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Evidence for the involvement of the monoaminergic system in the antidepressant-like effect of magnesium

Chandra C. Cardoso [a], Kelly R. Lobato [a], Ricardo W. Binfaré [a], Priscilla K. Ferreira [a], Angelo O. Rosa [a], Adair Roberto S. Santos [b], Ana Lúcia S. Rodrigues [a,*]

[a] Departamento de Bioquímica, Centro de Ciências Biológicas, Universidade Federal de Santa Catarina, Campus Universitário, Trindade, 88040-900, Florianópolis-SC, Brazil
[b] Departamento de Ciências Fisiológicas, Centro de Ciências Biológicas, Universidade Federal de Santa Catarina, Campus Universitário, Trindade, 88040-900, Florianópolis-SC, Brazil

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ABSTRACT

Literature data has shown that acute administration of magnesium reduces immobility time in the mouse forced swimming test (FST), which suggests potential antidepressant activity in humans. However, its mechanism of action is not completely understood. Thus, this study is aimed at investigating the antidepressant-like action of magnesium and the possible involvement of the monoaminergic system in its effect in the FST. The immobility time in the FST was significantly reduced by magnesium chloride administration (30–100 mg/kg, i.p.) without accompanying changes in ambulation when assessed in an open-field test. The pre-treatment of mice with NAN-190 (0.5 mg/kg, i.p. a 5-HT_{1A} receptor antagonist), WAY100635 (0.1 mg/kg, s.c., a selective 5-HT_{1A} receptor antagonist), ritanserin (4 mg/kg, i.p., a 5-$HT_{2A/2C}$ receptor antagonist), ketanserin (5 mg/kg, a preferential 5-HT_{2A} receptor antagonist), prazosin (1 mg/kg, i.p., an α_1-adrenoceptor antagonist), yohimbine (1 mg/kg, i.p., an α_2-adrenoceptor antagonist), haloperidol (0.2 mg/kg, i.p., a non selective dopaminergic receptor antagonist), SCH23390 (0.05 mg/kg, s.c., a dopamine D_1 receptor antagonist) or sulpiride (50 mg/kg, i.p., a dopamine D_2 receptor antagonist) 30 min before the administration of magnesium chloride (30 mg/kg, i.p.) significantly prevented its anti-immobility effect in the FST. Moreover, the administration of sub-effective doses of fluoxetine (10 mg/kg, i.p., serotonin reuptake inhibitor), imipramine (5 mg/kg, i.p., a mixed serotonergic noradrenergic reuptake inhibitor), bupropion (1 mg/kg, i.p., dopamine reuptake inhibitor) was able to potentiate the action of sub-effective doses of magnesium chloride. In conclusion, the present study provides evidence indicating that the antidepressant-like effect of magnesium in the FST is dependent on its interaction with the serotonergic (5-HT_{1A} and 5-$HT_{2A/2C}$ receptors), noradrenergic (α_1- and α_2- receptors) and dopaminergic (dopamine D_1 and D_2 receptors) systems.

1. Introduction

Magnesium (Mg^{+2}) is an essential intracellular bioelement which plays an important role in a wide variety of metabolic reactions, in particular energy-requiring processes (Ryan, 1991). In the central nervous system (CNS) it is involved in signal transmission, blocking the N-methyl-D-aspartate (NMDA) receptor ion channel in a voltage-dependent manner (Sobolevskii and Khodorov, 2002). Preclinical studies have shown that NMDA receptor antagonists display a variety of pharmacological and behavioral effects, including anticonvulsant (Wong et al., 1986), anxiolytic (Dunn et al., 1990) and antidepressant-like activities (Maj et al., 1992; Skolnick, 1999, 2002). Furthermore, Mg^{+2} deficiency is associated with behavioral and physiological alterations in patients with affective disorders (Hall and Joffe, 1973; Kirov et al., 1994), and in experimental animal models (Bac et al., 1995; Malpuech-Brugère et al., 2000).

Several studies have demonstrated that acute and chronic administration of Mg^{+2} reduces immobility time in the forced swimming test (FST) in mice and rats, and enhances the anti-immobility activity of imipramine in this model (Decollogne et al., 1997; Poleszak et al., 2004, 2005a,b, 2006). Recently, an indication that the serotoninergic system is involved in the antidepressant-like effect of Mg^{+2} was given by the fact that the pre-treatment of mice with an inhibitor of serotonin synthesis, p-chlorophenylalanine was able to reduce the anti-immobility effect of magnesium in the FST (Poleszak, 2007). Moreover, Mg^{+2} depletion in mice produces an increase in anxiety and depression-like behavior (Singewald et al., 2004). This data is consistent with clinical studies that demonstrated

Abbreviations: ANOVA, analysis of variance; 5-HT, serotonin; FST, forced swimming test; i.p., intraperitoneal; NMDA, N-methyl-D-aspartate; MAOi, monoamine oxidase inhibitor; NAN-190, 1-(2-methoxyphenyl)-4[-(2-phthalimido)butyl] piperazine); PCPA, p-chlorophenylalanine methyl ester; SCH23390, (*R*)-(+)-7 chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride; SSRI, selective serotonin reuptake inhibitor; WAY100635, N-{2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl}-N-(2-pyridynyl) cyclohexanecarboxamide.

* Corresponding author. Tel.: +55 48 37215043; fax: +55 48 37219672.
E-mail addresses: analucia@mbox1.ufsc.br, ana.rodrigues@pq.cnpq.br (A.L.S. Rodrigues).

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low serum Mg^{+2} levels in depressed patients (Hashizume and Mori, 1990; Rasmussen et al., 1989; Zieba et al., 2000), which suggests an important role of this ion in the pathophysiology of depression. However, its mechanism of action is not completely understood.

The monoaminergic system is one of the most important targets in the pathophysiology and treatment of depression (Elhwuegi, 2004; Millan, 2004). The monoaminergic hypothesis indicates that the pathology of depression involves dysfunction of monoamine neurotransmitter circuits in the CNS. It is supported by great number of neurochemical findings (Booij et al., 2003; Ruhé et al., 2007) and by the successful treatment of major depression with classical antidepressants, compounds that enhance monoaminergic neurotransmission (Nemeroff and Owens, 2002). Considering that substances which reduced NMDA transmission have antidepressant-like effect probably due a modulation of the monoaminergic pathways in the CNS (Loscher et al., 1991; Wedzony et al., 1997) and that treatment with antidepressants alters NMDA function (Skolnick, 1999), Mg^{+2}, which is a endogenous antagonist at NMDA receptors, may play a significant role in the modulation of depression. Thus, to further contribute to the understanding of the mechanisms underlying the antidepressant-like effects of Mg^{+2}, this study was aimed at investigating the possible involvement of the monoaminergic system in its effect in the FST.

2. Methods

2.1. Animals

Male Swiss mice (30–40 g) were maintained at 22–24 °C with free access to water and food, under a 12:12 h light:dark cycle (lights on at 7:00 h). Twenty mice were housed per cage (40×34×17 cm), which were placed in the experimental room 24 h before the test for acclimatization. All experiments were carried out between 12:00 and 16:00 h. Each experimental group consisted of 6–8 animals, with each animal used only once. All procedures in this study were performed in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals. The experiments were performed after approval by the Ethics Committee of the Institution and all efforts were made to minimize animal suffering and to reduce the number of animals used in the experiments.

2.2. Drugs and treatment

The following drugs were used: magnesium chloride ($MgCl_2$, Merck, Darmstadt, Germany), 1-(2-methoxyphenyl)-4[-(2-phthalimido)butyl] piperazine) (NAN-190), N-{2-[4-(2-methoxyphenyl)-1-piperazinyl] ethyl}-N-(2-pyridynyl) cyclohexanecarboxamide (WAY100635), ritanserin, ketanserin, prazosin, yohimbine, haloperidol, (*R*)-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (SCH23390), sulpiride, and the antidepressants fluoxetine, imipramine and bupropion (all from Sigma Chemical Company, St. Louis, MO, U.S.A.). All drugs were administered by intraperitoneal (i.p.) route in a constant volume of 10 ml/kg body weight except SCH23390 and WAY100635, that were administered by subcutaneous (s.c.) route (10 ml/kg body weight). Appropriate vehicle-treated groups were also assessed simultaneously. $MgCl_2$ was administered by i.p. route 30 min before the FST or the open-field test. These behavioral tests were performed by an observer blind to the drug treatment.

In order to investigate the possible involvement of the serotonergic system in the antidepressant-like effect of Mg^{+2}, independent group of mice were pretreated with NAN-190 (0.5 mg/kg, i.p. a 5-HT_{1A} receptor antagonist), WAY100635 (0.1 mg/kg, s.c., a selective 5-HT_{1A} receptor antagonist), ketanserin (5 mg/kg, i.p., a preferential 5-HT_{2A} receptor antagonist), ritanserin (4 mg/kg, i.p., a 5-$HT_{2A/2C}$ receptor antagonist) or vehicle and 30 later they received $MgCl_2$ (30 mg/kg, i.p.) or vehicle before being tested in the FST after 30 min.

To assess the possible involvement of the noradrenergic and the dopaminergic systems on the antidepressant-like effect of Mg^{+2} in the FST, independent group of animals were pretreated with prazosin (1 mg/kg, i.p., an α_1-adrenoreceptor antagonist), yohimbine (1 mg/kg, i.p., an α_2-adrenoreceptor antagonist), haloperidol (0.2 mg/kg, i.p., a non selective dopamine receptor antagonist), SCH23390 (0.05 mg/kg, s.c., a dopamine D_1 receptor antagonist), sulpiride (50 mg/kg, i.p., a dopamine D_2 receptor antagonist) or vehicle and after 30 min they received $MgCl_2$ (30 mg/kg, i.p.) or vehicle and were tested in the FST 30 min later.

In a separate set of experiments, independent group of animals were pretreated with sub-effective doses of the antidepressants fluoxetine (10 mg/kg, i.p., serotonin reuptake inhibitor), imipramine (5 mg/kg, i.p., a mixed serotonergic noradrenergic reuptake inhibitor), bupropion (1 mg/kg, i.p., dopamine reuptake inhibitor) or vehicle and after 30 min they received a sub-effective dose of $MgCl_2$ (10 mg/kg, i.p.) or vehicle. After 30 min the open-field test or the FST were carried out.

Doses and administration schedule were chosen on the basis of experiments previously performed in our laboratory and the literature data confirm the selectivity and efficacy of the above-mentioned treatments at the concentrations used (Brocardo et al., 2008; Kaster et al., 2005; Machado et al., 2007; O'Neill and Conway, 2001; Redrobe et al., 1996; Redrobe and Bourin, 1997; Rodrigues et al., 2002).

2.3. Forced swimming test (FST)

The test was conducted using the method of Porsolt et al. (1977) with some modifications. Mice were individually forced to swim in an open cylindrical container (diameter 10 cm, height 25 cm), containing 19 cm of water at 25±1 °C; the total duration of immobility during a 6 min test was scored live. This test procedure was carried out according to the previously standardized and validated animal in our laboratory (Brocardo et al., 2008; Eckeli et al., 2000; Kaster et al., 2005, 2007a,b; Rosa et al., 2008; Zomkowski et al., 2002, 2004). Classical antidepressants are reported to decrease immobility time in this paradigm (Brocardo et al., 2008; Dhir and Kulkarni, 2007; Kaster et al., 2007a; Rosa et al., 2008; Yamada et al., 2004). Each mouse was judged to be immobile when it ceased struggling and remained floating motionless in the water, making only those movements necessary to keep its head above water.

2.4. Open-field test

To assess the possible effects of magnesium on locomotor activity, mice were evaluated in the open-field paradigm as previously described (Rodrigues et al., 2002). Mice were individually placed in the left corner of a wooden box (40×60×50 cm) with the floor divided into 12 rectangles. The number of rectangles crossed with the four paws was registered during a period of 6 min. The arena floor was cleaned between the trials with a solution of ethanol 10% and the test was carried out in a temperature and light controlled room.

2.5. Statistical analysis

Comparisons between experimental and control groups were performed by one or two-way ANOVA followed by Tukey's HSD test when appropriate. A value of $P<0.05$ was considered to be significant.

3. Results

3.1. Effect of magnesium on the immobility time in the FST

The immobility time in the FST of animals treated with $MgCl_2$ is shown in Fig. 1A. The one-way ANOVA revealed a significant effect of $MgCl_2$ on immobility [$F(3.28)=22.18$, $P<0.01$]. $MgCl_2$, at the doses of 30 and 100 mg/kg, i.p., significantly decreased the immobility time when mice were tested in the FST. As shown in Fig. 1B $MgCl_2$ (10–