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Review

Antidepressant activity of zinc and magnesium in view of the current hypotheses of antidepressant action

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Abstract:
The clinical efficacy of current antidepressant therapies is unsatisfactory; antidepressants induce a variety of unwanted effects, and, moreover, their therapeutic mechanism is not clearly understood. Thus, a search for better and safer agents is continuously in progress. Recently, studies have demonstrated that zinc and magnesium possess antidepressant properties.
Zinc and magnesium exhibit antidepressant-like activity in a variety of tests and models in laboratory animals. They are active in forced swim and tail suspension tests in mice and rats, and, furthermore, they enhance the activity of conventional antidepressants (e.g., imipramine and citalopram). Zinc demonstrates activity in the olfactory bulbectomy, chronic mild and chronic unpredictable stress models in rats, while magnesium is active in stress-induced depression-like behavior in mice. Clinical studies demonstrate that the efficacy of pharmacotherapy is enhanced by supplementation with zinc and magnesium. The antidepressant mechanisms of zinc and magnesium are discussed in the context of glutamate, brain-derived neurotrophic factor (BDNF) and glycogen synthase kinase-3 (GSK-3) hypotheses.
All the available data indicate the importance of zinc and magnesium homeostasis in the psychopathology and therapy of affective disorders.

Key words:
zinc, magnesium, depression, antidepressants, NMDA, BDNF, GSK-3

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Zinc

Zinc is one of the most abundant trace elements in the body. It is a key structural component of many proteins and a co-factor of many enzymes that play an important role in brain function [20]. Zinc is present predominantly in the brain and is located in specific regions, including the hippocampus, amygdala, and cortex. The vast majority of brain zinc (95%) is bound to zinc metalloproteins; the rest is found in presynaptic vesicles [103]. Neurons containing these vesicles are termed zinc-enriched neurons (ZEN). In the cerebellum, these neurons are associated with -aminobutyric acid (GABA) neurotransmission [98, 108], whereas, in the cortex, amygdala, and hippocampus, the ZEN terminals are glutamatergic [19]. By inhibiting both the GABA and glutamatergic receptors, zinc seems to modulate neuronal excitability [20, 98], and it is also thought to play an important role in synaptic plasticity [47]. Recent data indicate that zinc can function as a signaling molecule modulating protein function [28, 43, 55, 56]. Dietary zinc deprivation influences zinc homeostasis in the brain and leads to behavioral disturbances, such as anorexia, dysphoria, impaired learning and cognitive function [103], and some neurological disorders [54, 103].

Zinc and depression

Experimental data

Experimental data have demonstrated the involvement of zinc in the pathophysiology and treatment of depression. Experiments performed on rats showed that chronic treatment with citalopram significantly increases the zinc level in blood serum [69]. Repeated administration of citalopram or imipramine (IMI) slightly increases the zinc level in the hippocampus and decreases it in the cortex, cerebellum, and basal forebrain, although the calculation of the ratio hippocampus/other brain regions zinc concentration displayed a significantly increased level of zinc in the hippocampus after treatment with these drugs [69]. Using Timm's histochemical method for zinc staining, two groups, Lamont et al. [46] and Vaidya et al. [104], showed that repeated treatment with electroconvulsive shock (ECS) induced hippocampal mossy fiber sprouting, which might indicate an increase in the vesicular zinc level in the hippocampus. This effect was not found after chronic antidepressant treatment [46]. Our recent data show that repeated administration of zinc increases the pool of synaptic zinc in the hippocampus [102], and this effect is similar to that observed after chronic ECS treatment [104].

One of the roles of zinc in the central nervous system is the modulation (inhibition) of the glutamate ionotropic N-methyl-D-aspartate (NMDA) receptor complex [5]. Our study, which examined the effect of IMI on the potency of zinc's inhibition of [^{3}H]MK-801 binding in mouse and rat brains, showed that chronic treatment with IMI increases the potency of zinc to inhibit [^{3}H]MK-801 binding in the mouse cortex but not the hippocampus [101]. However, this treatment did not influence the zinc affinity in rat tissue, which may suggest the existence of a species-dependent effect of IMI-induced mechanisms involving zinc sites on the NMDA receptor. However, the differences that we have observed in our study (increased inhibition of [^{3}H]MK-801 binding by zinc in the cortex but not in the hippocampus) may be due to the existence of multiple forms of the NMDA-channel complex (region-specific subunit composition and different physiological and pharmacological properties) [5]. Recent data indicated that zinc enhances the capability of detection of IMI-induced reduction in glycine potency at NMDA receptor labeled with [^{3}H]L-689,560, which may further confirm the importance of zinc in the mechanism of antidepressant treatment [11].

Most of the antidepressants, as well as ECS, induce an increase in brain-derived neurotrophic factor (BDNF) gene expression in the hippocampus. However, the elevated BDNF mRNA levels in the cortex were observed only after treatment with ESC and a few antidepressants [67]. Our data indicate that two weeks of zinc treatment at a high dose (11.5 mg/kg) increased the BDNF mRNA levels in the rat cortex [68] but not in the hippocampus. However, one to five weeks of treatment with zinc at a very low dose (1.8 mg/kg) increases the BDNF mRNA levels in the hippocampus [99]). Data collected by Franco et al. [17] indicate that chronic zinc treatment produces an increase in ERK phosphorylation and BDNF expression in the cerebral cortex in rats.

Recent data demonstrate that zinc exerts antidepressant-like effects in animal drug screening tests and models of depression. Zinc showed antidepressant-like activities in the forced swim test (FST) in both mice and rats and in the tail suspension test in mice [44, 45, 72, 90]. Moreover, doses of IMI and

citalopram that were low and ineffective in the FST were then administered together with low doses of zinc and proved to be active in this test [90, 100]. Zinc was also active in the olfactory bulbectomy (OB) model of depression. Both acute and chronic administration of zinc reduced the number of trials needed for learning passive avoidance and reduced the time of walking and the number of rearings and peepings in the bulbectomized rats [72]. Furthermore, recent findings have demonstrated an antidepressant-like activity of zinc in chronic unpredictable stress (CUS). It was found that CUS decreases the footshock-induced fighting behavior in rats and that various antidepressants given repeatedly prevent this kind of behavioral depression [74]. Similar to the effects of antidepressant drugs, chronic zinc administration prevented the deficit in fighting behavior in chronically stressed rats [7]. Additionally, zinc supplementation enhanced the effect of IMI in this behavioral model of depression [7]. Our recent data show that chronic treatment with zinc was also active in the chronic mild stress (CMS) model of depression in rats. Zinc reversed the CMS-induced reduction in the consumption of sucrose [99] (Tab. 1).

All these findings strongly suggest that zinc could also produce antidepressant activity in humans.

Human data

Several clinical and postmortem studies have indicated the role of zinc in depression and the mechanisms of action of antidepressant drugs. It was found that depressed patients showed a significantly lower serum zinc level than psychiatrically normal controls [51, 61, 73]. Moreover, the serum zinc concentration in patients with unipolar depression was negatively correlated with the severity of this illness [51]. Although the other study did not show any correlation between these parameters, the authors speculated that this lack of correlation might be due to the different populations of patients (mostly treatment-resistant) used in the study [53]. A recent preliminary study performed in pregnant women indicated that a lower serum zinc concentration may also accompany antepartum and postpartum depressive symptoms [111]. Also in this study, the serum zinc level was negatively correlated with the severity of the depressive symptoms. Some studies, which found low zinc levels in depressed patients, also reported an increase in the activation of markers of the immune system [51, 61]. It was found, however, that cytokine production and activation of the immune system can induce the development of clinical depression [2]. Thus, it is possible that the lower serum zinc in depression may be secondary to zinc sequestration by metallothionein, which may be related to the increase in cytokine production [50, 52].

Further support of the hypothesis that zinc concentration might be a sensitive and specific marker of depression comes from the findings that the lower serum zinc level may be normalized after successful antidepressant therapy [53, 61, 94]. There are also some preliminary data suggesting that zinc supplementation may enhance antidepressant therapy in patients with unipolar depression [70]. In this study, two groups of patients were used: placebo-treated and those receiving zinc supplementation (Farmapol, Poland). All patients received standard antidepressant therapy. The severity of depression was assessed by the Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory (BDI). Antidepressants reduced HDRS scores by the 2nd week of treatment in both groups and the BDI scores at the 6th week in the zinc-treated group. Zinc supplementation significantly reduced the scores in both HDRS and BDI measures after 6 and 12-week supplementation when compared with the placebo treatment [70]. These findings are the first demonstration of the benefits of zinc-supplementation in antidepressant therapy. Beyond this, our present unpublished clinical data indicate the beneficial effects of zinc as an adjunct agent in the treatment of resistant patients (Tab. 1).

Postmortem studies on suicide subjects and psychiatrically normal controls did not show any differences in the zinc concentrations in the hippocampal or cortical tissues of suicide victims; however, there was a statistically significant decrease in the ability of zinc to inhibit [^{3}H]MK-801 binding to NMDA receptors in the hippocampus, but not in the cortex of suicide victims, as compared to control subjects [71]. These data represent the first demonstration that the alterations in the interaction between zinc and NMDA may be involved in the psychopathology underlying suicidal attempts.

Zinc and immune system

Immunological studies have provided evidence that major depression is accompanied by alterations in the immune-inflammatory markers. It was found that depressed patients with melancholia especially exhibit

disruption in several aspects of immune functioning, including an increased number of leukocytes, monocytes, neutrophils, T-lymphocytes, neopterin and increased in prostaglandin secretion [33, 38, 52]. More recent studies have shown that depression is also associated with the activation of an acute phase response with increased plasma concentration of positive acute phase proteins (e.g., haptoglobin, α_1 and α_2 globulin fractions) and reduced negative acute phase proteins, such as albumin and transferrin [50, 52, 91]. In addition to these factors, it has been reported that severe depressive illness is also accompanied by elevated circulating cytokines (IL-β, IL-6) and interferon-γ (IFN-γ) [49, 50] as well as by increased production of the proinflammatory cytokines (IL-β, IL-6, TNF-α) [2, 52]. One of the characteristic features of an acute phase response is also a decreased serum zinc level. It has been hypothesized that the lowered serum zinc may be secondary to the sequestration of this metal by the intracellular metal binding protein metallothionein in the liver, which, in turn, may be a result of an increased production of the proinflammatory cytokines [106]. The other findings indicate a negative relationship between lower serum zinc and the increased neopterin levels in depression [51]. Neopterin is a highly sensitive marker of the activation of cell-mediated immunity. A decrease in serum neopterin suggests that the lower serum zinc levels observed in major depression may be secondary to the immune/inflammatory response in that illness. Several reports have indicated that lower serum zinc concentrations in major depression are related to an increase in other immuno/inflammatory markers, which include increased CD4+/CD8+ T cell ratios and serum neopterin and IL-6 serum levels [50]. Another sign of inflammatory response system activation reported in depression is a decrease in the serum concentration of albumin [52, 105], which is the major plasma zinc binding protein [105]. A significant positive relationship between serum zinc and serum albumin was found in patients with a major depressive disorder [52]. These data suggest that the lower zinc concentration observed in depression may in part be related to the decreased concentration of its "carrier" protein, albumin [52]. Therefore, these findings raise the hypothesis that alterations in serum zinc may be the result of depression-related mechanisms rather than their cause.

Mechanism of antidepressant activity

Glutamate receptors

Conventional antidepressants, which enhance the monoamine systems, increase BDNF activity, which may be connected to the reduction of NMDA ionotropic glutamate receptor function [76, 97]. Zinc is a potent antagonist of the NMDA receptor complex [30, 98]; thus, just as the organic NMDA receptor antagonists, it may induce antidepressant actions *via* this receptor complex. In fact, chronic treatment with zinc enhances BDNF gene and protein expression and reduces the affinity of glycine to glycine/NMDA receptors [68, 99, our unpublished data]. The antidepressant-like action of zinc in the forced swim test is antagonized by D-serine or NMDA co-treatment [80, our unpublished data]. The specificity of that method was earlier verified using selective NMDA receptor ligands [85]. Furthermore, zinc is also an antagonist of group I (mGlu1) and group II metabotropic glutamate receptors [114] and an enhancer of the AMPA ionotropic receptor [88], which are receptors involved in the mechanism of antidepressant activity (Fig. 1).

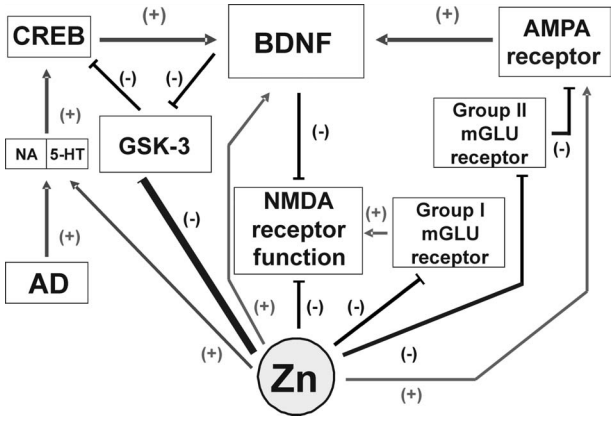

Fig. 1. Molecular mechanisms of antidepressant activity of zinc. Plus signs represent excitatory/enhancing interactions; minus signs represent inhibitory interactions. Three main targets, BDNF, NMDA, and GSK-3, of antidepressant treatment may also be involved in the antidepressant action of zinc. Zinc, like conventional antidepressants (AD), may enhance the CREB/BDNF pathway *via* the serotonergic system. Zinc may also affect BDNF by inhibiting the activity of GSK-3 by directly (or indirectly through group II mGluR) enhancing AMPA receptors or by an unknown yet direct influence. In addition, zinc inhibits function of NMDA receptors by direct interaction or *via* group I mGluR

Inhibition of GSK-3 enzyme

Another possible mechanism involved in zinc's antidepressant activity is the antagonism of glycogen synthase kinase-3 (GSK-3). GSK-3 is the enzyme that deactivates glycogen synthase by phosphorylation. However, glycogen synthase is not alone in being affected by GSK-3. Other pathways, such as the insulin/insulin-like growth factor (IGF-1) or neurotrophic factor signaling (e.g., CREB), are influenced by GSK-3 [26]. Lithium [26], zinc [37], and magnesium [26, 93] inhibit the phosphorylation activity of GSK-3, which may be related to the therapeutic activity of these ions. Antidepressant drugs, electroconvulsive shocks, and some antipsychotics inhibit the GSK-3 phosphorylation activity, and, GSK-3 inhibitors exhibit antidepressant-like effects in the FST [25] (Fig. 1).

GSK-3 inhibits CREB activity and is negatively regulated by BDNF, which remains under the control of CREB. Thus, the inhibition of GSK-3 leads to enhanced CREB activity and enhanced activity of BDNF, which, in turn, reduces GSK-3's function (negative loop). As such, zinc can also increase BDNF function through the inhibition of GSK-3 (Fig. 1).

Involvement of serotonergic system

The involvement of the serotonergic system in the antidepressant activity of zinc was observed. In the FST, the synergistic effect of zinc was shown by "serotonergic" (serotonin uptake inhibitors) but not by "noradrenergic" (noradrenaline uptake inhibitors) antidepressants (our unpublished data). Moreover, lesion of the serotonergic system (induced by pCPA) counteracted antidepressant-like effects induced by this ion (our unpublished data). Zinc differentially modulates the serotonin uptake *in vitro* [22], and such complex interaction of zinc with the serotonin transporter *in vivo* may be responsible for the positive zinc interaction with serotonin uptake inhibitors in the FST (Fig. 1).

Magnesium

Magnesium is a major biometal that plays a significant role in a variety of physiological mechanisms. Magnesium is the fourth (Ca > K > Na > Mg) most abundant cation in living organisms and the second (after potassium) most common intracellular cation [16]. A healthy adult human contains about 1000 mmol (24 g) magnesium distributed in various organs and compartments. It is mainly distributed in bones (half of the total magnesium in the body) and soft tissues: muscles (27%) and heart and liver (19%) [13, 89]. Tissue magnesium (intracellular magnesium fraction) is mainly bound to nucleic acids (RNA, DNA), ATP, ADP, proteins, phospholipids, and citrate [65]. Ninety percent of intracellular magnesium is bound to ribosomes or polynucleotides. Its physiological functions include structural stabilization of proteins, nucleic acids, and cell membranes, which it does by general surface binding [8]. Two to three percent of intracellular magnesium is free, and this pool regulates the intracellular magnesium homeostasis and cellular function [65, 89].

About 1% of the body's total magnesium is localized extracellularly, mainly in blood (serum and red blood cells), where it is present in three states: protein-bound (19%), complexes to anions, such as citrate, phosphate, and bicarbonate (14%), and ionized (biologically active form, 67%) [1, 14]. The balance between cerebrospinal fluid (CSF) magnesium concentration and plasma magnesium concentration is regulated by the active transport between these two compartments [62]. This mechanism leads to the stabilization of the intracerebral magnesium concentrations even in the case of magnesium depletion [64].

Magnesium is a co-factor of numerous enzymatic reactions involving energy metabolism [27, 92]. It is involved in transmembrane ion flux and the production or utilization of adenylate cyclase [60]. Magnesium is also a potent antagonist of the NMDA receptor complex [62]. The activation of the NMDA receptor ion channel is blocked by Mg^{2+} in a voltage-dependent manner [62]. *In vitro,* this blockade occurs at extracellular Mg^{2+} concentrations (less than 1 mM) that are within the range of the magnesium level found in CSF and plasma [62]. Lowering extracellular magnesium concentrations increases central hyperexcitability due to the disinhibition of the NMDA receptor channels' [59] magnesium levels, and the metabolism homeostasis is regulated by various hormones, while the magnesium deficiency causes alterations in the metabolism, secretion, and action of several hormones [57, 58]. Magnesium is necessary for the normal function of the parathyroid glands, the metabolism of vitamin D, and the sensitivity of tissues to the parathyroid

hormone (PTH), while PTH itself stimulates magnesium reabsorption in the renal, magnesium absorption in the ileum, and the release of magnesium from bone tissue [115]. Many of magnesium's actions have been linked to a physiological calcium antagonist [39]. It influences Ca^{2+} uptake, distribution, and content in cardiovascular cells [66, 95]. A high Ca/Mg ratio predisposes to arterial spasms and increases catecholamine release. Moreover, it is known that magnesium is needed for the activation of Na/K-ATPase [91]. In addition, at the cell level, magnesium modulates ion transport by pumps, carriers, and channels (thus modulating signal transduction) and has a membrane-stabilizing and protecting effect [4, 89].

Recent data from experimental and epidemiological studies suggest an important effect of magnesium deficiency in many diseases [36]. Disturbances of magnesium's metabolism have been reported in association with cardiovascular diseases (atherosclerosis, hypertension, congestive heart failure, arrythmias, and myocardial infarction [15]), obstetric conditions (preeclampsia, eclampsia [29]), neurological diseases (stroke, epilepsy [63, 107]) affective disorders [32, 64, 87] and alcohol withdrawal syndrome and delirium tremens [23].

Magnesium and depression

Experimental data

Magnesium plays a significant role in the behavior of animals. Hypomagnesemia produced anxiety- and depressive-like behaviors. Data indicate the contribution of magnesium to affective disorders. Magnesium depletion produces a reduction in offensive and an increase in defensive behaviors in animals [41]. Additionally, magnesium depletion in mice leads to an increase in anxiety and depression-like behavior, with an increased preference for the dark compartment in the light-dark test and a longer immobility time in the forced swim test [64]. Besides this, depression- and anxiety-related behavior in mice, produced by magnesium depletion, is reversed by antidepressant and anxiolytic drugs, respectively [96]. Furthermore, a correlation of the intracellular magnesium levels with behavior in mice was also found. Mice with low erythrocyte magnesium concentrations exhibited more restless and more aggressive behavior under stressful conditions than mice with high erythrocyte magnesium levels [35]. In the forced swim test, magnesium administration reduces the immobility time in rodents [9, 79, 81, 83] and enhances the action of antidepressant drugs in mice [78, 84]. Moreover, magnesium, similarly to imipramine, normalized the stress-induced increase of immobility in mice [82]. In addition, the anxiolytic-like activity of magnesium was observed in the elevated plus-maze test. Magnesium treatment increased the number of open arm entries in this test [79] (Tab. 2). Magnesium also enhanced the anxiolytic-like effects of classical benzodiazepines in this test [77].

Human data

Several clinical findings indicate the involvement of magnesium in the pathophysiology and treatment of depression. Disturbances in the magnesium levels in depression were observed, although the data are inconsistent throughout the study. In depressed patients with a low serum magnesium level [3, 32, 87, 113], no alteration or increase in the serum magnesium concentrations have been observed [18, 42, 109, 110, 112]. A correlation between low serum magnesium levels and incidence of depressive symptoms was observed. This correlation was observed in patients with long-lasting and unipolar depression, but not those with acute depression [12, 31, 32, 42, 48, 87]. The other study showed a decrease in the total magnesium plasma levels in depression and an increase in the magnesium levels during recovery [21, 32]. Furthermore, in patients with mania [75] and rapid cycling bipolar disorder [6], the mood-enhancing properties of magnesium have also been reported. In addition, it was found that supplementing lithium, benzodiazepines, and neuroleptics with magnesium significantly reduced the doses of these drugs [34] (Tab. 2).

Mechanism of antidepressant activity

Glutamate receptors

Similarly to conventional antidepressants and zinc, magnesium increases BDNF expression, which may be connected with the reduction of NMDA ionotropic glutamate receptor function [24]. Magnesium is a potent antagonist of the NMDA receptor complex [5]; thus, like organic and inorganic (zinc) NMDA receptor antagonists, it may induce antidepressant actions *via* this receptor complex [5]. The antidepressant-like action of magnesium in the forced swim test is antagonized by NMDA co-treatment (Fig. 3), while sub-

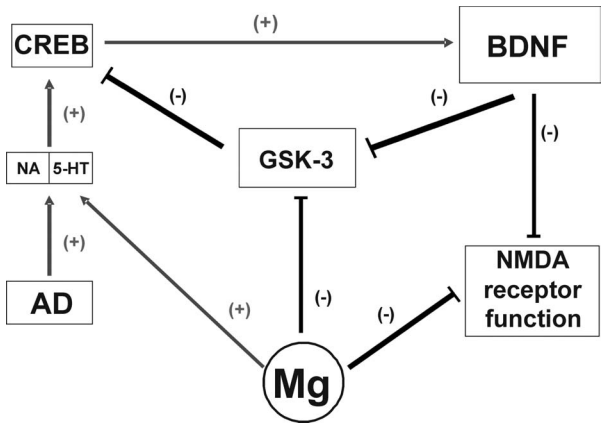

Fig. 2. Molecular mechanisms of antidepressant activity of magnesium. Plus signs represent excitatory/enhancing interactions, minus signs represent inhibitory interactions. Three main targets, BDNF, NMDA, and GSK-3 may be involved in the antidepressant action of magnesium. Magnesium, like conventional antidepressants (AD), may enhance the CREB/BDNF pathway *via* the serotonergic system. Magnesium may also affect BDNF by inhibiting the activity of GSK-3. In addition, magnesium directly inhibits the function of the NMDA receptors

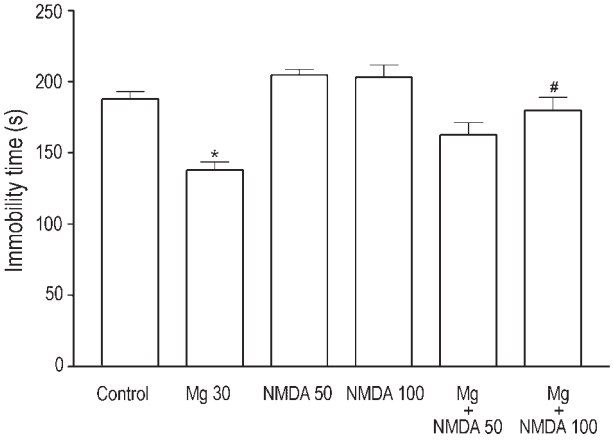

Fig. 3. Effect of NMDA co-treatment on magnesium-induced reduction in the immobility time in forced swim test (FST) in mice. Previously, we demonstrated that NMDA at a dose of 75 mg/kg *ip* antagonized the reduction in immobility time of magnesium at doses of 20 and 30 mg/kg in the FST in mice [86]. This figure demonstrates the effect of different doses of NMDA (50 and 100 mg/kg *ip*) on magnesium (30 mg/kg) activity in FST in mice (The values represent mean ± SEM; * $p < 0.001$ *vs.* control; # $p < 0.01$ *vs.* Mg). The experiment was performed according to previously published conditions [86]. The data together clearly indicate the dose response effect of NMDA on magnesium activity in this test

Tab. 1. Involvement of zinc in the pathophysiology and treatment of depression

	Antidepressant activity of zinc	
	Zinc treatment	Zinc supplementation
Rodents		
Forced swim test (mice, rats)	Active (acute and chronic)	Improvement
Tail suspension test (mice)	Active	ND
Olfactory bulbectomy (rats)	Active (acute and chronic)	ND
Chronic unpredictable stress (rats)	Active (chronic)	Improvement
Chronic mild stress (rats)	Active (chronic)	ND
Human (unipolar depression)		
HDRS, BDI	ND	Improvement

	Zinc concentration	
	Serum	Brain
Rodents (rats) (chronic treatment)		
Citalopram	Increase	Increase (hippocampus)
Imipramine	NA	Increase (hippocampus)
ECS	NA	Increase in synaptic zinc (hippocampus)
Zinc	Increase	Increase in synaptic zinc (hippocampus)
Human		
Suicide	ND	NA
Unipolar depression	Decrease	ND
Postpartum depression	Decrease	ND
Antidepressant treatment:		
Non effective treatment	Decrease	ND
Effective treatment	Normalization	ND

ND – no data; NA – no alterations; HDRS – Hamilton Depression Rating Scale; BDI – Beck Depression Inventory

active doses of magnesium were potentiated by subactive doses of the NMDA receptor complex antagonists (CGP 37849, L-701,324, D-cycloserine, MK-801) [86] (Fig. 2).

Inhibition of GSK-3 enzyme

As was described above, inhibition of the GSK-3 enzyme is involved in the mechanisms of action of anti-

Tab. 2. Involvement of magnesium in the pathophysiology and treatment of depression

	Antidepressant activity of magnesium	
	Magnesium treatment	Magnesium supplementation
Rodents		
Forced swim test (mice)	Active	Improvement
Stress-induced depression-like behavior	Active	ND
Human		
Bipolar depression	ND	Improvement

	Magnesium concentration	
	Serum	Brain
Human		
Depression	NA/Increase/Decrease	ND
Antidepressant treatment (depression)	No change/ Decrease	ND

ND – no data; NA – no alterations

depressant drugs [25, 40]. Since magnesium (like zinc and lithium) is a potent inhibitor of this enzyme, GSK-3 may well be a possible target of antidepressant activity of this ion (Fig. 2).

Involvement of serotonergic system

We demonstrated the enhancement of antidepressant-like activity by joint administration of magnesium and imipramine [84], citalopram, and tianeptine, but not with reboxetine, in the mouse FST [78]. Also, pCPA induced serotonergic lesion and abolished magnesium activity in FST [78]. These data suggest the involvement of the serotonergic, rather than the noradrenergic, pathway in magnesium-induced antidepressant-like activity in the FST. This biometal is also a cofactor of tryptophan hydroxylase and is necessary for serotonin receptor binding *in vitro* [41]. Additionally, the direct enhancing effect of magnesium on 5-HT_{1A} serotonin receptor transmission was reported [10] (Fig. 2).

Conclusion

Zinc and magnesium exhibit antidepressant-like activity in a variety of tests and models in laboratory animals and enhance the activity of conventional antidepressants. Clinical studies demonstrate the involvement of zinc and magnesium in affective disorders and an enhancement of the efficacy of pharmacotherapy by these ions' supplementation in these diseases. All the available data indicate the importance of zinc and magnesium homeostasis in psychopathology and therapy of affective disorders.

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