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Review

Magnesium in depression

Anna Serefko[1], Aleksandra Szopa[1], Piotr Wlaź[2], Gabriel Nowak[3,4], Maria Radziwoń-Zaleska[5], Michał Skalski[5], Ewa Poleszak[1]

[1]Chair and Department of Applied Pharmacy, Medical University of Lublin, Chodźki 1, PL 20-093 Lublin, Poland

[2]Department of Animal Physiology, Faculty of Biology and Biotechnology, Maria Curie-Skłodowska University, Akademicka 19, PL 20-033 Lublin, Poland

[3]Department of Neurobiology, Institute of Pharmacology, Polish Academy of Science, Smętna 12, PL 31-343 Kraków, Poland

[4]Department of Cytobiology, Jagiellonian University Medical College, Medyczna 9, PL 30-688 Kraków, Poland

[5]Department of Psychiatry, Medical University of Warsaw, Nowowiejska 27, PL 00-665 Warszawa, Poland

Correspondence: Ewa Poleszak, e-mail: ewa.poleszak@umlub.pl and Michał Skalski, e-mail: michal.skalski@wum.deu.pl

Abstract:
Magnesium is one of the most essential mineral in the human body, connected with brain biochemistry and the fluidity of neuronal membrane. A variety of neuromuscular and psychiatric symptoms, including different types of depression, was observed in magnesium deficiency. Plasma/serum magnesium levels do not seem to be the appropriate indicators of depressive disorders, since ambiguous outcomes, depending on the study, were obtained. The emergence of a new approach to magnesium compounds in medical practice has been seen. Apart from being administered as components of dietary supplements, they are also perceived as the effective agents in treatment of migraine, alcoholism, asthma, heart diseases, arrhythmias, renal calcium stones, premenstrual tension syndrome etc. Magnesium preparations have an essential place in homeopathy as a remedy for a range of mental health problems. Mechanisms of antidepressant action of magnesium are not fully understood yet. Most probably, magnesium influences several systems associated with development of depression. The first information on the beneficial effect of magnesium sulfate given hypodermically to patients with agitated depression was published almost 100 years ago. Numerous pre-clinical and clinical studies confirmed the initial observations as well as demonstrated the beneficial safety profile of magnesium supplementation. Thus, magnesium preparations seem to be a valuable addition to the pharmacological armamentarium for management of depression.

Key words:
magnesium, depression, antidepressant-like effect, antidepressant therapy

Introduction

Magnesium, one of the most essential minerals in the human body, a co-factor of many enzymatic reactions [43, 54], is known to be involved in proper functioning of cardiovascular, alimentary, endocrine and osteoarticular systems. An adult contains about 24 grams of magnesium, of which more than 50 percent is localized in bones while the rest is found in soft tissues and plasma/serum [33]. According to literature [20, 64] magnesium is widely connected with brain biochemistry as well as the fluidity of neuronal membrane. Thus, a variety of neuromuscular and psychiatric symptoms (i.e., hyperexcitability, agitation, tetany, headaches, seizures, ataxia, vertigo, muscular weakness, tremors, irritability, anxiety, insomnia, nervous

fits, lipothymias, fatigue, confusion, hallucinations, depression) was observed in magnesium deficiency. All of them were reversible by restoration of normal brain magnesium level [66, 84]. Experimentally induced magnesium deficiency resulted in depression-like behavior in rodents [57, 78, 80, 88], which was effectively managed by antidepressants [78, 88].

The diet of depressed people appears to be impoverished in magnesium [41]. Jacka et al. [41] found an inverse relationship between magnesium intake and depressive symptoms in community-dwelling adults. However, the authors wonder if the poor quality of depressives' diet was a causative factor or a consequence of their mental disorder. Apart from malnutrition, low magnesium level in the body may occur due to defects in its absorption or as a result of its renal loss (for example in case of diabetes, alcoholism, treatment with antidiuretics, aminoglycosides, fluoroquinolones, cisplatin, digoxin, cyclosporine, amphotericin B) [34]. Acute emotional stress and stressful activities increase magnesium excretion as well [22]. It has also been proposed that the transfer of large amounts of this element from mother's blood to fetus with other nutrients may contribute to occurrence of postpartum depression [20]. Some authors try to associate a long-term insufficient intake of magnesium with development of systemic inflammation, which in turn is likely to aggravate the symptoms of depression [23, 49, 50, 67, 86]. Major and suicidal depression particularly seems to be related with magnesium insufficiency. Literature data indicate that cerebrospinal fluid magnesium concentration was low in patients with history of suicidal behavior [4, 5] while serum and cerebrospinal fluid calcium to magnesium ratios were usually elevated in acutely depressed individuals when compared to the healthy subjects [46]. As pointed out by Eby and Eby [20], this connection is not so obvious for "melancholy", depression developed as a result of hormonal imbalance, low cholesterol, food allergy, Wilson's disease and other ailments or depression being an adverse reaction to drugs.

Magnesium levels in depression

There is evidence of rise in erythrocyte magnesium levels in severely and moderately depressed people *versus* the slightly depressed ones and healthy individuals [28, 89–91]. Positive correlation between erythrocyte magnesium concentration and the clinical progress of this disorder was also noted [60, 89]. In contrast, Nechifor et al. [60] showed a decrease of erythrocyte magnesium in patients with severe and medium major depression. Magnesium decrease was positively correlated with the severity of clinical symptoms measured by Hamilton scale. The same author [59] observed lower erythrocyte magnesium level (*versus* the control group) in adult patients with major depression who had received antidepressant therapy before hospital admittance. On the other hand, antidepressant therapy with amitriptyline or sertraline increased concentration of erythrocyte magnesium level [60]. Data of another trial showed that significantly lower erythrocyte magnesium level in patients with major depression was associated with diminished magnesium plasmatic level as well as increased plasmatic concentration of copper [59]. A positive correlation between serum level of magnesium and thyroid hormone T4 [42] along with the involvement of an imbalance in the serum magnesium/copper ratio have been found in depressed patients [96]. Opposing results were obtained by Hasey et al. [32], who noticed an inverse correlation between serum magnesium concentration and T3 and T4 levels. No relationship was demonstrated between zinc and magnesium or/and copper concentrations or ratios [96].

Plasma/serum magnesium levels do not seem to be appropriate indicators of depressive disorders, since ambiguous outcomes, depending on the study, were obtained. There are several reports on higher concentration of magnesium in depressed patients [8, 37, 48] and more than a few on the lower magnesium level [6, 38, 75, 96]; some authors claim that there is no difference in the serum/plasma concentrations of magnesium ion or calcium/magnesium ratios between the affected subjects and the control group [46, 93]. Levine et al. [46] compiled data from multiple researches on plasma/serum levels of magnesium and calcium in depressives. Similar non-consistency of results was noted in relation to magnesium plasma/serum levels after initiation of antidepressant drug therapy – Frizel et al. [29] showed a significant increase of magnesium concentration while Naylor et al. [58] found no differences. Most probably, all these divergences occurred because of the influence of distinct factors and methodology of clinical trials on the obtained results [46, 60]. One of them might have been the implemented therapy – for example, some studies demon-

strated that neuroleptics [2, 40], antidepressants [5, 90] and lithium treatments promote alterations in plasma/serum levels of magnesium [37]. These divergent results have made recognition of depression as being caused by magnesium deficiency nearly impossible to the clinician and have very greatly retarded research. Eby et al. [22] suggested that tissue magnesium level is a much better indicator than magnesium plasma/serum concentration. Iosifescu et al. [38] and Nowak et al. [62] reported the link between reduced content of magnesium in brain and depression. Phosphorus magnetic resonance spectroscopy seems to be currently the best tool for *in vivo* assessing magnesium level in the human brain [39]. It has a potential to become a reliable method that could help in diagnosis of different pathological conditions associated with low brain magnesium, e.g., major depression [22, 39].

Mechanism of antidepressant action

The emergence of a new approach to magnesium compounds in medical practice has been seen. Not only are they administered as components of ordinary dietary supplements but also they are perceived as the effective agents in treatment of migraine, alcoholism, asthma, heart diseases, arrhythmias, renal calcium stones, premenstrual tension syndrome and many others [3, 17, 19, 27, 44, 52, 77, 94, 95]. The role of magnesium preparations in management of a range of mental disorders as well as emotional problems [20, 55] cannot be neglected. For many decades magnesium has had its essential place in homeopathy as a remedy for a range of mental health problems, including depression [20]. Promising preclinical and clinical reports support therapeutic potential of diverse magnesium compositions in different kind of depression (Tab. 1). Antidepressant activity of magnesium was observed after both short-term and chronic administration [69, 81, 82].

Mode of action of antidepressant-like effect of magnesium is not fully understood yet [10]. There is strong evidence that magnesium influences several systems associated with development of depression. This cation is known to modulate the activity of NMDA and GABA receptors, play an important role in suppression of hippocampal kindling and release of adrenocorticotropic hormone and interact with the limbic-hypothalamus-pituitary-adrenal (HPA) axis, frequently dysregulated in depressives [56]. Besides, it probably affects access of corticosteroids to the

Tab. 1. Preclinical and clinical reports supporting the involvement of magnesium in treatment of depression

Study	References
I. Preclinical studies	
Magnesium deficiency and depression-like behavior in rodents	[57, 78, 80, 88]
Antidepressant activity of magnesium	
– after short-term and chronic administration	[69, 81, 82]
– in post-traumatic depression (decreased incidence and severity)	[30]
– in the FST in mouse and rat models	[16, 69, 72–74]
Effect of joint administration of magnesium and other agents	
– enhancement of the antidepressant-like activity of magnesium by NMDA antagonists	[71]
– inhibition of the antidepressant-like activity of magnesium by NMDA agonists	[70, 71]
– synergistic antidepressant-like effect of magnesium and fluoxetine, imipramine, citalopram, tianeptine, bupropion	[10, 68, 74]
II. Clinical studies	
Efficacy of magnesium treatment/supplementation	
– in postpartum and major depression	[20]
– in reducing depressive symptoms in chronic fatigue syndrome	[13]
– in reducing depressive symptoms in women with premenstrual syndrome	[25]
– in elderly depressives with hypomagnesaemia and type 2 diabetes	[7]
– in depressive states and paresthesia	[24]

brain *via* influence on P-glycoprotein, participates in inactivation of protein kinase C neurotransmission and stimulates activity of Na^+/K^+ATPase [1, 31, 35, 55, 76, 92]. Depletion of magnesium, a physiological voltage-dependent blocker of NMDA receptor ion channel, allows calcium and sodium ions to enter the postsynaptic neuron and to exit potassium ions [21, 51, 53]. Increased influx of calcium ions leads to production of toxic reactive oxygen species and toxic amount of nitric oxide radicals as well as neuronal swelling and neuronal death [9, 21, 51]. Neuronal dysfunction and depression as a consequence of an excessive leak of calcium into cells triggering the synaptic release of glutamate, depolarization of neurons and further increase of calcium ions is also observed in ATP insufficiency in neurons. Magnesium ions are known to take part in a proper formation and utilisation of ATP [12, 21]. Some authors confirmed that the shortage of magnesium ions along with the excess of calcium ions and glutamate are the cause of brain cell synaptic dysfunction leading to mood and behavioral disorders, including depression [20]. Although the antidepressant activity of magnesium is predominantly attributed to the blockade of NMDA receptor [14, 63], animal studies performed by Carsodo et al. [10] confirmed that various receptors from several other systems: serotonergic (5 HT_{1A}-, 5 $HT_{2A/2C}$-receptors), noradrenergic (α_1-, α_2-receptors) and dopaminergic (D_1-, D_2-receptors) are relevant, as well. Involvement of serotoninergic system in anti-depressant action of magnesium ions was also demonstrated by Poleszak [68] in the forced swimming test (FST) in mice – an anti-immobility activity of magnesium was diminished by pre-treatment with p-chlorophenylalanine, an inhibitor of serotonin synthesis. Since it was shown that 15 mg/kg of magnesium moderately stimulates the reward system in rats [45], there are some suppositions that the brain reward system may contribute to the antidepressant effect of magnesium [45, 60]. Supplementation of magnesium ions prolongs duration of slow wave sleep which is decreased in the course of depression [11, 34].

Pre-clinical and clinical studies

The first information on the beneficial effect of magnesium sulfate given hypodermically to patients with agitated depression was published almost 100 years ago [87]. Administration of magnesium sulfate to rats subjected to traumatic brain injury significantly decreased both incidence of post-traumatic depression and its severity [30]. Decollogne et al. [16] and Poleszak et al. [69, 72–74] observed that the immobility time in forced swimming test in mouse and rat models was significantly reduced by magnesium ions. The obtained results were comparable to those recorded for imipramine and MK-801 [16]. Moreover, the ineffective doses of NMDA antagonists (MK-801, CGP 37849, L-701,324, D-cycloserine) given jointly with a low and also subactive dose of magnesium hydroaspartate shortened the immobility time in the FST [71]. On the other hand, the agonists of different binding sites of the NMDA receptor complex (i.e., NMDA and D-serine) abolished the magnesium-induced antidepressant-like effect [70, 71]. Co-treatment of magnesium salts and antidepressants from different classes (i.e., fluoxetine, imipramine and bupropion) results in the synergistic antidepressant-like effect, measured by the standard broadly accepted FST, used in behavioral experiments [10, 74]. Similar outcomes were also observed by Poleszak [68] for combination of magnesium ions and citalopram or tianeptine. Depression-like behavioral disturbances induced in rats by magnesium-deficient diet were reversed by treatment with Mg L-aspartate and magnesium chloride hexahydrate combined with vitamin B_6 [80]. Similar results were obtained after joint administration of magnesium and pyridoxine hydrochloride in experiments carried out in animal model of chronic alcoholism [36]. According to Singewald et al. [78], chronic oral administration of desipramine or hypericum extract as an addition to a 21-day magnesium-deficient diet prevents development of depression-like behavior disturbances. In experiments performed by Nikseresht et al. [61] on female mice, a single joint administration of zinc, magnesium and vitamin B_1 3 days after delivery improved depressive behavior.

Co-administration of a high dose of sildenafil citrate (20 mg/kg) with magnesium hydroaspartate thoroughly inhibits the antidepressant properties of the latter [79]. Because of the sedative activity of magnesium, caution is advised when anesthetic drugs and this element are given together. Reduction in anesthetic dose may be needed [18].

Eby and Eby [20] observed the efficacy of magnesium supplementation in patients with postpartum and major depression. Magnesium treatment also improved symptoms of depression in chronic fatigue

syndrome [13] and in women with premenstrual syndrome [25]. Randomized clinical trial performed by Barragan-Rodriguez et al. [7] demonstrated that 12-week oral administration of 5% solution of magnesium chloride to elderly depressives with hypomagnesemia and type 2 diabetes exerts therapeutic effect similar to imipramine 50 mg daily. A recovery within less than 7 days from major depression after taking magnesium glycinate and magnesium taurinate with each meal and at bedtime, was reported for several cases [20]. However, some authors wonder to what degree magnesium given alone may decrease the intensity of depression symptoms [60]. Depressive states and paresthesia immediately resolved after intravenous administration of magnesium sulfate to 69-year-old woman with Gitelman's syndrome [24].

Magnesium preparations

The outcomes of several studies on preparations of magnesium proved that not all magnesium compositions are equally absorbed into the bloodstream. Chloride, sulfate, citrate, lactate, malate, glycinate and taurinate are highly biologically available [26, 47, 85], while magnesium oxide is essentially not bioavailable. It should be underlined that too high concentration of calcium ions may disturb bioavailability of magnesium after oral administration. Intake of calcium and magnesium in quantities similar to 1 : 2 ratio is recommended as beneficial for patients with osteoporosis, cardiovascular diseases and depression [20]. Moreover, Mark et al. [51] reported that compositions of magnesium glutamate or aspartate should not be used by depressive individuals since the depression of 59-year old patient worsened significantly after administration of these compounds, since excesses of glutamate and aspartate in the brain are neurotoxic [22].

Magnesium supplementation is generally considered as safe and well tolerated [20]. However, development of tolerance to the antidepressant effect was noted in rats treated chronically with magnesium chloride [73]. These data were in contrast to the results of previous experiments performed using a mouse model [69]. The adverse effect occurring most frequently after intake of a high dose of magnesium was diarrhoea which can be avoided by giving magnesium preparation by parenteral route. Interestingly, daily topical application of 25% magnesium chloride solution to the chest and back was proposed as well [20, 83], since this route can result in increases in brain magnesium without diarrhoea.

Given that standard antidepressant therapies, though varied but with numerous side effects, do not meet clinical expectations [15, 65] in about 60% of patients [22], magnesium preparations with their overall beneficial safety profile seem to be a valuable addition to the pharmacological armamentarium for management of depression. As a prevention strategy, Eby et al. [22] recommended daily intake of 600 to 800 mg of magnesium, with the exception of ineffective magnesium oxide.

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