Lublin, Jaczewskiego 8, PL 20-090 Lublin, Poland
[d] Department of Neurobiology, Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, PL 31-343 Kraków, Poland
[e] Department of Drug Management, Collegium Medicum, Jagiellonian University, Grzegórzecka 20, PL 31-531 Kraków, Poland
[f] Department of Cytobiology and Histochemistry, Collegium Medicum, Jagiellonian University, Medyczna 9, PL 30-688 Kraków, Poland

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Abstract

Antidepressant-like activity of magnesium in forced swim test (FST) was demonstrated previously. Also, enhancement of such activity by joint administration of magnesium and antidepressants was shown. However, the mechanism(s) involved in such activity remain to be established. In the present study we examined the involvement of NMDA/glutamate pathway in the magnesium activity in FST in mice.

In the present study we investigated the effect of NMDA agonists on magnesium-induced activity in FST and the influence of NMDA antagonists with sub-effective doses of magnesium in this test. Magnesium-induced antidepressant-like activity was antagonized by *N*-methyl-D-aspartic acid (NMDA). Moreover, low, ineffective doses of NMDA antagonists (CGP 37849, L-701,324, D-cycloserine, and MK-801) administered together with low and ineffective doses of magnesium exhibit significant reduction of immobility time in FST. The active in FST doses of examined agents did not alter the locomotor activity (with an exception of increased activity induced by MK-801).

The present study indicates the involvement of NMDA/glutamate pathway in the antidepressant-like activity of magnesium in mouse FST and further suggests antidepressant properties of magnesium.

Keywords: Depression; Magnesium; NMDA ligands; Forced swim test; Mice

1. Introduction

Excitatory amino acids (glutamic acid, aspartic acid) are present in abundance in the brain. They act at two main receptor subtypes: ionotropic receptors (iGluR) and a family of metabotropic receptors (mGluR). Three classes of ionotropic glutamate receptors have been characterized: *N*-methyl-D-aspartic acid (NMDA), amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainate (Collingridge and Lester, 1989). The NMDA receptor is composed of an oligomer of neuromodulatory subunits including at last one NR1 entity necessary for channel function and several other sites termed NR2A–NR2D that associate to form the channel (Waxman and Lynch, 2005). These subunits include a numerous modulatory binding sites with an integral ion channel with multiple, allosterically coupled recognition sites among them a high affinity site for glutamate and a strychnine-insensitive glycine binding site, termed glycine$_B$ receptor (Kleckner and Dingledine, 1988; Reynolds and Miller, 1988; Waxman and Lynch, 2005). The glycine binding site is activated by endogenous glycine and it is an absolute requirement for NMDA receptor activation by glutamate (Kemp and Leeson, 1993), and thus acts as coagonist with glutamate (Johnson and Ascher, 1987). In the clinical aspects the NMDA receptor has been implicated in

* Corresponding author. Tel.: +48 81 5324240.
E-mail address: ewa.poleszak@am.lublin.pl (E. Poleszak).

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various neurological disorders. Dysfunction of NMDA receptors seems to play a crucial role in the neurobiology of disorders such as Parkinson's disease, Alzheimer's disease, epilepsy ischemic stroke, anxiety and depression (Tzschentke, 2002). Thus, ligands interacting with different sites of NMDA receptor complex are widely investigated as potential agents for the treatment of a variety of neuropsychiatric disorders. In recent years, numerous experimental data have demonstrated the antidepressant-like effects of various antagonists of NMDA receptors. It was shown that a competitive and noncompetitive antagonist, polyamine site antagonist and inorganic inhibitors of NMDA receptor function—zinc (Harrison and Gibbson, 1994) produced antidepressant-like effect in preclinical antidepressant screening procedures (Kroczka et al., 2000, 2001; Nowak et al., 2003b; Skolnick, 1999; Skolnick et al., 1996, 2001; Trullas and Skolnick, 1990). Moreover, an antagonist of the NMDA receptor complex, ketamine, is effective in human depression (Berman et al., 2000; Zarate et al., 2006). However, the fact that competitive and noncompetitive NMDA antagonists usually induce severe side effects (Willetts et al., 1990) limits their applicability as antidepressants for the treatment in humans. Thus, an alternative strategy to the use of competitive and noncompetitive NMDA antagonist might be a modulation of the glycine co-agonist site at the NMDA receptor (Kemp and Leeson, 1993). Antagonists and partial agonists at the glycine site exhibit antidepressant-like activity in experimental screening procedures (Przegaliński et al., 1997; Trullas and Skolnick, 1990; Vamvakides, 1998). Magnesium, similar to zinc, is an inorganic inhibitor of NMDA receptor function (Nowak et al., 1984). It exhibits antidepressant-like activity in the forced swim test (Decollogne et al., 1997; Poleszak et al. 2004, 2005). Also, enhancement of such activity by joint administration of magnesium and imipramine, citalopram and tianeptine was demonstrated (Poleszak et al., 2005; Poleszak, 2007). Furthermore, mood stabilizing properties of magnesium supplementation have been observed in an open study in patients with rapid cycling bipolar disorders (Chouinard et al., 1990). In addition, magnesium used as supplementary therapy in mania to lithium, benzodiazepines and neuroleptics, significantly reduced the use of these drugs (Heiden et al., 1999).

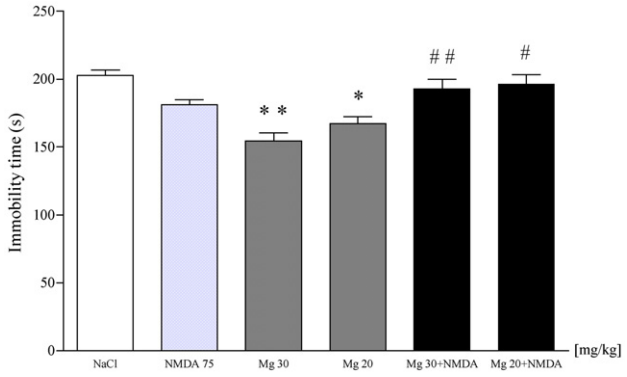

Fig. 1. Effect of joint administration of magnesium and NMDA on immobility time in the FST in mice. Magnesium hydroaspartate (i.p.) was administered 0.5 h before the tests, and NMDA(i.p.) 0.5 h after magnesium administration. The values represent means+SEM (n=7–11 mice per group). * p<0.01, ** p<0.001 vs. NaCl group; # p<0.01 vs. Mg 20 group; ## p<0.001 vs. Mg 30 group (Student–Newman–Keuls test).

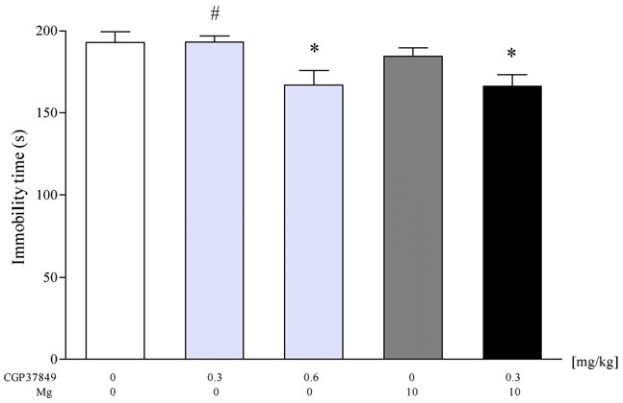

Fig. 2. Effect of joint administration of magnesium and CGP 37849 on immobility time in the FST in mice. Magnesium hydroaspartate (i.p.) was administered 0.5 h before the tests, and CGP 37849 (i.p.) 0.5 h before magnesium administration. The values represent means+SEM (n=8–10 mice per group). * p<0.05 vs. control group; # p<0.05 vs. CGP 37849+Mg grup (Student–Newman–Keuls test).

Since the mechanism involved in such activity is not established, in the present study we examined the involvement of NMDA/glutamate pathway in the magnesium activity in FST in mice.

2. Experimental procedures

2.1. Animals

All procedures were approved by the Ethical Committee of the Medical University, Lublin. The experiments were carried out on adult male Albino Swiss mice (25–30 g) purchased from the licensed breeder (Górzkowska, Warsaw. Poland). The animals were kept in cages (10 per cage) on a natural day–night cycle with free access to food and water and they were used after 7 days of acclimatization to laboratory conditions. Each experimental group consisted of 8–18 animals.

2.2. Drug administration

Magnesium hydroaspartate (Farmapol, Poznań, Poland) was always administered i.p. 30 min before the test. Dosages of magnesium refer to pure magnesium ions. 7-chloro-4-hydroxy-3-(3-phenoxy)phenylquinolin-2[1H]-one (L-701,324, Sigma) was suspended in a 1% aqueous solution of Tween 80 and administered i.p. 60 min before the test. *N*-methyl-D-aspartic acid (NMDA, Sigma), DL-/E/-amino-4-methyl-5-phosphono-3–pentenoic acid (CGP 37849, Tocris), l5R,10S)-(+)-5-methyl-10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5,10-imine hydrogen maleate (MK-801, Sigma), D-cycloserine (D-4-amino-3-isoxazolidone) (Sigma) were dissolved in 0.9% saline and administered i.p. 60 min before the test. Control animals received an i.p. injection of saline (vehicle) at respective times. The volume of vehicles or drug solutions administrations was 10 ml/kg.

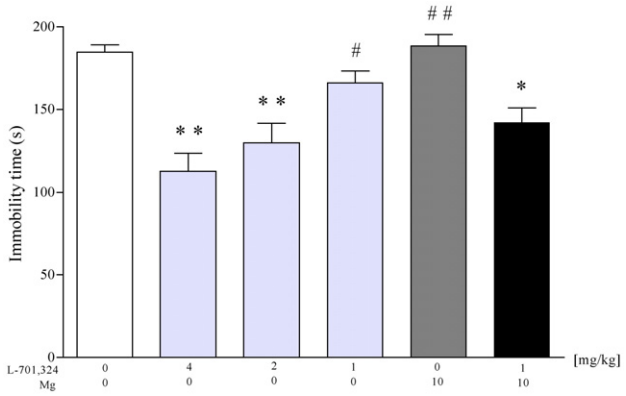

Fig. 3. Effect of joint administration of magnesium and L-701,324 on immobility time in the FST in mice. Magnesium hydroaspartate (i.p.) was administered 0.5 h before the tests, and L-701, 324 (i.p.) 0.5 h before magnesium administration. The values represent means+SEM (n=7–9 mice per group). * p<0.01, ** p<0.001 vs. control group; # p<0.05; ## p<0.01 vs. L-701,324+Mg grup (Student–Newman–Keuls test).

2.3. Forced swim test

The studies were carried out on mice according to the method of Porsolt et al. (1977). Mice were propped individually into glass cylinders (height 25 cm, diameter 10 cm) containing 10 cm of water, maintained at 23–25 °C. The animals were left in the cylinder for 6 min. After the first 2 min the total duration of immobility was measured during a 4-min test. The mouse was judged to be immobile when it remained floating passively in the water.

2.4. Locomotor activity

Locomotor activity of mice was measured with photoresistor actimeters (circular cages, diameter 25 cm, two light beams). The animals were placed individually in an actimeter for 5 min. The number of crossings the light beams by the mice was recorded as the locomotor activity.

2.5. Statistics

The obtained data were evaluated by the one-way analysis of variance (ANOVA) followed by Student–Newman–Keuls multiple comparison test or Dunnett's test (locomotor activity). All results are presented as means±SEM. p<0.05 was considered as statistically significant.

3. Results

3.1. Effect of joint administration of magnesium and NMDA on total immobility duration in the FST

The effects of combined administration of magnesium and NMDA on total duration of immobility in mice are shown in Fig. 1 (ANOVA: $F(5,43)=11.15$, p<0.0001).

Magnesium at the dose of 20 and 30 mg/kg significantly reduced the immobility time in mice in a dose-dependent manner, p<0.01 and p<0.001, respectively. NMDA, a competitive NMDA receptor agonist given alone at the dose of 75 mg/kg had no significant effect on the immobility time, however when administered with both doses of magnesium, it abolished the magnesium-induced antidepressant-like effects.

3.2. Effect of joint administration of magnesium and CGP 37849 on the total immobility duration in the FST

The effects of combined administration of magnesium and CGP 37849 (the competitive NMDA receptor antagonist) on total duration of immobility in mice are shown in Fig. 2 (ANOVA: $F(4, 41)=4.247$, $p=0.0057$). Magnesium at the dose of 10 mg/kg had no effect on the immobility time in mice. CGP 37849 given alone at the dose of 0.6 mg/kg reduced the immobility time in mice (p<0.05) but at the dose of 0.3 mg/kg

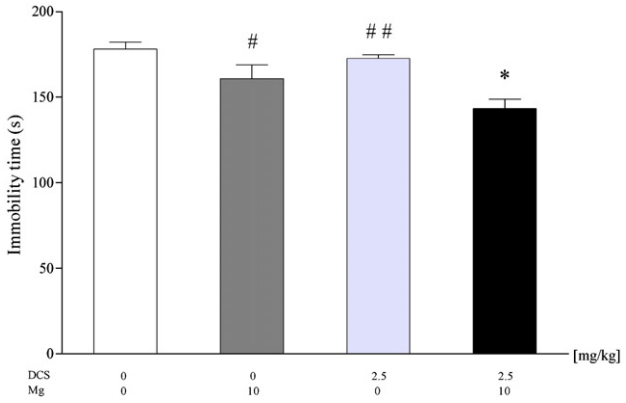

Fig. 4. Effect of joint administration of magnesium and D-cycloserine on immobility time in the FST in mice. Magnesium hydroaspartate (i.p.) was administered 0.5 h before the tests, and D-cycloserine (i.p.) 0.5 h before magnesium administration. The values represent means+SEM (n=6–10 mice per group). * p<0.01 vs. control group; # p<0.05, ## p<0.01 vs. DCS+Mg grup (Student–Newman–Keuls test).

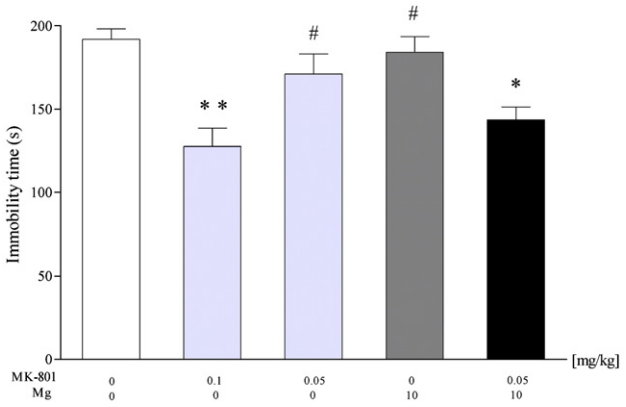

Fig. 5. Effect of joint administration of magnesium and MK-801 on immobility time in the FST in mice. Magnesium hydroaspartate (i.p.) was administered 0.5 h before the tests, and MK-801 (i.p.) 0.5 h before magnesium administration. The values represent means+SEM (n=8–10 mice per group). * p<0.01, ** p<0.001 vs. control group; # p<0.05 vs. MK-801+Mg grup (Student–Newman–Keuls test).

was ineffective. The combined administration of magnesium with CGP 37849 (0.3 mg/kg) significantly reduced the immobility time in FST ($p<0.05$).

3.3. Effect of joint administration of magnesium and L-701,324 on the total immobility duration in the FST

The effects of combined administration of magnesium and L-701,324 (the glycine B receptor antagonist) on total duration of immobility in mice are shown in Fig. 3 (ANOVA: $F(5,39)=11.83$, $p<0.0001$). L-701,324 given alone at the dose of 2 and 4 mg/kg reduced the immobility time in mice ($p<0.001$) while the dose of 1 mg/kg was ineffective. Magnesium at the dose of 10 mg/kg had no effect on the immobility time in mice. The combined administration of magnesium with L-701,324 (1 mg/kg) significantly reduced the immobility time in FST ($p<0.01$).

3.4. Effect of joint administration of magnesium and D-cycloserine on total immobility duration in the FST

The effects of combined administration of magnesium and D-cycloserine (a partial agonist at glycine B receptors) on total duration of immobility in mice are shown in Fig. 4 (ANOVA: $F(3,28)=6.794$, $p=0.0014$). Magnesium at the dose of 10 mg/kg had no effect on the immobility time in mice. D-cycloserine given alone at the dose of 2.5 mg/kg was also ineffective. The combined administration of magnesium with D-cycloserine (2.5 mg/kg) significantly reduced the immobility time in FST ($p<0.01$).

Table 1
Effect of administration of magnesium and NMDA receptor ligands on spontaneous locomotor activity in mice

Compound	Number of animals	Dose mg/kg (i.p.)	Activity counts
A			
Control	16	–	118±12.7
Magnesium hydroaspartate	16	10	128.1±12.7
Magnesium hydroaspartate	8	20	123.0±12.8
Magnesium hydroaspartate	18	30	96.2±10.5
NMDA	16	75	113.1±5.9
L-701,324	8	2	94.6±11.1
L-701,324	8	4	119.0±16.5
MK-801	8	0.05	86.38±9.3
MK-801	8	0.1	180.5±23.4 *
DCS	8	2.5	113.6±6.7
Mg+NMDA	8	20+75	98.5±9.9
Mg+NMDA	8	30+75	80.1±10.8
DCS+Mg	8	2.5+10	110.0±15.4
MK-801+Mg	8	0.05+10	128.9±16.7
L-701,324+Mg	8	2+10	87.2±27.8
B			
Control	8	–	107.6±11.6
CGP 37849	8	0.3	116.5±12.1
CGP 37849	8	0.6	92.5±21.0
CGP 37849+Mg	8	0.3+10	76.3±5.2
Magnesium hydroaspartate	8	10	103.9±5.5

NMDA receptor ligands (NMDA, L-701,324, MK-801, D-cycloserine (DCS), CGP 37849) were administered 60 min before test, magnesium hydroaspartate was administered 30 min before the test. Control animals received two i.p. injections given at respective times. The values represent means±SEM of *n* mice per group.
ANOVA: $F(14,139)=3.05$, $p=0.0004$ for A and $F(4, 35)=1.545$, ns for B part.
* $p<0.001$ vs. control group.

3.5. Effect of joint administration of magnesium and MK-801 on the total immobility duration in the FST

The effects of combined administration of magnesium and MK-801 (a noncompetitive NMDA receptor antagonist) on total duration of immobility in mice are shown in Fig. 5 (ANOVA: $F(4,43)=7.705$, $p<0.0001$). Magnesium at the dose of 10 mg/kg had no effect on the immobility time in mice. MK-801 given alone at the dose of 0.1 mg/kg reduced the immobility time in mice ($p<0.001$) but at the dose of 0.05 mg/kg was ineffective. The combined administration of magnesium with MK-801 (0.05 mg/kg) significantly reduced the immobility time in FST ($p<0.01$).

3.6. Effect of magnesium and NMDA ligands administration on spontaneous locomotor activity in mice

The effects of magnesium, NMDA ligands and their combined administration on locomotor activity are shown in Table 1. MK-801 at dose of 0.1 mg/kg significantly increased activity counts at both determined time (Table 1A). The other tested agents did not significantly influence the locomotor activity in mice (Table 1).

4. Discussion

Experiments described in this study showed that competitive (CGP 37849) and noncompetitive antagonists (MK-801), and two glycine$_B$ receptor ligands, namely L-701,324 (antagonist) and D-cycloserine (partial agonist) significantly reduced the immobility time in the FST in mice which is in line with previously published data (Lopes et al., 1997; Panconi et al., 1993; Przegaliński et al. 1998; Trullas and Skolnick, 1990). Moreover, all the used compounds acting at various modulatory sites on the NMDA receptor complex, enhanced the antidepressant-like action of magnesium. These effects induced by combined treatments, although not huge (16–25%), indicate the common site of action—the NMDA receptor complex.

MK-801 blocks the neurophysiologic effects of the NMDA receptor complex by binding to a site in the ion channel of the receptor, thereby blocking the channel for cations (Wong et al., 1986). It has anxiolytic-like effects (Dunn et al., 1989; Karcz-Kubicha et al., 1997), anticonvulsive activity (McNamara et al., 1988; Wlaź, 1998) and antidepressant-like effects (Maj et al., 1992; Trullas and Skolnick, 1990). Acute MK-801 treatment has been found to be active in the FST in mice and rats at the range of doses 0.05–1.0 mg/kg (Decollogne et al., 1997; Maj et al., 1992; Trullas and Skolnick, 1990). It must be remarked, that the reduction in immobility induced by MK-801 is related to the increase of locomotor activity observed at the same doses (0.1 mg/kg) (Liljequist et al., 1991; Maj et al., 1992; present

data) which may be related to its activity on brain dopamine system (Hiramatsu et al., 1989). On the other hand, in the study of Trullas and Skolnick 1990), MK-801 affected immobility time in mice at lower doses, than those required to stimulate motor activity. The observed diversity may be the result of the use of a different strain of mice, administration route and tests used. In the present study to evaluate the effect of MK-801 on the antidepressant-like activity of magnesium we chose the dose of 0.05 mg/kg, which by itself was ineffective both in locomotion and FST. The joint administration of this low dose of MK-801 with an ineffective dose of magnesium reduced the immobility time in the FST. Thus, the combined treatment with magnesium and NMDA receptor antagonists produced a synergistic antidepressant-like effect in the FST in mice.

Because of the adverse effects, including motor impairment, hyperactivity, stereotypy and psychotomimetic-like symptoms, produced by both competitive and noncompetitive NMDA receptor antagonist (Willetts et al., 1990), the use of such compounds as antidepressant agents in human is rather excluded. After the discovery that glycine strongly amplifies the action of glutamate at the NMDA receptor, and therefore is a co-agonist (Johnson and Ascher, 1987), it has been hypothesized that glycine receptor antagonists could act as functional NMDA receptor blockers (Trullas et al., 1989). Several lines of evidence confirm this hypothesis. For example, antagonists and partial agonists of glycine$_B$ receptors evoke behavioral effects similar to those exerted by competitive and noncompetitive NMDA receptor antagonists (Anthony and Nevins, 1993; Karcz-Kubicha et al., 1997; Trullas and Skolnick, 1990; Trullas et al., 1991). Such functional antagonism was observed for the ACPC, a glycine site partial agonist that mimics the action of competitive and noncompetitive NMDA receptor antagonists (Trullas and Skolnick, 1990), including anticonvulsant (Skolnick et al., 1989), anxiolytic (Anthony and Nevins, 1993), and antidepressant actions (Trullas and Skolnick, 1990). ACPC in mice produced effect comparable to that of clinically effective antidepressants in both FST and tail suspension test (Trullas and Skolnick, 1990). Also an antagonist of the glycine site of the NMDA receptor complex, L-701,324, also exhibits properties typical for classical NMDA antagonists. It possesses anticonvulsant (Bristow et al., 1996; Wlaź, 1998; Wlaź and Löscher, 1998) and anxiolytic-like (Kotlińska and Liljequist, 1998; Popik et al., 2000; Przegaliński et al., 1998) properties. In the present study, L-701,324 produced dose-dependent antidepressant-like effect and at the used doses it did not affect the locomotor activity of animals. It should be noted that the present results are consistent with those obtained by other authors (Przegaliński et al., 1998). D-cycloserine, a partial agonist of glycine site of the NMDA receptor complex (Hood et al., 1989) produced similar effects to those of competitive and noncompetitive NMDA antagonists. It reveals anxiolytic-like activity in the fear-potentiated startle response (Anthony and Nevins, 1993), and the Vogel conflict drinking test (Kłodzińska and Chojnacka-Wójcik, 2000), anticonvulsant effects (Peterson and Schwade, 1993; Löscher et al., 1994; Wlaź, 1998), and antidepressant activity in the forced swim test (an effect comparable to that observed with imipramine) (Lopes et al., 1997). The antidepressant-like activity of D-cycloserine was first shown in tuberculosis patients (Kendig et al., 1956; Lewis et al., 1957) and provides indirect support for the hypothesis that glycine site partial agonists may be potentially useful as antidepressants (Skolnick et al., 1992; Trullas and Skolnick, 1990). However, it may act as an agonist or antagonist of the glycine$_B$ receptor depending on the dose. At low doses, D-cycloserine exerts an agonist profile as it mimics the action of endogenous glycine at its site. However, higher doses competitively antagonize the glycine site (Watson et al., 1990). In the present study, D-cycloserine produced a weak antidepressant-like effect after a dose of 100 mg/kg. The used doses are comparable to those used in cognitive, anxiolytic and anticonvulsant studies (Lanthorn, 1994; Wlaź et al., 1996), but lower than those used in the forced swim test by other authors (200 mg/kg) (Lopes et al., 1997). Moreover, the results of our study show that a lower dose of D-cycloserine (2.5 mg/kg) that was not antidepressant-like active by itself, potentiated the antidepressant effects of magnesium. It should be emphasized that L-701,324 and D-cycloserine used even at relatively high doses did not produce behavioral untoward effects which are the characteristic for MK-801.

Recently we demonstrated that activation of the NMDA receptor complex by NMDA or D-serine (glycine$_B$ site selective agonist) counteracted the NMDA receptor antagonists-induced antidepressant-like activity in the FST (Poleszak et al., in press). Since the antidepressant-like activity of magnesium was also antagonized by NMDA and NMDA receptor antagonists potentiated such activity of magnesium, these data indicate that magnesium behaved as typical NMDA antagonist in FST. In fact, NMDA antagonists were successfully used in human studies. As mentioned in the introduction ketamine exhibited fast therapeutic antidepressant effect in major depression (Berman et al., 2000; Zarate et al., 2006). Also, amantadine and zinc were effective as adjunct treatment in human depression (Nowak et al., 2003a; Rogóż et al., 2004).

The present study indicates the involvement of NMDA/glutamate pathway in the antidepressant-like activity of magnesium in mouse FST and further point to magnesium as potential antidepressant agent.

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