Magnesium in major depression

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Abstract. There are contradictory data regarding the levels of magnesium in patients with major depression (MD) and how antidepressants influence their concentration. Our results show erythrocyte magnesium in patients with MD (44.39 ± 2.7 mg/L vs 59.1 ± 3.2 mg/L in control group, p < 0.05) and only in patients with severe MD (Hamilton score > 23) was a moderate decrease in plasmatic magnesium observed (17.7 ± 1.5 mg/L vs 22.9 ± 3.3 mg/L in control group). Therapy with antidepressants from different groups and with different mechanisms of action, such as amitriptyline (25 mg x 3/day per os, 4 weeks) and sertraline (50 mg x 3/day per os, 4 weeks) leads to a significant increase of magnesium concentration in erythrocytes (57.6 ± 4.5 mg/L after amitriptyline, respectively 56.9 ± 3.2 mg/L after sertraline, p < 0.05 vs before therapy). At the same time, in patients with MD, plasmatic levels of zinc were significantly decreased before therapy and increased after treatment with amitriptyline and sertraline (0.68 ± 0.09 mg/L before treatment vs 0.9 ± 0.07 after amitriptyline). There is a positive correlation between concentrations of magnesium in erythrocytes and the clinical evolution of patients with MD. We consider that increasing intracellular concentration is a component of the antidepressant mechanism of sertraline and amitriptyline and maybe of other antidepressants. Anhedonia and autolytic tendencies are important elements of MD symptomatology. We tested the influence of MgCl₂ 0.2 mM/kg/day on a reward system using conditioned place preference (Panlab) in rats. Our data show a moderate stimulation of the reward system by magnesium (290.6 ± 27 s time spent in a conditioned compartment before magnesium treatment and 363.3 ± 16 s after magnesium treatment) that reflects a stimulation of the reward system (RS). We consider that a magnesium-induced stimulation of the RS is an important issue for treating anhedonia in patients with MD. An increase of intracellular magnesium may be part of the mechanism of action of antidepressants.

Key words: magnesium, major depression, reward system, amitriptyline, sertraline

Major depression (MD) is one of the most important psychiatric diseases with an increasing frequency. This disease is relatively frequently found in elderly patients with non-insulin dependent diabetes mellitus. There are different data regarding variations of magnesium levels in patients with MD.

Barragán-Rodríguez et al. [1] have shown that MgCl₂ (450 mg/day, 12 weeks) has a significant effect toward decreasing depression, correlated with increasing serum concentrations of magnesium. In contrast to Widmer et al. [2], our data showed a decrease of erythrocyte magnesium in patients with MD. The magnesium decrease was positively correlated with the intensity of clinical symptoms, determined using the Hamilton scale. Our data are in agreement with Barra et al. [3] who did not find any correlation between plasmatic levels of magnesium and the intensity of depression in mild to moderately depressed patients. We found a negative correlation between magnesium concent-
trations in erythrocytes and the intensity of MD (determined with the Hamilton scale). Data linked with intracellular concentrations of magnesium in patients with MD are controversial.

Concentrations of magnesium in red blood cells are highly correlated with the psychomotor retardation score of depressed patients [4]. In our study in patients with medium and severe MD, magnesium concentration in erythrocytes was decreased [5]. A significant positive correlation could be established between a decreasing magnesium concentration in red blood cells in adult patients with MD and their depression scores on the Hamilton scale. In three animal models of depression: chronic severe stress, chronic mild stress and olfactory bulbectomy in rats, Zieba et al. [6] found no correlation between serum magnesium and severity of depression, but identified a significant positive correlation between the serum magnesium/copper rate and severity of depression. Hasey et al. [7] observed an inverse correlation between serum magnesium concentration and T3 and T4 levels, in contrast to Joffe et al. [8] who found a positive correlation. This relationship between T3 and T4 might be important, due to the influence of thyroid hormones on magnesium entrance into the cell. After traumatic brain injury a variable percent of patients develop depression [9].

Chronic intake of ethanol is frequently related with depressive states [10]. It is known that ethanol increases urinary elimination of magnesium and sometimes also decreases its absorption through the digestive system. We consider that magnesium deficit is involved in the pathogenicity of depression in alcoholics. Although a magnesium deficit has been identified in many studies of depressive states, it is not clear what the exact role and effect of magnesium intake is, in patients with depressive disorders. In a group of 5 708 adult patients who participated in the Hordaland Health Study in Western Norway, the inverse relationship between magnesium intake and the self reported score, using the hospital anxiety and depression scale, was weaker and not statistically significant [11]. In psychiatric patients suffering from MD, the magnesium level in CSF was found to be significantly lower versus the control group. Patients with MD who had made suicide attempts had particularly lower levels of magnesium in CSF [12]. In depressed patients with chronic pain, the level of magnesium was decreased in 67% of cases. Increasing intra-cellular concentrations of magnesium leads to decreasing anxiety [13], another major characteristic of MD (together with lack of pleasure). There are authors who claim that 300 mg magnesium/day (gluconate or taurinate) was found effective for the treatment of depression, but it is not clear to what degree magnesium alone decreased the intensity of the depression [14]. Our data [15] showed that, in adult patients of both genders with MD who received antidepressant therapy before hospital admittance, erythrocyte concentrations of magnesium were significantly lower versus the control group. The erythrocyte concentrations of magnesium were inversely correlated with the gravity of MD (estimated with the Hamilton scale). Our data are in agreement with Szewczyk et al. [16], who found increased concentrations of calcium and lower concentrations of magnesium in the brain (neocortex) of patients with depression. In our studies [17] in patients with MD (Hamilton score > 23), the erythrocyte level of magnesium was significantly decreased and was associated with a drop in plasmatic concentration and an increase in plasmatic levels of copper. Antidepressant therapy with amitriptyline increases concentrations of erythrocyte magnesium (44 ± 27 mg/L before treatment and 57.6 ± 4.5 mg/L after treatment, p < 0.05). A similar effect was observed in the case of sertraline, when increasing concentrations of magnesium in erythrocyte and zinc plasmatic concentrations were positively correlated with an improvement in the clinical symptoms of patients with MD [17]. Antidepressant drugs with different mechanisms of action and different chemical structures (such as amitriptyline and sertraline) show an improvement in the clinical state of patients with MD and are correlated with increasing erythrocyte concentrations of magnesium. This leads to the idea that this increase in magnesium concentration is a component part of the mechanism of action of antidepressants.

Levine et al. [18] found no significant changes in plasmatic and CSF calcium and magnesium concentrations in patients with depression. Our data also show a lack of significant changes in plasmatic calcium and magnesium levels in medium and mild MD, but erythrocyte magnesium was significantly decreased. In patients with severe MD (Hamilton score > 23), the concentration of total plasmatic magnesium was lower compared to the control group, but it was not changed in mild to moderate depression. We think that the heterogeneity of data about variations in plasmatic and tissue concentrations of magnesium (and other cations) in patients with depression is due to the different degrees of depression (in some studies with MD and in others with different depressive states). The studies were performed at different moments in the evolution of
the disease and the effects of therapy on the concentrations of bivalent cations were not investigated.

In some experimental models in animals, magnesium decreased the intensity of the depression. These experimental models do not reproduce human depression. Also, the ways of evaluating depressive symptoms in animals are not the same as in human MD but some mechanisms are close enough or similar.

Magnesium decreased post-traumatic depression following different traumatic brain injuries in rats [19]. Animals that receive MgSO₄ 30 minutes after injury, had a significantly decreased incidence and severity of depression. In this study, locomotion in an open field was considered to reflect general activity and a decrease in mobility was considered an indicator of depressed behavior. Rats fed with a Mg deficient diet for 48 days (Mg content < 15 mg/kg/day) and demineralized water show magnesium deficiency, associated with depression-like and anxiety-related behavior. The anxiolytic mechanism of magnesium is linked with its action at the level of NMDA receptors. There are at least two aspects of this action: the action to partially block the calcium channel linked with the NMDA receptor; the action on the glycine B site in the NMDA receptor. This magnesium action is antagonized by D-serine (100 nmol/mouse). D-serine significantly decreases the anxiolytic effect of magnesium [20].

Studies of magnesium concentrations in rats that developed depressive disturbances after traumatic brain injury (TBI) observed that magnesium administration 30 minutes after TBI reduced the incidence of depression. In these animals, locomotion (tested with open field tests for exploratory activity) decreased in animals that developed depressive and anxious symptoms and that had an increased degree of post traumatic disorder (alleviated by magnesium). Magnesium had an immediate effect on depressed rats’ motor activity.

Spasov et al. [21] showed that a magnesium-deficient diet in rats is associated with depression-like and anxiety behavior and that Mg-l-aspartate and MgCl₂ × 6H₂O in combination with pyridoxine led to a correction of behavioral disturbances in those rats. Iezhitsa et al. [22] showed that magnesium administration associated with vitamin B6 corrected depression-like behavioral disturbances in rats with chronic alcoholism. Some experimental studies have shown that concomitant administration of magnesium increased the effect of imipramine on immobility in stress-induced depression-like behavior in forced swim tests on mice [23]. Compared to mice fed with a normal diet, mice receiving a low magnesium diet for 4-8 weeks show an increased immobility time in the forced swim test. This fact is considered as an indicator of depressive states even if it is not identical to human depression [24]. Therapy with a tricyclic antidepressant such as desipramine decreases immobility after a hypoglycemic diet. Magnesium depletion increases anxiety and depression in rodents.

Because anhedonia (lack of activity to pleasurable stimuli) is a major feature of depression, involvement of the brain reward system is very important [25]. One of the pathways that magnesium and other bivalent cations might influence in the evolution of MD and the effects of antidepressant medication, is through action on the brain reward system. We tested the influence of different Mg²⁺ doses on the reward system (RS), using conditioned place preference (CPP). Our data shows that magnesium (0.2 mM/kg/day) moderately increases CPP in rats, which proves a stimulation of the reward system [26].

The results of Lawley and Kantak [27] and our data support the idea that magnesium moderately stimulates the reward system. MgCl₂ induced place preference in rats at 15 mg/kg [27], respectively 0.2 mM/kg i.p. [26]. Our data showed a moderate stimulation of RS by magnesium (290.6 ± 27 s time spent in a conditioned compartment before magnesium administration and 363.3 ± 16 s after magnesium treatment, p < 0.05) which reflects stimulation of the RS and is a measure for pleasant stimulation. We consider that magnesium stimulation of the RS is an important issue for treating anhedonia in patients with MD and increasing intracellular concentrations of magnesium is a component of the mechanism of action of antidepressants.

References


