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LITERATURE REVIEW

Zinc as an inhibitor of NMDA receptor can exhibit antidepressant effect

Novi Dewi Tanjung[1], Ninik Mudjihartini[2]

1. *Master Program in Biomedical Sciences, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia*
2. *Department of Biochemistry and Molecular Biology, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia*

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Abstract

Background : New antidepressant strategies are needed, due to unsatisfactory clinical efficacy and many side effects of commonly used drugs. Recent studies linking the pathophysiology of depression with glutamatergic imbalance. There is hyperactivity of the main excitatory system (glutamatergic) to its inhibition (GABAergic). N-methyl D-aspartate (NMDA) receptors as a part of glutamatergic synapses are potential targets for intervention. Antagonist administration for glutamatergic systems, such as zinc, can exhibit antidepressant effects.

Objective : To observe the effect of zinc administration on NMDA receptors in depressed subjects

Methods : In this paper, we provide a literature review. The method to achieve the objective consists of using literature exploration, which was conducted from February to June 2022 by searching the relevant studies from several databases.

Results : Study trials both in human and animal subjects reveal that depression is associated with a lower concentration of zinc. Comparison between the lowest zinc intake with the highest zinc intake had significantly lower incidence of developing depression. Dietary zinc deficiency induces depression along with upregulation of the NMDA receptor complexes. Zinc's antidepressant effects might be mediated through its action reducing NMDA channel-opening frequency.

Conclusions : The presence of zinc may downregulate the glutamate response in binding to NMDA receptors. Because of numerous studies about the connection between zinc and depression, it seems that zinc may have the potency to develop new antidepressants. Since the capability of zinc administration to reduce depressive symptoms, it is expected leading to increased medication adherence, lower costs and better outcomes.

Keywords : zinc, antidepressant, depression, NMDA

Introduction

Depression causes significant morbidity and mortality affecting around 280 million people worldwide.[1] The World Health Organization (WHO) stated that depression is a leading cause of disability worldwide and is a major contributor to the overall global burden of disease.[2] Depression is different from mood fluctuations or short-term emotional responses to daily life. When depression happens recurrently with moderate or severe intensity, it can be a serious health condition. This causes the affected person to suffer greatly and can have a negative impact both at work or at school and in family.[2] Associated with reduced quality of life, depression causes more than 700,000 suicide deaths per year. Suicide is the fourth leading cause of death among 15-29 year olds.[1]

Corresponding author:
Ninik Mudjihartini
Biochemistry and Molecular Biology, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia Email: ninikbiokim@gmail.com

Generally, people are lack aware of the connection between nutrition and depression. Depression is more often thought of as an illness that is emotionally rooted.[3] Though nutrition can play a key role in the onset, severity and duration of depression. Poor eating patterns are easily seen in people with depression, such as skipping meals, decreased appetite, or a dominant desire to consume sweet foods.[4] Currently, several researchers in the field of nutritional neuroscience are highlighting nutritional factors related to human cognition, behavior, and emotions.[3] In addition, when it comes to treating depression, most prescription drugs, including antidepressants, cause side effects. In some cases, chronic use or higher doses may lead to drug toxicity. An effective way for psychiatrists to deal with these problems is with alternative treatment, such as complementary nutritional therapy.[5]

One of the nutrients that affect the incidence of depression is zinc. Zinc plays a role in DNA replication, transcription and protein synthesis, influencing cell division and differentiation.[6] The highest amounts of zinc are in the brain, especially in the hippocampus and cerebral cortex.[7] In the central nervous system, zinc exists in two forms, first bound to protein, and second in free form. Free zinc resides in the cytoplasm of neurons, packaged as vesicles. Under normal conditions, zinc is released from the presynaptic vesicles, modulating postsynaptic receptors. Zinc deficiency can lead to an increased risk of neurological disorders, affect neurogenesis and increase neuronal apoptosis, resulting in memory deficits.[8] Zinc insufficiency is also associated with neuropsychiatric manifestations that can appear as changes in behavior and cognition, decreased ability to learn, and depression.[9] Thus, disruption of zinc homeostasis is considered as risk factor for depression.

Zinc might influence depression through its interaction with NMDA receptors. The NMDA receptor is a type of ligand-gated ion channel, one of ionotropic glutamate receptors, the other being the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor and kainate receptors.[10] Considerable evidence indicates that glutamate homeostasis is dysregulated in depressive disorder. Several lines of studies, both in humans and in animal models, support the concept that neurotransmission via the NMDA receptor is disrupted in depression. Thus, the NMDA receptor has become a target of interest in research related to depression.[11] Dietary zinc deficiency induces depression along with upregulation of the NMDA receptor complexes. Zinc's antidepressant effects might be mediated through its action reducing NMDA channel-opening frequency.[12] Furthermore, a review will be made to give a possible explanation of the mechanisms by which zinc interacts with the NMDA receptors in the context of depression.

Methods

This review was designed as a literature study to analyze the existing information about the effect of zinc administration on depression. Literature was explored from the following electronic databases: PubMed, ScienceDirect, Web of Science and Google Scholar. All databases were searched from February to June 2022. A combination of key words addressing "zinc deficient" or "zinc diet", "NMDA receptors" and "depression" or "depressive disorder" were used. There were no language restrictions set in the search strategy. The titles and abstracts of relevant articles were screened first, then the full articles were read and further observed to identify the eligible studies.

This review summarizes important clinical and basic science evidence for zinc's role in depression and draws connection to NMDA receptors. The abstracts, titles and full texts of all retrieved studies were comprehensively reviewed independently. The included studies were required to meet the following criteria: (1) the study design is observational study, experimental study, cohort prospective study, meta-analysis, randomized controlled trials, case reports, or systematic review; (2) the study included both human and animal subjects; (3) the association between dietary zinc intake and NMDA receptor; (4) depression status as the outcome were reported. The exclusion criteria were listed as follows: duplicated or irrelevant articles and letters.

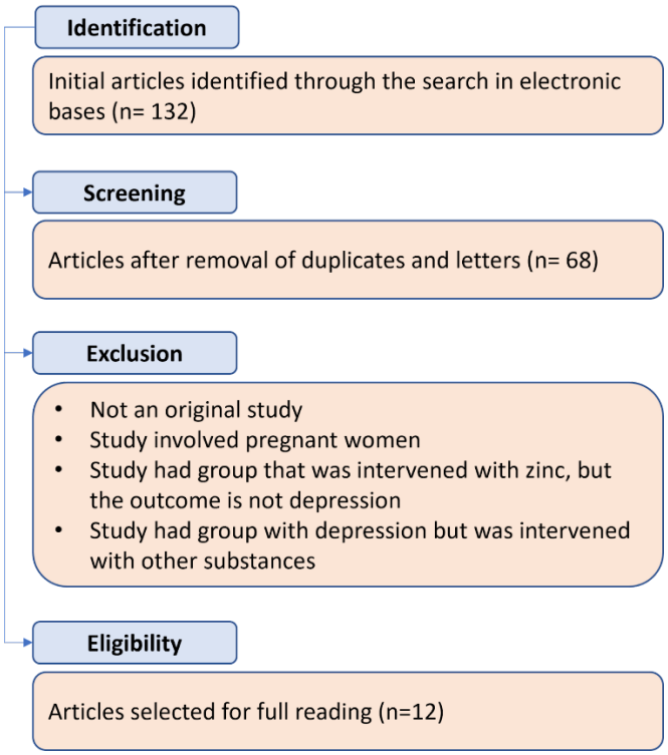

Figure 1 Scheme of article's extraction

The searching results from each included study were extracted independently. The eligible study included the following information about the first author, year of publication, location, age, gender, animal model, sample size, study design, dietary zinc assessment, exposure, and diagnostic criteria of depression. The appropriate information also clarified the connection between zinc and NMDA receptors. Detailed article's extraction was represented in **figure 1**.

Results

Numerous study trials both in human and animal subjects reveal that depression is associated with a lower concentration of zinc. A meta-analysis of human observational studies demonstrated the concentration of zinc in the peripheral blood of depressed patients to be approximately 1.850 µmol/L lower than in healthy controls, with significant inverse associations between depression severity scores and serum zinc concentrations.[13] Cross-sectional study involving postmenopausal women who were not using menopausal hormone therapy reported that the women with higher levels of zinc serum had less depressive symptoms.[14] Dietary zinc has an inverse association with risk of depression. Comparison between the lowest zinc intake with the highest zinc intake had significantly lower incidence of developing depression with a reduction of about 30-50%.[15] Zinc supplementation significantly improved mood, reduced depression scores, and facilitated the treatment outcome in cases with antidepressant treatment-resistant patients.[16] Randomized controlled trials reveal the potency of zinc as adjunctive therapy for improving mood in depressed individuals through increasing BDNF levels. Higher serum zinc and greater reduction in Beck Depression Inventory (BDI) score was found in the zinc-supplemented group, and there was significant positive correlation between serum BDNF and zinc levels at baseline.[17]

The relationship between zinc and depression may be linked to its action on NMDA receptors. Zinc restriction in rats causes behavioral alterations that refer to some similarities to the pathophysiology of depression. In addition, depressive-like behavior led by zinc deficiency is related with the changes in NMDA receptor signaling pathway.[18] Since zinc is involved in pathophysiology of depression, it is sufficient to consider that disturbances of zinc homeostasis might occur in the brain tissue. Based on research conducted on suicide victims due to depression, although there was no alteration of zinc level in the hippocampal tissue compared to controls, however there is a statistically significant decrease in the potency of zinc to prevent the activity of NMDA receptors in the hippocampal tissue of suicide subjects.[19] Antagonist activity of zinc to NMDA receptor has antidepressant-like effects, attributed to inhibition of NMDA-sensitive glutamate channels. It was observed that zinc administration in rats and mice reduced the number of NMDA receptor complexes, which in turn led to their downregulation.[20] Conversely, a zinc deficient diet induces an upregulation of the NMDA receptor complex.[18] Besides NMDA, zinc also can potentially be beneficial to help

depression through its action to influence other types of receptors, such as the AMPA receptor, metabotropic glutamate receptor (mGluR) and gamma-aminobutyric acid (GABA) receptor. It is hypothesized that zinc may have the ability to maintain homeostasis between excitatory and inhibitory systems via GPR39 as a zinc receptor, which seems to be a promising target to improve depressive symptoms.[21]

Depressive-like effects are thought to be consequences of altered NMDA receptor subunits levels.[22] Research on the effects of antidepressants on NMDA receptors also supports the consideration of changes in the receptor complex during depressive disorders.[23] Chronic antidepressant treatment decreases glycine affinity and function of the NMDA receptor complex in the hippocampus.[23] Chronic antidepressant treatment was also observed altering mRNA expression of the genes encoding for the NMDA receptor subunit, as a result there was downregulation of expression and/or function of NMDA receptor, which in turn to help protect against glutamate-mediated excitotoxicity.[20] Chronic antidepressant treatment not only caused changes in the human NMDA receptors, but also zinc levels that were previously decreased, apparently normalized.[24] Since the hippocampus is the main site of synaptogenesis, where zinc levels are markedly reduced in depressive disorders, increasing hippocampal zinc concentrations after antidepressant treatment promotes neurogenesis as well as in neuroprotection.[24]

Discussion

Zinc is the second highest trace element after iron in the human body. Human adults have 2 to 3 grams of total zinc, most of which is stored in bone, brain, and skeletal muscle, whereas in plasma, zinc levels are only 0.1%. Usually, levels of zinc plasma are used to estimate nutritional status of zinc.[25] Zinc is necessary for different biological roles. It is involved in enzyme activation, gene expression, cell division, cell growth, and it is needed for the immune system to function correctly. Recommended dietary intake of zinc for adults is between 8-11 mg/day. Food sources to meet daily zinc requirements can be found in beef, lamb, nuts, whole grains, legumes, and yeast. Zinc is also found in most multivitamins and mineral supplements. Tolerable intake levels of zinc supplements should be below 40 mg/day.[26] Although it is not recommended to take zinc supplements beyond 40 mg/day, zinc is considered nontoxic. There is no standard treatment to overcome zinc overdose. Zinc taken in large amounts can manifest nausea, vomiting, diarrhea, abdominal cramps, lethargy, and fatigue within 3 to 10 hours of consuming the supplement. An extremely high intake of zinc also can result in copper and iron deficiency.[27]

In the central nervous system, zinc is the most prominent micronutrients. Zinc concentration is highest in the brain compared to other organs in the human body, where it is about 150 μmol/L, this level is 10 times higher than serum zinc. Mostly, zinc in the brain presents as a structural component of proteins, and about 10–15% of brain zinc exists in a chelatable form. In addition, in brain extracellular fluids, chelatable zinc occurs at much lower concentrations, it is estimated only about 500 nM.[28] One of the essential functions of zinc is its role as a neuromodulator. During synaptic transmission, zinc is released then it binds to synaptic membrane receptors.[29] In synaptic cleft, zinc reacts with excitatory NMDA and AMPA receptors, as well as the inhibitory GABA receptors.[30] Moreover, extracellular zinc effects on various voltage-gated ion channels, with the result that alteration of neuronal excitability.[31]

The NMDA receptor is a ligand-gated ion channel receptor that is permeable to calcium and, to a lesser extent, also permeable to sodium and potassium.[23] In general the structure of the NMDA receptor includes two glycine-binding subunits (NR1) and two glutamate-binding subunits (NR2).[32] NMDA receptors are located on the postsynaptic neuron membrane and collaboratively modulate glutamate-stimulated post-synaptic transmission.[23] Magnesium ion (Mg^{+2}) is located at the entrance of a NMDA

channel. At resting state, it forms a plug that blocks the channel. In order to depolarize a postsynaptic neuron, both glutamate and glycine must bind to their respective sites on NMDA, releasing Mg^{+2} and allowing Ca^{+2} entry.[33] NMDA receptors activation results in long-term potentiation and increased synaptic plasticity.[32] In contrast, when zinc is present at the synapse, NMDA receptor activation is inhibited.[19] Therefore it becomes a consideration that antidepressant effects of zinc are managed via zinc-containing neurons. Neurons that contain zinc ions in their presynaptic vesicles are predominantly glutamatergic, and are generally called zinc-enriched neurons (ZEN). Hippocampus is the area of the brain where the highest concentrations of zinc are found.[34] Zinc penetrates the brain through the blood brain barrier systems (BBB). The BBB dissociates plasma zinc from the brain under physiological conditions. Zinc, iron – regulated transporter like protein (ZIP) and zinc transporter (ZnT) are two proteins that have been identified to regulate zinc concentration and maintain zinc homeostasis in the brain. ZIP protein increases zinc uptake by the brain so that plasma zinc concentrations decrease, whereas ZnT protein exports zinc out of the brain thereby increasing plasma zinc concentrations.[35]

Zinc is released simultaneously with glutamate by ZEN and rapidly reaches the micromolar levels required for synaptic modulation. Mechanism of the antidepressant action of zinc is direct inhibition of the NMDA receptor. The dynamics of zinc binding to the NR2 subunit of the NMDA receptor varies according to the glutamate-binding isoform. NR2A has high sensitivity to extracellular zinc and requires only nanomolar concentrations to produce voltage-independent inhibition.[36] In contrast, NR2B subunit binds zinc at 100-fold lower affinity than NR2A to produce voltage-dependent inhibition.[32] Besides modulating NMDA receptor activity via allosteric site binding, zinc provokes the release of the inhibitory neurotransmitter i.e. GABA from interneurons to inhibit presynaptic glutamate release.[37] Since less glutamate at the synapse, glutamate binds to the NMDA receptor will be reduced. Furthermore, another potential mechanism of zinc to act as antidepressant is the indirect inhibition of the NMDA receptor by promoting mGluR inhibition. When zinc inhibits mGlur, it will result in a decrease of intracellular release of Ca^{+2} from neuronal stores. Ca^{+2} increases the activity of NMDA receptors, so that the role of zinc in reducing the availability of Ca^{+2} will further reduce the functionality of the NMDA receptors (**figure 2**).[38]

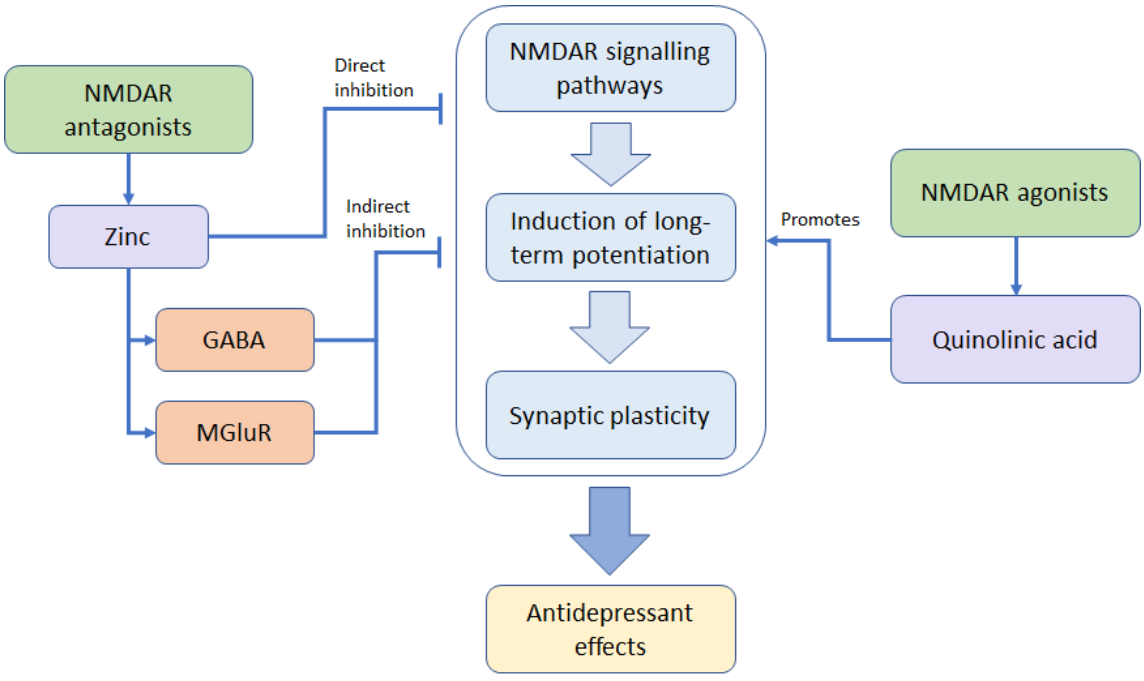

Figure 2. Mechanism of NMDA receptor inhibition and promotion
Figure explanation: NMDAR: N-methyl D-aspartate receptors, GABA: gamma-aminobutyric acid, MGluR: metabotropic glutamate

Patients with depression who do not show any response to antidepressants, or have a recurrence are suggested to consume zinc supplementation as an adjunct to antidepressant drugs to improve their therapeutic effects.[39] In addition, some studies have shown the low serum zinc levels in depressed patients are normalized during treatment with antidepressants.[40,41] One of the symptoms of depression is lack of appetite, therefore it lessens zinc intake. However, instead of finding a decrease in serum zinc levels, on the contrary, normal serum zinc levels were found in depressed patients during treatment with antidepressants. It can be inferred that the enhanced serum zinc up to normal levels may be due to antidepressants. Antidepressants are thought able to stimulate zinc release from the body's stores such as muscles and bones, besides that, zinc supplementation on these patients restored the zinc pools in blood circulation.[41] In a study on patients with major depression who were given imipramine combined with supplementation of 25 mg zinc revealed a significantly reduced rate of depression. These patients were resistant to antidepressant medication, so that zinc supplementation may help to facilitate treatment with antidepressants.[42] A meta-analysis study that determines whether zinc supplementation or placebo can improve depressive symptoms in children, adolescents, or adults, also concludes that zinc supplementation may have a contribution reducing depressive symptoms in individuals treated with antidepressant drugs for clinical depression. [43]

Antidepressant's effect of zinc in inhibiting NMDA receptors is also observable through its involvement in the inflammatory process. Proinflammatory cytokines levels, such as interleukin 6 (IL-6) and tumor necrosis factor a (TNF-a) increase when zinc deficiency occurs.[44] The presence of proinflammatory cytokines may cause depression by altering serotonin regulations in the brain. Increasing number of proinflammatory cytokines are associated with indoleamine 2,3-dioxygenase (IDO) activation. IDO will reduce the level of amino acid tryptophan which is necessary for serotonin synthesis. IDO catalyses the conversion of tryptophan to metabolites kynurenine. Subsequently, kynurenine will be metabolized to quinolinic acid by kynurenine 3-monooxygenase.[45] Augmentation of quinolinic acid metabolism over kynurenine facilitates neurodegeneration, including depression. Quinolinic acid is a neurotoxic metabolite which is considered as an NMDA receptor agonist that causes excessive release of glutamate in hippocampus, striatum, and cortex (**figure 2**).[46]

Conclusions

Glutamatergic system disruption, i.e. imbalance condition between excitatory and inhibitory systems leads to the development of depressive symptoms. Since there is numerous evidence about decreased zinc levels in depressive disorders, it is possible that zinc may have the potency as a state marker of that disease. The presence of zinc can downregulate the glutamate response by inhibiting NMDA receptors. This inhibitory activity is impaired under conditions of zinc deficiency. The ability of zinc as an NMDA inhibitor can be a chance to develop new antidepressants, but further research is still needed. Considering that pharmacotherapy has potential adverse side effects, this review suggests that zinc can be used as an adjuvant to help reduce depressive symptoms in individuals with a clinical diagnosis of depression. Zinc supplementation is also expected to lessen the amount of required psychotropic medication, thereby leading to increased medication adherence, lower costs, and better outcomes.

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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