



The Role of Zinc in Mood Disorders

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Abstract

Mood disorders have many forms, from anxiety attacks, depression, Obsessive Compulsive Disorder (OCD) to Post Traumatic Disorder (PTSD). Recently, many studies have shown that zinc may act as a crucial neuromodulator in glutamatergic and GABAergic balance. What's more, growing evidences considered that zinc be a trait marker of mood disorder. It was reported that zinc deficiency induces depression, while supplementing with this mineral improved mood as well as cognitive function. In this present review, the links of zinc in the mood disorder and zinc in the Alzheimer's disease were systemically reviewed. It may be helpful for zinc application in clinical thus address zinc as a new target of research for therapy.

Keywords

Mood disorders; Genetics; Antidepressants

Abbreviations

A β : Amyloid- β Protein; AD: Alzheimer's Disease; BD: Bipolar Disorder; BDNF: Brain-Derived Neurotrophic Factor; CMS : Chronic Mild Stress; CNS: Central Nervous System; CRE: Camp Reponse Element; DA: Dopamine; DALY: Disability Adjusted Life Years; DM: Diabetes Mellitus; HPA: Hypothalamic-Pituitary-Adrenal; FST: Forced Swim Test; GABA: γ -Aminobutyric Acid; KO: Knockout; PD: Parkinson's Disease; PSD: Postsynaptic Density; MAPK: Mitogen-Activated Protein Kinase; MAP-Tau: Microtubule-Associated Protein Tau; MDDL: Major Depression Disorder; MT: Metallothionein; NF- κ B: Nuclear Factor Kappa B; Nfts: Neurofibrillary Tangles; NMDA: N-Methyl-D-Aspartate; OB: Olfactory Bulbectomy; OCD: Obsessive Compulsive Disorder; ROS: Reactive Oxygen Species; PTSD: Post Traumatic Disorder; SOD: Superoxide Dismutase; SSRI: Selective Serotonin Reuptake Inhibitor; TGF β 1: Transforming Growth Factor Beta1; TST: Tail Suspension Test; WHO: World Health Organization; Znt: Zinc Transporter; ZIP: Zn²⁺ IRT-Like- Protein

Introduction

Mood disorder is a major public health concern of global significance that affects millions of people worldwide with an increasing trend in the aging population [1-5]. Several factors contribute to the cause of mood disorder, such as genetics, environment, and intra-personality [6-9]. The symptoms of mood disorder vary quite a lot according to different phases of the disease, they can be transient, chronic or recurrent. Therefore, it is difficult to summarize their characteristics. Despite growing evidence on the etiology of mood disorder, understanding the neurobiological mechanisms that underlie the development of mood disorder remains a challenge. Over the past few decades, considerable advances have been achieved on the development of novel classes of antidepressants, but none was effective to all patients. Take the widely promoted monoaminergic antidepressant for example, more than 30% of the patients did not respond to this treatment [10,11]. In other words, antidepressant is effective only to a certain amount of patients rather than all patients.

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Because of the unsatisfactory clinical efficacy and numerous side effects of commonly used drugs, we are confronted with a pressing need to develop novel treatment strategies and ultimately understand the etiology and pathophysiology of mood disorder.

Zinc, an essential nutritionally element secondary only to iron in trace metal abundance, plays a key role in more than 1,000 proteins, including enzyme catalysis, cell signaling, DNA replication and transcription [12,13], and thus is essential for neural development [14,15], learning and memory function^[16] as well as mood disorders [17-19]. Human body contains 2-3 mg of zinc throughout the body, with the concentrations especially high in the regions of the brain involved in emotions, such as the hippocampus, frontal cortex, amygdala and olfactory bulb [13,14,20,21]. A body of evidence has emerged linking the pathophysiology of mood disorder to the dyshomeostasis of trace element zinc. It is reported that zinc deficiency might act negatively on mood, leading to the development of depressive-like symptoms [1,22-28]. What's more, a mounting evidence has also found a significant improvement in depressive symptoms after zinc supplementation [29,30].

Therefore, the present paper will review the role of zinc in the neurogenesis of mood disorder as well as its potential effect as a putative therapeutic agent towards mood disorder. We focused our discussion on the mood disorders, including major depression disorder (MDD) and bipolar disorder (BD), which have been most extensively examined in epidemiologic studies, as well as Alzheimer's disease.

Zinc in the Central Nervous System (CNS)

Zinc is prevalent in the glutamatergic neurons throughout the limbic system including hippocampus, hypothalamus and amygdala, and is thought to be involved in emotion, learning and memory. In these structures, ionic zinc is highly enriched in the vesicles with many but not all glutamatergic nerve terminals [15,31]. Therefore, zinc can modulate the neuronal activity via its influence on glutamatergic and γ -aminobutyric acid (GABA)ergic receptors due to its location [32].

The requirement for zinc is closely related to its vital roles in regulating numerous aspects of cellular metabolism, such as immune [33-36], protein [37], hormone [38,39], antioxidant

[40-43], transcription, and replication functions [37,44]. Zinc is not only important for DNA repair and protein synthesis which influences cell division and differentiation, but also an ionic signal [13]. Zinc deficiency has been shown to contribute to alterations in behavior, abnormal neurological development and diseases as well [22,26,27,45]. On the other hand, overabundant levels of zinc can also be cytotoxic, resulting in neuron apoptosis [46-48] and neuronal death [49,50].

There is an abundance of evidence regarding the influence of zinc on the neurotransmitter involved in emotional processes, such as the serotonergic, noradrenergic, dopaminergic, glutamatergic and GABAergic systems [51-54]. Therefore, intracellular zinc concentration is strictly controlled to maintain zinc homeostasis by zinc importers, exporters, and binding proteins like metallothioneins.

Zinc and CNS physiology

In the central nervous system, zinc is highly concentrated in the synaptic vesicles of specific neurons, called "zinc-containing" neurons, which are also subsets of glutamatergic neurons. The ionic form of Zn^{2+} in the brain is synaptically released into the synaptic cleft during neuronal activity, therefore the term "gluzinergetic neurons" has been proposed for neurons that release zinc and glutamate [13,55,56]. Because of its location, zinc can modulate excitability in the brain via its influence on the glutamatergic (including ionotropic and metabotropic) and GABAergic receptors [32]. Therefore, zinc plays a prime role in synaptic transmission and acts as a modulator of both excitatory and inhibitory neurotransmission. Moreover, zinc is also important for the regulation of postsynaptic density (PSD) stability [57]. Extracellular Zn^{2+} promotes cell survival and growth by activating and regulating major downstream signaling pathways.

A variety of effects has been unraveled on zinc within the nervous system and these effects depend on an accurately regulated and precisely balanced zinc concentration [14,16,58,59].

It seems that zinc modulate the overall excitability of the brain through its effect on voltage-gated calcium channels [60], glutamate [61], GABA[61], dopamine (DA) [62,63] and serotonin receptors [64] as well as zinc transporter (ZnT-3), Zn^{2+} IRT-like protein (ZIP), and

metallothionein (MT) [65], and its activity is intimately dependent on its concentration. Zinc is also part of a family of transcription regulatory proteins known as zinc finger proteins. It plays an important role in transcriptional regulation of cellular metabolic network interacting with zinc-binding domains [66]. Zinc also acts as a modulator and a potent antagonist of the N-methyl-D-aspartate (NMDA) glutamate receptor, whose excessive activation and associated processes of excitotoxicity belong to the pathophysiology of mood disorders [67-69].

Zinc and CNS pathology

The influence of nutritional element zinc and depression are highly connected, i.e. zinc activates hormonal, neurotransmitter and signaling pathways in the gut which modulate brain functions like appetite, sleep, neurogenesis, cognitive function and mood [70-73]. Disruption of these biological rhythms have been considered trait-markers of mood disorders. Cognitive dysfunction is a recognized feature of mood disorders, including MDD and BD.

Recent studies indicate that zinc may act as a neurotransmitter in the central nervous system via the GPR39 receptor, which is activated by zinc ions [74] GPR39 belongs to the ghrelin receptor family and is a metabotropic receptor widely expressed in regions of the brain that involved in emotional processes--the frontal cortex, the amygdala and the CA3 region in the hippocampus [75,76] GPR39 is thought to inhibit apoptosis and mediate neural synaptic signaling [77]. It is reported that zinc-deficient diet in mice or rats leads to a lower expression of the GPR39 receptor in both hippocampus and frontal cortex, leading to depressive-like symptoms [22,75]. What's more, depressive-like behavior in GPR39 knockout (KO) animals with immune response presented similar to that observed in depressive disorder [45].

It is found in the animal studies that changes in Zn homeostasis caused by acute Zn depletion is associated with impaired spatial learning [45,46,78,79], whereas developmental Zn deficiency results in working memory deficits [80,81] as well as mood disorder. Based on preclinical studies, deficiency of zinc elements can lead to neurodegenerative processes and, by association, learning and memory impairments [77]. A recent study reported low zinc level in serum was related with cellular aging [82]. Feng *et al.* [83] found in their study that

zinc deficiency in 10-month-old APP/PS1 transgenic mice induced learning and memory impairment, neuroapoptosis as well as tau-protein phosphorylation.

Members of the solute carrier 39 (SLC39) gene family encoding the ZIPs are important components of cellular Zn²⁺ homeostasis and encode proteins that promote cellular Zn²⁺ uptake in a wide range of species [84]. SLC39 acts in collaboration with another family of transporter as ZnT in mammals [85], to regulate the distribution of zinc in the extra-versus intracellular milieu and within cellular compartments [86]. Therefore ZnT plays a crucial role in maintaining zinc homeostasis that is essential for the normal functioning of the central nervous system, which is 47-fold higher in the brain than in other tissues [15,87,88].

Studies have shown that administration of low zinc diet leads to the development of depressive-like behavior in mice and rats [22-27]. Most of the clinical studies have also demonstrated reduction of blood zinc concentration in depressed patients [89,90]. It has been reported that patients suffering from depression showed lower serum zinc than healthy controls [91]. Swardfager *et al.* found in a meta-analysis that depressed subjects was associated with a significant lower peripheral blood zinc concentration [92]. In pregnant women, zinc deficiency may lead to less fetal brain cells which affect normal growth and intellectual and sexual development [93].

Overall, zinc is the authoritative metal that is present in the CNS. It has been found that alterations in brain zinc status have been involved with a wide range of neurological disorders including impaired brain development and neurodegenerative disorders such as mood disorders, Alzheimer's disease, and Parkinson's disease.

Zinc and Mood Disorder Diseases

Zinc has been associated with several mood disorders, such as major depressive disorders and bipolar depression. It has been reported that the mechanisms underlying depression was associated with the following possible theories [1] : 1) Glutamatergic theory of depression: imbalance of glutamatergic system including excitatory (glutamatergic) and inhibitory (GABAergic); 2) Monoaminergic theory of depression: insufficient concentrations of monoamines in brain; 3) Neurotrophic theory of depression:

reduction in brain derived neurotrophic factor (BDNF), nerve growth factor (NGF), decreased neurons and reduced hippocampal volume; 4) Hypothalamic-pituitary-adrenal (HPA) axis theory of depression: an increase in corticosterone concentrations, reduced glucocorticoid receptors and enlarged adrenal gland; 5) Immunological theory of depression: inflammation and increased cytokines levels. Many of the studies on pathophysiology and drug development of mood disorders major focused on zinc alteration associated with those five possible theories.

Early clinical studies reported lower zinc serum in depressed patients compared to healthy patients and later was proposed as a state marker of depressive disorder [91,94]. Numerous studies have sought to determine the causality between low zinc levels and the development of depressive symptoms. Behavioral paradigms such as the forced swim test (FST) and tail suspension test (TST) are used to observe the immobility duration in pre-clinical studies to determine the cause of depression and to screen for potential antidepressant treatments. Animals fed a zinc deficient diet exhibited increased immobility time in FST [24-27,95,96] or TST [23], indicating that zinc deficiency contributes to the development of depressive-like behavior. Moreover, zinc deficiency impaired the efficacy of numerous antidepressants which have different mechanisms of action [23,25,26]. Together, these results indicate that zinc deficiency plays a crucial role in the development of depression, and the subsequent restoration of zinc reverses behavioral signs of depression in animal models.

Reactive oxygen species (ROS) have also been implicated in pathophysiology of MDD. Zinc deficiency increase ROS that appears to be, at least in part, the result of mitochondrial ROS production [97]. One of the most important functions of zinc in organism is an antioxidative protection [98]. Zinc decreased ROS generation through activation of superoxide dismutase (SOD) [99], MT binding and neutralizing ROS [98] as well as the influence of zinc on signal transduction pathway via inhibition of nuclear factor kappa B (NF- κ B), transforming growth factor beta1 (TGF β 1) and mitogen-activated protein kinase (MAPK) [100,101]. This may be one of the mechanisms that zinc plays a crucial role in mood disorder.

■ Zinc and major depressive disorder

Major depressive disorder (MDD) affects millions of individuals and is highly comorbid

with many age-associated diseases such as cardiovascular disease, immune-inflammatory dysregulation, diabetes mellitus (DM), and dementia [102-104] and are at higher risk of premature death associated with these diseases than the general population. Numerous clinical studies confirmed the role of zinc deficiency in the development of depressive symptoms in major depressive disorder [92,105-107].

Maes *et al.* [108] studied on 48 MDD patients which they found that not only the zinc level was significantly lower in patients group, but also negatively correlated with the severity of depressive symptoms. In two further studies on 31 and 48 patients (respectively) diagnosed with MDD, Maes *et al.* also confirmed previous observations [91,109], which is consistent with the study by Swardfager *et al.* [92]. Moreover, growing evidence for the valuable effects of zinc therapy from clinical studies demonstrated that zinc supplementation significantly reduced depression severity and facilitated the outcomes in patients with the antidepressants treatment resistant [29,94,110]. Also, zinc monotherapy reduced symptoms of depression in patients with coexisting obesity [111]. These results indicated that significantly lowered zinc blood concentrations might be a biological marker of MDD and restorage of zinc level might also be a sign of symptoms remission.

■ Zinc and bipolar disorder

Bipolar disorder, formerly manic depression, is a mental disorder with periods of depression and periods of elevated mood, mania [112]. Growing evidence has involved zinc dyshomeostasis in the pathophysiology and treatment of depressive disorder, however, the data on bipolar disorder are limited.

Siwek *et al.* [113] for the first time investigated in detail the issue of the concentration of zinc in BD, with a particular focus on the subtypes, phases and stages of the illness. They revealed that the concentrations of zinc in blood serum of patients diagnosed with BD type I in the depressive phase was significantly reduced as compared with healthy subjects. However, both in remission and in mania zinc concentration was not different from that seen in healthy control. By 2016, an analysis of zinc concentration in the blood of patients with a diagnosis of BD was the subject of only two clinical reports [114,115]. Stanley and Wakwe observed a reduction in serum zinc levels across all of the groups including 61 patients (21 with MDD, 20 with

BD and 20 with schizophrenia) [114]. Another study measured trace element concentration only in BD patients, and found that a significant increase was noted only in serum zinc level in the manic phase as compared with the healthy individuals.^[115] The concentration of zinc in an episode of mania was not significantly higher than in the control group, but was higher than in depression, suggesting that mania is a phenomenon opposite to depression in the cortex of zinc concentration [113].

■ Zinc, depression and Alzheimer's disease

Cognitive dysfunction is a recognized feature of mood disorders, including MDD and BD, which is associated with poor quality of life and is therefore an important feature of illness to optimize for patients' occupational and academic outcomes. While generally people with BD appear to have a greater degree of cognitive impairment than those with MDD [116], direct comparisons of both patient groups within a single study are still lacking. A number of patients with cognitive decline and dementia due to Alzheimer's disease (AD) and related conditions like Parkinson's disease (PD), lewy body disease and other neurodegenerative diseases experience depressive symptoms at some point during the course of the illness.

Alzheimer's disease is the major cause of dementia and a leading cause of death in the elderly. The hallmark of AD neuropathology includes extracellular amyloid plaques composed largely of amyloid- β protein (A β), intracellular neurofibrillary tangles (NFTs) composed of hyper-phosphorylated microtubule-associated protein tau (MAP-tau), and microtubule destabilization. Zinc has previously been shown to promote the aggregation of β -amyloid, leading to formation of A β plaque [117]. Growing evidence implicated the impact of zinc dyshomeostasis in the onset and progression of AD pathogenesis [118-121]. Zinc deficiency was proved to induce hippocampal neuronal apoptosis, synaptic loss, and learning and memory impairment [101,120,122,123]. A recent study demonstrated that zinc deficiency aggravated A β aggregation and tau-phosphorylation in 10-month-old APP/PS1 transgenic mice, leading to learning and memory impairment [83]. Clinical studies also found that patients suffering from depression showed disturbances of cognition and reversing the deficit of the essential element concerned with improved memory function [124].

Zinc in the Treatment of Mood Disorder

With regard to therapy, a significant proportion of mood disorder patients are partial or non responders, and there has been no major breakthrough in finding novel effective drug targets since the introduction of the currently used antidepressants from the 1950s to the 1980s, which all based on monoaminergic pharmacological effects. A study of outpatients with MDD found that, despite receiving an adequate trial of a first-line treatment such as a selective serotonin reuptake inhibitor (SSRI), only 29-46% of patients had an adequate response [125]. Similarly, a large multicenter study also found that only a minority of patients with MDD achieved remission within 10-14 weeks [126]. Consequently, there exists an urgent request to develop novel treatment strategies and effective therapy agents.

Zinc has been found to exhibit an antidepressant-like profile, as demonstrated in both preclinical and clinical studies. Preclinical studies provide evidence that zinc deficiency leads to depressive-like behavior related to down-regulation of the GPR39 Zn²⁺-sensing receptor [127]. Zinc binds to the GPR39 and triggers signals, leading to cAMP response element (CRE)-dependent gene transcription, resulting in increases in proteins such as BDNF, which plays a pivotal role in antidepressant action. Chronic administration of many antidepressants induces GPR39 up-regulation, indicating that Zn²⁺-sensing receptor may be a new target for drug development in the field of mood disorders.

Different zinc salts such as zinc sulphate, zinc hydroaspartate or zinc chloride showed antidepressant properties in the FST [18,128-130], TST [131], chronic mild stress (CMS) [132], chronic unpredictable stress [133] and olfactory bulbectomy (OB) [128] models of depression. In addition, joint administration of zinc and antidepressants, both ineffective doses, was active in the FST [18,130], TST [131] and CMS [133]. This suggests that zinc may enhance antidepressant action and reduce side effects of commonly used antidepressants. Zinc supplementation seems also to reduce the time required therapeutic effect.

The antidepressant properties of zinc may be explained by attenuation of the glutamatergic system via inactivation of the glutamatergic NMDA receptor [134]. Zinc inhibits excessive activation of the NMDA receptor via its binding site, while intra-peritoneal administration

of NMDA (75 mg/kg) antagonized the antidepressant action of zinc [135]. Additionally, joint administration of NMDA antagonists and zinc, both in ineffective doses, exhibited a significant reduction of immobility time in the FST [136]. Significant differences between patients who respond to antidepressant therapy and non-responders were also found [137].

The zinc receptor was found to be up-regulated in the frontal cortex of mice receiving selective antidepressants such as escitalopram, reboxetine and bupropion, but not imipramine in chronic doses. Evidence shows that GPR39 receptor may modulate glutamatergic neurotransmission which might be the mechanism underlying the depressive-like phenotype found in zinc-deficient or GPR39 KO mice.

Zinc supplementation has also been used in MDD. A mounting evidence has uncovered a significant improvement in depressive symptoms after zinc supplementation [29,30] and a systematic review suggests potential benefits of zinc as a stand-alone intervention or as an adjunct to conventional treatment [19].

Conclusion

Mood disorder is a major public health concern of global significance and part of this impact is the result of limitations of available treatments. The effect of zinc throughout the entire lifespan are obvious, from brain development to the progression of mood disorders, such as MDD, BD, and many neurological disorders, like AD

and PD. Zinc mainly acts as a neuronal messenger and modulator of synaptic transmission and plasticity and influences the activity of many enzymes and proteins that are important for normal functioning of learning and memory. Zinc is good for health at normal level, whereas dyshomeostasis will lead to neuronal death by different pathways.

Therefore, it is concluded that zinc treatment will be beneficial for neuronal diseases and emerges as a new target of research for therapy of different mood disorders and neurodegenerative diseases. Administration of low dose antidepressants supplemented with zinc is effective and can reduce unwanted side effects in different types of depression.

Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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