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MAGNESIUM IN PATHOPHYSIOLOGY AND THERAPY OF AFFECTIVE DISORDERS

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INTRODUCTION

Magnesium is an essential mineral that is needed for a broad variety of physiological mechanisms. The importance of magnesium deficiency for animal organisms was first described by LEROY (1926) and KRUSE et al. (1933). The first clinical data of magnesium depletion in humans was published in 1934 (HIRSCHFELDER and HAURY, 1934), and the involvement of magnesium deficiency in various pathological conditions in human was described by FLINK (1956).

Recent data from experimental and epidemiological studies suggest an important role of magnesium deficiency in many diseases (IANELLO and BELFIORE 2001). It was shown its role and therapeutic value in variety of human illness, especially cardiovascular diseases (atherosclerosis, hypertension, congestive heart failure, arrythmias and myocardial infraction; ELWOOD and PICKERING, 2002), obsteric conditions (preeclampsia, eclampsia; HANDWERKER et al. 1995), neurological diseases (stroke, epilepsy; MUIR 2002, VINK and NIMMO 2002) and affective disorders (RASMUSSEN et al. 1989, HASIZUME and Mori 1990, MURCK 2002).

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The present review describes some aspects related to the role of magnesium in pathophysiological and therapeutical mechanisms of affective disorders in clinical and experimental studies.

BIOCHEMICAL AND PHYSIOLOGICAL ROLE OF MAGNESIUM

Magnesium is the fourth (Ca > K > Na > Mg) most abundant cation in the body, and the second most common intracellular cation after potassium (Fawcett et al. 1999). An adult human contains about 1 mol (24 g) magnesium distributed to various organs and compartments. It is distributed principally between bones(53%) and the intracellular compartments of muscles (27%) and soft tissues (heart, liver) (19%) (Elin 1994, Romani and Scarpa 2000). Tissue magnesium (intracellular magnesium fraction) is mostly bound to chelators, such as adenosine triphosphate (ATP), adenosine diphosphate (ADP), negatively charged to phospholipids and proteins (Murphy 2000). Only 2-3% of intracellular magnesium is free, and this is the fraction that respond for regulation of intracellular magnesium homeostasis and cellular function (Romani 2000, Murphy 2000).

Less than 1% of total body magnesium is fund in serum and red blood cells (extracellular magnesium fraction) where it is present in three states: protein bound (19%), complexed to anions such as citrate, phosphate and bicarbonate (14%) and ionized (67%), that is biologically active form (Altura 1994, Elin 1994). Magnesium balance between cerebrospinal fluid (CSF) and plasma is regulate by existence of active transport systems between that both compartments (Moris 1992), which results in a stability of the intracerebral magnesium concentrations even in the case of magnesium depletion (Murck 2002). Magnesium homeostasis is regulated by the metabolic and hormonal effects on gastrointestinal absorption and renal excretion (McLean 1994, Massry and Coburn 1973).

Magnesium is a cofactor in more than 300 enzymatic reactions, particularly in those involved in energy metabolism (transfer, storage and utilization) (Grubbs and Maquire 1987, Ryan 1991), protein and nucleic acid synthesis, and ion transport processes (McLean 1994). About 90% of intracellular magnesium is bound to ribosomes or polynucleotides. Its biologic functions include structural stabilization of proteins, nucleic acid, and cell membranes by general surface binding (Cowan 1995). It is also involved in hormone receptor binding, gating of calcium channels and neurotransmitter release (Fawcett et al. 1999). Magnesium may be considered as an intracellular calcium antagonist. It directly influences Ca^{2+} uptake, distribution and content in cardiovascular cells (Ryan 1991, Nakajima et al. 1997). It competes with calcium for membrane binding sites, modulates Ca^{2+} –

binding release from reticular stores and thereby influences Ca^{2+} – dependent signaling events (Resnik 1992). Magnesium also regulates Na^+/K^+ transport thus is a determinant of the electrical potential across the cell membrane (Fischer and Giroux 1987). Moreover, on the cell level, magnesium modulates ion transport by pumps, carriers and channel (thus modulate signal transduction) and has a membrane-stabilizing and protecting effect (Bara et al. 1990, Romani and Scarpa 2000).

MAGNESIUM AND NEUROPSYCHIATRIC DISORDERS

Hyperexcitability is induced by chronic magnesium deficiency. Its appears in a non-specific clinical pattern associated with central and peripheral neuromuscular symptoms (Durlach et al. 1997). The most common neurological signs and findings reported in hypomagnesemia are irritability, neuromuscular hyperactivity (eg. tremor), ataxia and dysphagia (Fink 1981). Some clinical conditions, such as stress, acute illness and trauma, with enhanced serum catecholamine concentrations may lower serum magnesium level (Durlach 1992). Under conditions of stress, whether physical or emotional (pain, anxiety, depression) intensified release of catecholamines and increase need for magnesium may appears (Frakes 1996). Moreover a significantly decrease concentration of magnesium in plasma was found in epilepsy (especially in children), with a positive correlation of hypomagnesemia with severity of epilepsy (the more severe epilepsy, the lower the plasma Mg) (Benga et al. 1985). In this disease a significant increase of magnesium in cerebrospinal fluid was reported, most likely due to a functional impairment of the cell membranes which might occur in epilepsy (Banga et al. 1985).

Several clinical studies demonstrated low serum Mg level in depressed patients (e.g. Banki et al. 1985, Hashizume and Mori 1990, Rasmussen et al. 1989, Zięba at al. 2000), however, the data are inconsistent, since no alterations or increases in blood Mg have been also observed (Frazer et al. 1983, Kirov et al. 1994, Young et al. 1996, Widmer et al. 1992, 1995). A relation between low Mg concentration in cerebrospinal fluid and depressive disorders has also been suggested in subjects after suicidal attempts (Banki et al. 1985). Moreover, the mood stabilizing properties of Mg have been demonstrated in case reports in patients with mania (Pavinac et al. 1979). 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). Depressive symptoms were connected with low serum magnesium in patients with long-lasting depression (Linder et al. 1989) and in patients with unipolar depression (Hasey et al. 1993). A lower magnesium plasma concentration was demonstrated in depressed patients, and the increased magnesium level was shown during recovery (Frizel et al. 1969, Hasizume and Mori 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).

MAGNESIUM IN ANIMAL MODELS

It was shown that magnesium play a significant role in behavior of animals. Magnesium deficiency leads to reduction in offensive and to increase in defensive behavior (KANTAK, 1988), indicated a development of depression-like behavior (BLANCHARD et al. 1993). Other studies found that Mg-depletion leads to an increase in depression- and anxiety-related behavior in mice, which was further validated by the reversibility of the behavioral changes by known antidepressant and anxiolytic drugs (SINGEWALD et al. 2004). Moreover, magnesium depletion for 21 days in mice leads to an increase in anxiety- and depression-like behavior, manifested with a decreased struggling in the forced swim test and increased preference for the dark compartment in the light-dark test (MURCK, 2002). Further it was shown dependency of intracellular magnesium and behavior in mice. Mice with the low erytrocyte magnesium levels showed a more restless behavior, a more aggressive behavior under stressful conditions compared to mice with high erythrocyte magnesium levels (HENROTTE et al. 1997).

On the other hand, magnesium administration reduces immobility time in the forced swim test (FST) in rodents, which indicate possible antidepressant activity in humans (DECOLLOGNE et al. 1997, POLESZAK et al. 2004, 2005a). Moreover magnesium enhanced the action of antidepressant drugs in mice. We observed the enhancement of antidepressant-like activity by joint administration of magnesium and imipramine (POLESZAK et al. 2005b), citalopram and tianeptine, but not with reboxetine in FST (unpublished data). The data suggested the involvement of serotonergic but nor noradrenergic pathway in magnesium/antidepressants-induced potentiation of antidepressant-like activity in FST.

POSSIBLE MECHANISM OF ANTIDEPRESSANT MAGNESIUM ACTIONS

The role of magnesium in the central nervous system could be mediated via N-methyl-d-aspartate acid (NMDA), g-aminobutyric acid (GABA) and other neurotransmitters.

Lowering extracellular magnesium concentration has been shown to facilitate the activation of NMDA receptors leading to enhanced neuronal excitability (MAYER et al. 1984). On the other hand, the activation of NMDA

receptor ion channel is blocked by Mg^{2+} in a voltage-dependent manner (Mori et al. 1992). In vitro, this blockade operates at extracelullar Mg^{2+} concentrations of less than 1 mM, which are within the range of those found in the cerebrospinal fluid and plasma of humans and animals (Morris, 1992). NMDA glutamate receptor is involved in the pathophysiology and treatment of depression (Steward and Reid 2002, Skolnick 2002). Thus, antagonists of NMDA receptors, either organic or inorganic (magnesium, zinc), exhibit antidepressant properties in animal models and in preliminary clinical studies (e.g. Bergman et al. 2000, Trullas and Skolnick 1990, Decollogne et al. 1997, Kroczka et al. 2000, 2001, Murck 2002, Nowak et al. 2003, Poleszak et al. 2004) – Fig. 1.

Besides, magnesium modulate catecholaminergic and serotonergic systems. Magnesium is a cofactor for tyrosine and tryptophan hydroxylases, and is also necessary for serotonin and adrenergic receptors' *in vitro* binding (Kantak 1988). These data, together with our unpublished behavioral results indicated involvement of serotonergic transmission in magnesium-induced antidepressant-like activity, suggest a significant role of serotonergic (and noradrenergic ?) system in the antidepressant mechanism of magnesium (Fig. 1).

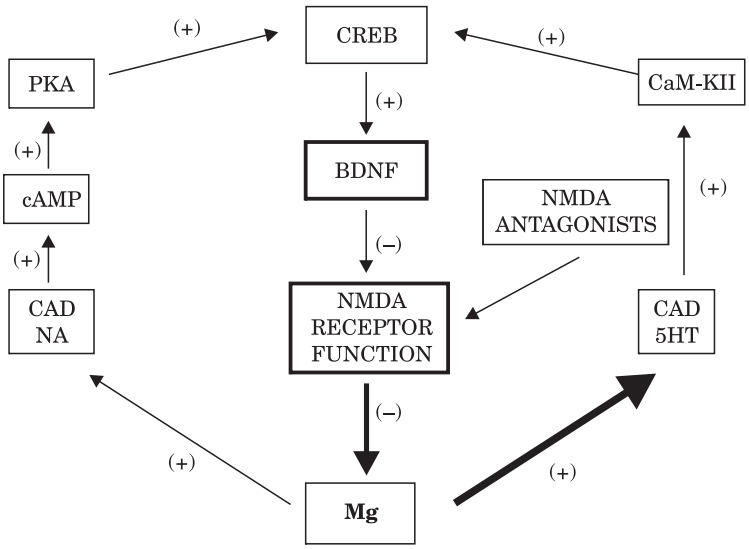

Fig. 1. Possible multidirectional mechanism of antidepressant magnesium (Mg) action. Classic antidepressants (CADNA) by enhancing noradrenergic transmission stimulate β-adrenoceptors and increase cAMP coupled elevation of activity of protein kinase A (PKA), which lead to activation of cyclic AMP response element binding protein (CREB). On the other hand antidepressants (CAD5HT) by enhancing serotonergic transmission lead to activation calcium-calmodulin dependent kinase II (CaM-KII) and also activation of CREB. Activated (phoshorylated) CREB increase concentration of brain-derived neurotrophic factor (BDNF), which together with BDNF-induced reduction of N-methyl-D-aspartate (NMDA) receptor function exhibit neuroprotective activity in the brain

A functional agonistic interaction between magnesium and GABAergic system was demonstrated. Muscimol-induced GABAA receptor response of muscimol in rat cerebral cortical synaptosoms is enhanced by magnesium (SCHWARTZ et al. 1994), and epileptiform activity induced by low magnesium concentrations can be reduced by vigabatrin (GABA agonist) (ENGEL et al. 2000). Thus, based on role of GABAergic transmission in the mechanism of antidepressant drugs (PILC and NOWAK, 2005), GABAergic-mediated antidepressant mechanism of magnesium should be also considered.

All the available data indicate the importance of magnesium homeostasis in pathophysiology and therapy of affective disorders.

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Key words: magnesium, affective disorders, depression, mania, animals, humans.

Abstract

Magnesium possesses activity in a broad range of biochemical processes in living organisms. This review focus on the role of magnesium in pathophysiological and therapeutical mechanisms of affective disorders. Magnesium as an antagonist of the N-methyl-D--aspartate (NMDA)/glutamate receptor complex, is active in the antidepressant screen test, forced swim test in rodents. Clinical studies, although providing very limited amount of data, suggest possible efficacy of magnesium in mania (bipolar affective disorders). Magnesium deficiency induced depression-like behavior in animals, and such an effect in humans is also suggested. All the available data indicate the importance of magnesium homeostasis in pathophysiology and therapy of affective disorders.

MAGNEZ W PATOFIZJOLOGII I TERAPII ZABURZEŃ AFEKTYWNYCH

Słowa kluczowe: magnez, zaburzenia afektywne, depresja, mania, zwierzęta, ludzie.

Abstrakt

Magnez odgrywa znaczącą rolę w funkcjonowaniu wielu procesów biochemicznych w żywym organizmie. W pracy dokonano oceny roli magnezu w patofizjologii i terapii zaburzeń afektywnych. Magnez jako antagonista receptora NMDA wykazuje aktywność w teście wymuszonego pływania u zwierząt. Badania kliniczne, chociaż dostarczają bardzo ograniczonej liczby danych, sugerują prawdopodobną skuteczność magnezu w terapii manii (zaburzenia afektywnego dwubiegunowego). Niedobór magnezu prowadzi do pojawienia się zaburzeń depresyjnych zarówno u zwierząt, jak i ludzi. Dostępne dane wskazują na ważną rolę homeostazy magnezowej w patofizjologii i terapii zaburzeń afektywnych.