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Review

Zinc and depression. An update

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Abstract:
Unsatisfactory clinical efficacy and a variety of adverse effects of current antidepressant drugs have incited search for better therapy. Zinc, an antagonist of the glutamate/N-methyl-D-aspartate (NMDA) receptor, exhibits antidepressant-like activity in rodent tests/models of depression. Similarly to antidepressants, zinc induces brain derived neurotrophic factor (BDNF) gene expression and increases level of synaptic pool of zinc in the hippocampus. Clinical observations demonstrated serum hypozincemia in depression, which was normalized by effective antidepressant treatment. Moreover, our preliminary clinical study demonstrated the benefit of zinc supplementation in antidepressant therapy. All the data indicate the important role of zinc homeostasis in psychopathology and therapy of depression and potential clinical antidepressant activity of this ion.

Key words:
zinc, depression, antidepressants, NMDA, BDNF

Introduction

Depression is a psychiatric disorder with high morbidity and mortality. It is estimated that depression is the cause of 50–70% suicides [10]. The World Health Organization predicts that depression will be the second most important cause of human disability – adjusted life years by the year 2020 [16]. In spite of many years of research, clinical efficacy of new antidepressants is unsatisfactory and the psychopathology of depression remains not fully understood. Therefore, the search for new more effective and safer therapy is continuously in progress.

During the last several years, many articles have been presented indicating important role of zinc in the psychopathology and therapy of depression.

Zinc is a trace element, essential for living organisms. More then 300 enzymes require zinc for their activity. Zinc plays an important role in the DNA replication, transcriptions and protein synthesis, influencing cell division and differentiation [4]. Dietary zinc deprivation retards growth of human and animal organisms [38]. The highest amounts of zinc are pres-

ent in the brain, especially in the hippocampus and cerebral cortex [4, 40]. Zinc deprivation influences brain zinc homeostasis and leads to alteration in behavior, learning, mental function and susceptibility to epileptic convulsions [38].

This review focuses on the involvement of zinc in psychopathology and therapy of depression.

Zinc, depression and antidepressants – experimental data (Tab. 1)

Recent results demonstrate that chronic treatment with antidepressants and electroconvulsive shock (ECS) induces an increase in zinc concentrations in the rat brain.

Tab. 1. Summary of the effects of zinc in animal tests/models of depression

Test/model	Effect
Forced swim test	Active [7, 8, 23, 31]
Zinc + antidepressant treatment (ineffective doses)	Active [8, 36]
Tail suspension test	Active [31]
Olfactory bulbectomy	Active [23]
Chronic mild stress	Active
Chronic unpredictable stress	Active [25]
Zinc + antidepressant treatment (ineffective doses)	Active [26]

Chronic treatment with citalopram or imipramine slightly increases the zinc level in the hippocampus and slightly decreases it in the cortex, cerebellum and basal forebrain. Calculation of the hippocampus/brain region zinc concentration ratio within each group demonstrated a significantly higher value after treatment with both drugs. Chronic ECS treatment induces the robust increase in the zinc level in the hippocampus and a slight increase in the cortex and cerebellum [19]. Moreover, chronic treatment with citalopram but not with imipramine or ECS increases the serum zinc level in the rat [19].

Several groups using Timm's histochemical method for zinc staining demonstrated that repeated treatment with ECS induced hippocampal mossy fiber sprouting, which indicates an increase in the vesicular zinc level in the hippocampus [9, 39]. However, alterations in vesicular zinc in the hippocampus were not detected by this method following antidepressant drugs.

Furthermore, chronic imipramine treatment increases the ability of zinc ion to inhibit the N-methyl-D-aspartate (NMDA) receptor complex in the cerebral cortex but not in the hippocampus in mice [37]. Such effect has not been demonstrated in rats, which suggests the existence of species-dependent imipramine-induced adaptive mechanisms (involving zinc sites on the NMDA receptor complex). A number of recent studies indicated that NMDA receptor-coupled channel complex could exist in multiple forms, which have different physiological and pharmacological properties and are differentially distributed throughout the brain [1]. Based on this studies, we propose that the differences which we have observed in our study (concerning the potency of zinc to inhibit [^{3}H] MK-801 binding in the cortex and hippocampus) could reflect region-specific subunit composition of the NMDA receptor complex. Both these alterations (increase in zinc concentration in the rat hippocampus and increase in the potency of zinc to inhibit NMDA receptor activity) may lead to the reduction of function of NMDA receptor complex [38], like in the case of other antidepressant-induced adaptive changes [33].

On the other hand, zinc exhibits antidepressant-like effects in tests and models, which are used for evaluation of antidepressant activity. Zinc produced antidepressant-like effects in the forced swim test, both in mice and rats and in tail suspension test [7, 8, 23, 31]. Moreover, it is interesting that very low doses of zinc administered together with low, ineffective doses of imipramine or citalopram enhanced antidepressant-like effect in this test [7, 36]. Zinc is also active in olfactory bulbectomy (OB), chronic mild stress (CMS) and chronic unpredictable stress (CUS) animal models of depression. Our recent study indicated antidepressant-like activity of acute or chronic treatment with zinc in passive avoidance test in the bulbectomized rats (zinc treatment produced statistically significant reduction in the number of trials needed to learn passive avoidance) [23]. Zinc also significantly decreased the time of walking and number of rearings and peepings in the bulbectomized rats [23]. Chronic treatment with zinc was also active in CMS model in rats; namely zinc reversed the CMS-induced reduction in the consumption of 1% sucrose solution (our unpublished data). Recently, it was found that prolonged treatment with zinc prevented the deficit in fighting behavior in

rats in CUS model [25]. Moreover, the results suggest that zinc supplementation potentiates the antidepressant effect of imipramine in such model of depression [26]. All these animal data strongly suggest possible antidepressant activity of zinc in human depression.

Antidepressant drugs or electroconvulsive therapy induce an increase in the hippocampal (and cortical) brain derived neurotrophic factor (BDNF) mRNA level [17]. Chronic, two-week treatment with zinc increases level of BDNF mRNA in the rat cerebral cortex but not in the hippocampus [18]. However, our recent unpublished data demonstrated an increase in hippocampal but not cortical BDNF mRNA following a very low dose of zinc administered for 1 week (Tab. 2). These observations indicate that zinc increases cortical/hippocampal BDNF gene expression, which is the effect shared by most of clinically effective antidepressants.

Tab. 2. Effect of chronic (1-week) treatment with zinc (1.8 mg/kg *ip*) on BDNF mRNA level in the rat brain. Results are expressed as % of controls (mean ± SEM)

	frontal cortex	hippocampus	n
transcript 4.2 kb	99 ± 16	136 ± 11*	6
transcript 1.8 kb	102 ± 6	117 ± 3*	6

* $p < 0.05$ *vs.* control group

Our results demonstrate that chronic zinc administration increases also the synaptic pool of zinc in the rat hippocampus (our unpublished data).

Zinc and depression – clinical data (Tab. 3)

Involvement of zinc in antidepressant therapy, which was indicated by animal experiments, has also some clinical correlates. It was demonstrated that human depression might be accompanied with lower serum zinc concentrations [14, 15, 21]. These findings were confirmed by Maes et al. [12] who found that the subjects suffering from major depression showed significantly lower serum zinc levels than non-depressed controls. Interestingly, they also observed that the patients with minor depression showed intermediate zinc levels. Moreover, the unipolar depression was not only associated with lower blood zinc levels, but the severity of the illness [expressed according to Hamilton Depression Rating Scale (HDRS)] was negatively correlated with serum level of this ion [12, 24, 32]. However, another study of Maes et al. [13] did not show any correlation between these two parameters (HDRS and serum zinc). These authors suggest that the latter study examined different population of patients, mostly treatment-resistant. The findings that the lowered serum zinc concentrations may be normalized after successful antidepressant therapy [13, 15, 32] further support the notion that serum zinc concentrations are a sensitive and specific marker of depression.

Maes et al. [12] further reported that there were no significant relationships between hypozincemia and anorexia (or weight loss), and between serum zinc levels and signs of hypothalamic-pituitary-adrenal (HPA)-axis hyperactivity in major depression. These results suggest that anorexia or HPA-axis hyperactivity may be excluded as a possible cause of hypozincemia in major depression [12]. On the other hand, there is now some evidence that major depression is accompanied by the activation of the inflammatory response system (IRS). A positive correlation was demonstrated between serum zinc and albumin levels in the patients with major depression. Since serum zinc is closely bound to albumin, these results suggest that lower serum zinc concentration in depression may be in part related to lowered concentrations of its protein "carrier" albumin [11]. Moreover, a significant inverse relationship between lower serum zinc concentration and markers of IRS activation was demonstrated in depression [e.g. increased CD4+/CD8+ T cell ratio, serum neopterin, increased serum interleukin (IL)-6] [13]. It is also well established that lower serum zinc levels impair some aspects of immunity. Zinc is required for biological activity of the thymic peptide, thymulin, which is critical for normal T-cell functions. Zinc deficiency impairs function of T-cell-dependent immune system, which is likely attributable to the reduced T-cell cytokine production [28]. The increase in the levels of IL-6 and soluble IL-6 receptor (sIL-6R) in depression are probably related to an increase in the number of macrophages. On the other hand, IL-1 stimulates production of pro-inflammatory cytokines by T-cells [35]. The above data indicate a significant and complex role of zinc homeostasis in the mechanism of psychopathology and treatment of depression.

Tab. 3. Summary of clinical data on the involvement of zinc in the pathophysiology and treatment of depression

Subject/parameter	Effects
Zinc concentration	
depression	↓ serum [11–15, 24]
	↔ brain (suicide) [22]
depression + non-effective antidepressant treatment	↓ serum [13]
depression + effective antidepressant treatment	↔ serum* [13, 32]
Depression + zinc supplementation + antidepressant treatment	
HDRS	improvement# [20]
BDI	improvement# [20]
Zinc affinity for NMDA receptor	↓ hippocampus ↔ cortex (suicide) [22] (suicide) [22]

↓ decrease; ↔ no alterations *vs.* appropriate controls; * – back to normal control values of non depressed subjects; # – *vs.* depression + placebo + antidepressant treatment; HDRS – Hamilton Depression Rating Scale; BDI – Beck Depression Inventory

In our previous paper, we demonstrated the reduction in the potency of zinc to inhibit NMDA receptor activity in the hippocampus of suicide victims [22]. These data represent the first demonstration that the alteration in zinc interaction with NMDA receptors may be involved in psychopathology of suicide disorder (Tab. 3). Our preliminary clinical study demonstrated the benefit of zinc supplementation in antidepressant therapy in major depression [20]. The study was conducted in patients who fulfilled DSM IV criteria for major depression and a placebo-controlled, double blind procedure was used. Patients received zinc supplementation or placebo and were treated with standard antidepressant therapy. To assess efficacy of antidepressant therapy we used Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory (BDI). We observed that zinc supplementation significantly reduced scores in both measures after 6- and 12-week supplementation when compared with placebo treatment (Fig. 1).

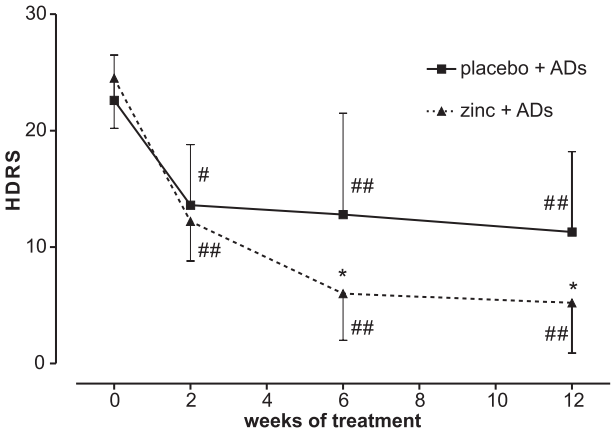

Fig. 1. The effect of placebo and zinc supplementation on antidepressant therapy evaluated by Hamilton Depression Rating Scale (HDRS) scores in patients with unipolar depression. Data represent the mean ± SD of 8 – placebo- and 6 – zinc-supplemented subjects per group. * $p < 0.05$ *vs.* placebo; # $p < 0.01$, ## $p < 0.001$ *vs.* respective value at the beginning of the treatment (week 0). (Reprinted by permission from Pol J Pharmacol, 2003, 55, 1143–1147)

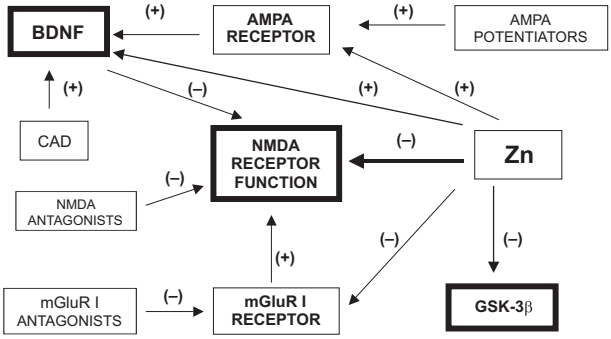

Fig. 2. Multidirectional effects of zinc (Zn). Possible molecular mechanisms of antidepressant zinc action. CAD – classic antidepressants; BDNF – brain derived neurotrophic factor; GSK-3β – glycogen synthase kinase-3β

Possible molecular mechanisms of antidepressant zinc actions (Fig. 2)

Clinically effective antidepressants (affecting monoamine transmitter re-uptake or metabolism) may inhibit function of NMDA receptor by increasing in BDNF activity [2, 3, 35]. Inhibition of NMDA receptor function is induced also by NMDA receptor antagonists, AMPA potentiators and antagonists of mGlu1 receptor [27, 34]. Since zinc is an antagonist of the NMDA receptor complex, one of the potential mechanisms of antidepressant activity of zinc might be related to its direct antagonism of NMDA receptor [5]. The second considered mechanism might be connected with zinc antagonistic action on group I metabotropic glutamate receptors [41] or potentiation of AMPA receptors [30] which both may attenuate the NMDA receptor func-

tion [26, 34]. The another, possible antidepressant mechanism of zinc action might be related to its direct inhibition of glycogen synthase kinase-3β (GSK-3β) [6], which is proposed to be a target for treatment of affective (bipolar) disorder [29].

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