THE ROLE OF ZINC IN THE PATHOGENESIS AND TREATMENT OF CENTRAL NERVOUS SYSTEM (CNS) DISEASES. IMPLICATIONS OF ZINC HOMEOSTASIS FOR PROPER CNS FUNCTION

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Abstract: Zinc, the essential trace element, is known to play multiple biological functions in human organism. This metal is a component of many structural as well as regulatory and catalytic proteins. The precise regulation of zinc homeostasis is essential for central nervous system and for the whole organism. Zinc plays a significant role in the brain development and in the proper brain function at every stage of life. This article is a review of knowledge about the role of zinc in central nervous system (CNS) function. The influence of this biometal on etiopathogenesis, prevention and treatment of selected brain diseases and disorders was discussed. Zinc imbalance can result not only from insufficient dietary intake, but also from impaired activity of zinc transport proteins and zinc dependent regulation of metabolic pathways. It is known that some neurodegenerative processes are connected with zinc dyshomeostasis and it may influence the state of Alzheimer's disease, depression and ageing-connected loss of cognitive function. The exact role of zinc and zinc-binding proteins in CNS pathogenesis processes is being under intensive investigation. The appropriate zinc supplementation in brain diseases may help in the prevention as well as in the proper treatment of several brain dysfunctions.

Keywords: zinc, central nervous system, Alzheimer's disease, depression, brain ischemia

Abbreviations: 5-HT – 5-hydroxytryptamine, AD – Alzheimer's disease, ADHD – attention deficit-hyperactivity disorder, AMPA – 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)-propanoic acid, ASD – autism spectrum disorder, BDNF – brain-derived neurotrophic factor, CMS – chronic mild stress, CNS – central nervous system, CTR1 – copper transporter (SLC31A1 member 1), DMT1 – divalent metal-ion transporter 1 (DMT1/DCT1/SLC11A2), ERK – extracellular-signal-regulated kinase, FST – forced swim test, GABA – γ-aminobutyric acid, IFN – interferon, IL – interleukin, LTD – long term depression, LTP – long term potentiation, MAPK – mitogen-activated protein kinases, MT – metallothionein, MTF1 – metal-regulatory transcription factor 1, NF-κB – nuclear factor of κ-light-polypeptide gene enhancer in B-cells, NGF – nerve growth factor, NK cells – natural killer cells, NMDA – N-methyl-D-aspartic acid, PD – Parkinson's disease, ROS – reactive oxygen species, SOD – superoxide dismutase, TGFB1 – transforming growth factor β1, TNF – tumor necrosis factor, TrkB – tyrosine-related kinase B, TST – tail suspension test, ZIP – Zrt- and Irt-like proteins (SLC39 – solute-linked carrier 39), ZnT/CDF – zinc transporter (SLC30 – solute-linked carrier 30)

Zinc plays an essential role in the number of biochemical processes crucial for cell survival (Fig. 1). Evidently, unbalanced homeostasis of this biometal affects cell function. This bivalent metal constitutes a prostetic group of a number of enzymes like carbonic anhydrase, alcohol dehydrogenase, alkaline phosphatase, phospholipase C, carboxypeptidase, Zn-Cu superoxide dismutase (SOD) and others regulatory proteins (1, 2). It is also a critical component of DNA and RNA polymerases and has a fundamental role for nucleic acid metabolism and gene activation and repression. At the transcriptional level of protein expression, zinc fingers structure enables transcription factors to anchor to DNA helix (3). This biometal regulates cell cycle by the influence on cyclines and cyclin-dependent kinases (4). The activities of many growth factors are zinc dependent, hence cell proliferation is regulated by the concentration of zinc ions (5). Zinc regulates microtubule polymerization process in the division

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of cells, providing the correct cell cytoskeletal formation and cell mitosis (4).

One of the most important functions of zinc in organism is an antioxidative protection (6, 7). Zinc decreases ROS generation by several mechanisms. Firstly, the zinc antioxidative effect occurs through activity of zinc dependent enzyme, superoxide dismutase (1). Secondly, zinc metallothioneins (MT) can bind and neutralize ROS due to their sulfhydryl groups (7). Additionally, zinc ions have influence on signal transduction pathway *via* inhibition of NF-κB, TGFB1 and MAPK (8, 9).

Zinc activity occurs through inhibition of caspases and protection from ROS-related release of cytochrome C from mitochondria and this way suppresses apoptosis induction process (9). It was established that zinc in hippocampus could inhibit cell apoptosis and prevent mitochondrial dysfunction through the activation of BDNF and the regulation of TrkB pathway (9). The proper zinc balance and the expression of zinc transporters in organism is crucial for anticancerogenic protection (7, 10), because optimal zinc levels have an impact on growth factors and cytokines, which enables to remove malicious cells in apoptosis process. Other mechanism of cell protection by zinc ions is according to expression and folding regulation of tumor suppressor genes products. Notably, this metal ion is crucial for immunoregulation due to decreasing the synthesis of TNF-α, and other interleukin proinflammatory cytokines (7). Zinc is also indispensable for proliferation and proper function of T lymphocyte subpopulations (11). Additionally, zinc ions are necessary for proper hormonal balance and in this way exert the effect on the whole organism (5, 12). Zinc ions are components of hormones (i.e., thymus hormones) or regulate hormones synthesis and ensure the appropriate hormone trails (i.e., insulin). The disturbances in zinc homeostasis are important causative factors of unbalanced organism functioning, which may lead to inflammation process and the development of diseases like arthritis, ulcers, cancer, and brain disorders (10).

Zinc absorption and transport

The total content of zinc in the adult human body is approximately 2 grams (10, 13). The requirement for this element for adult women is about 8 mg and for adult men about 11 mg per day and the similar amount is excreted daily (14). There is no mechanism enabling to store zinc in the body so it should be ingested regularly. In physiological conditions, zinc homeostasis strictly depends on maintaining its amounts on stable level in the organ-

ism. The importance of keeping zinc homeostasis is reflected by the complexity of zinc transport into and inside the cells (15, 16). There are two families of mammalian specific zinc transporters identified: ZIP/SLC39 family transporter, which transports zinc into the cytoplasm and ZnT/CDF/SLC30 family transporter, which acts in efflux zinc ions from the cell. Zinc transporters expression is regulated by zinc level in cytoplasm and outside the cells, according to the cell type and function, by zinc dependent transcription factors, especially metal regulatory transcription factor 1 (MTF1) (1, 16).

In human, the dietary zinc is mostly absorbed in duodenum, ileum and jejunum by active transport trough ZIP4/SLC39A4 zinc transporter, localized on the apical surfaces of the enterocytes (16). However, there are other zinc uptake possibilities in the intestinal tract i.e., ZIP1/SLC39A1 transporter expressed in small intestine, divalent metal-ion transporter 1 (DMT1/DCT1/SLC11A2) as well as copper transporter 1 (CTR1/SLC31A1) (16, 17). Zinc absorption can be affected by cations like copper, chromium, calcium, manganese and cadmium ions that can compete for zinc transporters (15, 17). The process of absorbance, transport and bioavailability may be affected by diet composition. The influence of diet components on zinc absorption and reabsorption was a subject of interest (18).

It is known that zinc ions in cell cytoplasm are accumulated bound to metallothionein proteins (1, 15). Further zinc transport from enterocytes into the bloodstream occurs through the ZnT1 transporter. Zinc ions in the blood are transported as complexes with albumins (52%), macroglobulins (40%), and amino acids (8%). In human serum there is about 15 µM/L of zinc and this concentration is similar to that in other mammals (10, 16). Zinc is absorbed to tissues and cells from blood mostly by ZIP1 and ZIP4 zinc transporters, and then, inside the cells, with both, ZIP and ZnT family (ZnT2/SLC30A2, ZnT4/SLC30A4, ZnT5/SLC30A5, ZnT6/SLC30A6, ZnT7/SLC30A7, ZIP7/SLC39A7, ZIP8/SLC39A8) to nucleus or other cell compartments, where it plays catalytic roles or is stored in Golgi apparatus vesicles (15–17). Zinc is excreted from cells by the zinc efflux transporter ZnT1/SLC30A1 and is eliminated from the organism with feces (over 10 mg/day) and urine (0.4 mg/day) (10).

The role of zinc in brain function

Zinc is transported from blood trough blood brain barrier system, mostly in the form of complexes with amino acids, especially L-histidine and cysteine (15, 19). Zinc transport in nervous cells is

shown in Figure 1. The average zinc concentration in brain is between 10 and 15 µg/g wet tissue (13), however, it may vary in different brain parts. The highest zinc level in the brain was found in hippocampus, amygdala and cerebellum (13, 19). There are three pools of zinc considered in the brain (15, 21). First, about 90% of total zinc, is the metal tightly bound to proteins. Second pool includes about 10% of brain zinc, which is present in a form of ions; this pool is stored in presynaptic vesicles of glutamatergic neurons where it is transported by specific transporter ZnT3/SLC30A3. Third pool, free zinc ions in non-precised compartments, is less than 1%. The measured zinc contents, especially in last two (labile, chelatable) pools vary depending on sample preparation method and measurement techniques (13, 19).

This element is reported to have a second messenger activity in the brain (22). Accordingly, in mammals zinc containing vesicles were found mostly in the glutamatergic neurons in brain cortex, hippocampus and amygdala, brain compartments responsible for learning, memory, cognition and mood regulation (10, 23, 24). During the neuronal activity, when zinc with glutamate is released from synaptic vesicles into synaptic cleft, zinc interac-
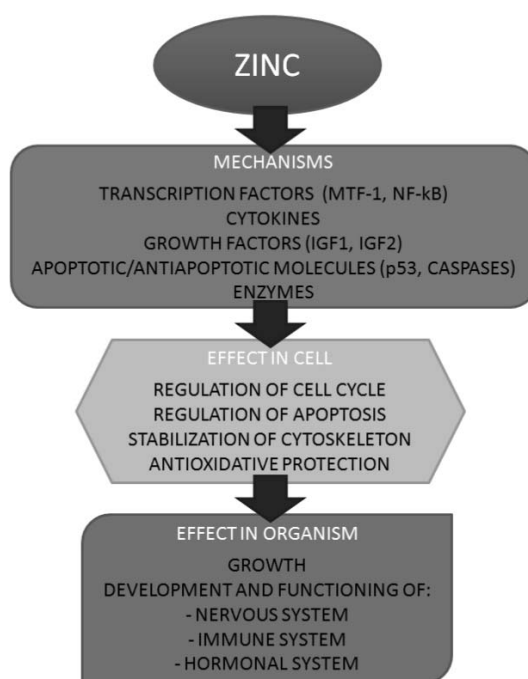

Figure 1. The mechanisms of zinc action in the organism. The scheme presents zinc action including the level of the particular cells and the whole organism as an integral system (1, 2)

tions with postsynaptic receptors may occur. The well known process of zinc inhibition of NMDA receptors in synapses occurs through two mechanisms, voltage independent allosteric inhibition, which reduce ion cannel opening frequency, and voltage dependent inhibition by blocking open channels (21, 25). Another interaction mechanism consists of inhibition of GABA receptor-mediated response, which leads to reduction of neuronal excitability. Furthermore, zinc can enhance AMPA receptors in postsynaptic cells and in that way zinc may regulate cell excitation (22, 25). Extracellular zinc in synaptic cleft may be reuptaken by both pre- and postsynaptic neurons and also glial cells (22).

The adequate zinc level is critical for CNS development and the differentiation of nervous stem cells in mammals (9, 26). The sustainable zinc homeostasis is necessary for the proper development of brain, especially for cerebellum, stellate, basket and also for Purkinje and granule cells. It was observed, that in the developing rat brain zinc accumulates in those cells, which should be eliminated for proper development (26). On the other hand, inadequate zinc status affects growth and maturation of neurons by disturbing zinc-dependent receptor functions. The rat model experiments showed decreased proliferation of neural precursor cells in adults as a result of the postnatal zinc deficiency (9). Studies with primary cultures of rat cortical neurons and human neuroblastoma IMR-32 cells proved that low zinc level reduced cell viability, decreased cell proliferation and increased neuronal apoptotic cell death (8). Zinc regulative role in the cortical plasticity is important for brain development and functioning of processes like learning and memory (25, 26). The experiments with cultured rat cortical neurons and hippocampal slices showed that zinc ions can transactivate TrkB through pathway independent on neurotrophins. Zinc can modulate long-term potentiation (LTP), long term depression (LTD) and synaptic plasticity in this process (25). Additionally, zinc may increase postsynaptic density of excitatory synapses in BDNF activation pathway (9).

The elevated zinc level, about 300 µM extracellular and over 400 nM intracellular (10, 27), is toxic to neurons. The experiments with cultured cortical neurons demonstrated that elevated zinc concentrations result in lower ATP synthesis caused by inhibition of glycolytic pathway enzymes such as glyceric aldehyde 3-phosphate dehydrogenase and phosphofructokinase and that way affects cells survival (27). The synaptically released extracellular zinc can reach the toxic amounts during pathological states like seizure, cerebral ischemia and trau-

matic brain injury (21, 27). Moreover, other observations indicate that glucose starvation may increase zinc ions toxicity for rat cerebellar granule neurons (29). In proposed mechanism, a lack of glucose induces activation of NMDA-channels and growing accumulation of calcium and zinc ions in mitochondria, which lead to severe neuronal damage. However, in neuroblastoma IMR-32 cell *in vitro* model, it was shown that high concentrations of zinc ions may reduce toxic effect of other toxic metals (8, 17).

Disturbances of zinc homeostasis are considered as important factors in neurodegenerative brain disorders. Adequate zinc intake is crucial for proper cognitive functions, especially in children and elderly human (19, 23, 24, 26, 30, 31). The alterations in zinc level have been reported in such diseases as depression and ADHD, Alzheimer's disease (AD), Parkinson's disease (PD) as well as in brain ischemia and traumatic brain injury.

The role of zinc in ischemic brain injury

In the conditions of brain ischemia, which can be caused by stroke and traumatic brain injury, zinc ions seem to play an important role in the neuronal damage process (27, 28). The synaptically released zinc ions are proposed as a critical component of the excitotoxicity cascade occurring in the course of ischemia (27). During ischemia, oxygen deficit results in increasing acidosis (21). In turn, acidosis can trigger more zinc release from MT proteins, which was demonstrated *in vitro* in rat-cultured neurons (21, 27, 28). Therefore in the conditions of growing oxidative stress typical for ischemia, additional MTs release of zinc ions can finally lead to apoptosis of neurons and glial cells (27). In addition, *in vitro* studies demonstrated that zinc insults affect cellular respiration and ATP depletion (27). Moreover, when ATP deficits cause progressive depolarization and affect ionic homeostasis of the cells, the repetitive waves of zinc release from synaptic vesicles into extracellular space were observed (27). The spreading depolarization and intensive zinc efflux can increase intracellular calcium flow (21) and that way calcium and zinc ions may work synergistically causing neurotoxicity (21). This results in alterations of plasma membranes permeability, mitochondrial damage and release of glutamate from neuronal vesicles (27, 28). In ischemic conditions large amounts of zinc may enter postsynaptic neurons through routes that are normally used by calcium. The studies with rat cortical neurons primary cultures showed, that zinc ions were influxed to postsynaptic neurons and glial cells after depolarization through voltage dependent calcium channels (21, 25). Additionally, this process
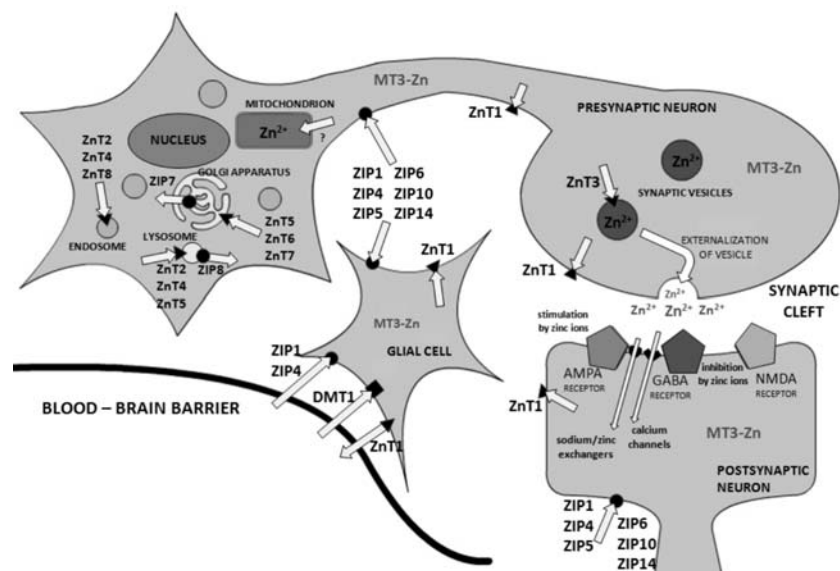

Figure 2. The mechanisms of zinc transport in nervous system. The direction of zinc ions flux presented with arrows; black circles – ZnT family of zinc transporters, black triangles – ZIP family of zinc transporters , black square – DMT1 transporter, MT3 – metallothionein 3 (neuron specific protein) (10, 15, 16, 24, 32)

may be enhanced by activity of glutamate, which, as mentioned, is released altogether with zinc (32). The rising glutamate amounts in extracellular space may cause additional opening of calcium channels leading to increased excitotoxicity (21). The studies on animal ischemic models confirmed extracellular accumulation of high zinc amounts in neurons and in extracellular space (27, 32).

On the other hand, it was demonstrated in ischemic state models that zinc chelation can decrease zinc accumulation and therefore degradation of nervous cells (27). However, there is also evidence that in ischemic conditions high zinc ions level may exert a neuroprotective effect (19). It is presumed that zinc downregulates the NMDA receptors and in that way may decrease toxicity of calcium ions (21, 25). Also the effectiveness of zinc bondage to metallothioneins may play a protective role in the brain injury (32). Zinc-dependent antioxidative enzymes may also have beneficial effect in conditions of ion dyshomeostasis caused by ischemia. *In vitro* studies with hippocampal rat neurons confirmed important role of proper zinc transport during ischemia (27, 28), because very high zinc concentrations (150 mM/L) were shown to increase (transiently) ZnT1 mRNA level in cells. These findings suggest that increased ZnT1 expression could be a defense mechanism from delayed, zinc-related neuronal damage caused by elevated zinc efflux (27, 32).

In reperfusion process, which follows ischemia, changes of zinc concentration in particular compartments can be continuously injuring for neurons (27, 28) but exact mechanism of action is under investigation. However, the effect of regulation is not clear, because inflammation process occurs in parallel, where zinc is ascribed to play beneficial role.

All presented findings and mixed data indicate that proper zinc level in specific neuronal compartments is essential for brain function and need to be precisely controlled in narrow concentration range, since even slightly disturbance may lead to neuronal damage during pathological ischemic conditions.

The role of zinc in depression

Despite of intensive clinical studies on depressive disorders, it is difficult to elucidate its pathophysiology. The most probable causes are connected with the loss of homeostasis of the stress hormones, neurotransmitters, neurotrophic factors, and additionally, disturbed trace elements levels (33, 34). Moreover, all those factors apply to only some types of depressed patients but not for others.

Regardless of exact cause of this disease, the increased neuronal death by ROS formation and inflammation was postulated in most cases (35). The excessive inflammation process in depressed patients is manifested by elevated levels of pro inflammatory mediators (IL-1, IL-2, IL-6, TNF-α, IFN-γ) (35). As it was mentioned before, disregulation of inflammatory pathways may be correlated with decreased zinc level. In zinc deficiency conditions the proper function of immune system, differentiation of the immune cells and response of T helper lymphocytes is usually inappropriate. Schmidt considered that early life stress is a major risk factor for development of later depression due to affected neurogenesis in brain, especially in hippocampus (33, 34). On the molecular level, these processes may be zinc-dependent *via* antioxidative activity changes and its influence on proper course of brain development process. Additionally, Takeda hypothesized that corticosterone-mediated increase in postsynaptic zinc signal may decrease synaptic plasticity LPT and in that way affects hippocampal functions and in consequence induces depression in chronic stress conditions (36). Animal models of depression are commonly based on measuring acute or chronic stress, i.e., in FST and TST or chronic mild stress (CMS). It was observed that administration of zinc as well as antidepressants could reduce the durance of depressed behavior of animals in these models (33, 37). The other rodent models of depression are based on diet zinc-deprived, which can also generate depression-like behavior. These findings were consistent with clinical evidences, especially obtained in the treatment resistant cases when patients with depression had significantly lower serum zinc level compared to non-depressed. On the other hand, it has been reported that successful depression therapy can lead to zinc level normalization (33).

The important zinc dependent mechanism, which disturbances may exert influence on depression in patients is neuromodulation of NMDA receptors (25). The altered regulation of these receptors may lead to the development of depression symptoms. As previously mentioned, zinc ions released in synaptic cleft causes effective inhibition of NMDA receptors. The antidepressant mechanism, proposed by Duman and Violets, is based on rapid induction of synaptogenesis by NMDA receptor inhibition agents (34). Additionally, important role in the synaptogenesis is also played by NGF, BDNF and neurotrophins, which concentrations can be reduced by stress in rodents and in depressed human patients (37, 38). Moreover, it was demon-

strated that zinc supplementation could increase BDNF protein level in rodents (38).

In a view of these findings, it seems obvious that there is a relationship between zinc homeostasis and depression progress in humans. Unfortunately, there is no exact *in vitro* cell culture model of depression, which could help study the exact mechanisms in physiologically active nervous cells.

The role of zinc in Alzheimer's disease

Alzheimer's disease is an age-related neurodegenerative disorder manifested by the progressive dementia. It is well documented that brains of AD patients typically exhibit intracellular neurofibrillary tangles deposits of τ protein and extracellular β-amyloid plaques (39). However, the exact mechanism of neurodegeneration in AD is unclear and still there is no effective therapy of this disease. Clinical examinations data revealed the noticeable disturbances in zinc concentration in serum, brain cells and compartments and in synaptic vesicles of AD patients compared with control subjects (19, 23). It was considered that etiology of AD might involve abnormal concentration and disturbed compartmentalization of zinc ions. Indeed, increased concentration of extracellular zinc ions in the brain can be of importance in AD pathogenesis (40, 41). It has been demonstrated that β-amyloid plaques contain high concentrations of metal ions, especially iron, copper and zinc. In addition, results of *in vitro* studies demonstrated that zinc binding could accelerate the β-amyloid peptide formation (42). In consistence with these findings, it was observed that the formation of amyloid plaques in APP transgenic mice (AD model with mutations of amyloid precursor protein) was effectively inhibited due to the application of metal chelating agents. The maintenance of proper zinc concentration is crucial, because the enzymes, which restrain abnormal folding and aggregation of the β-amyloid such as neprilysin and insulysin, are zinc dependent proteins (39).

The changes in zinc levels can be caused by the altered expression of zinc transporters, especially ZnT1, ZnT3, ZnT4, ZnT6 and MT proteins (24, 40–42, 44). The extracellular concentration of zinc in hippocampus and cerebral cortex depends on the activity of zinc transporter ZnT3. The abnormally increased activity of ZnT3 may additionally elevate the extracellular zinc and in that way it induces the formation of β-amyloid plaques. This process is thought to be the first step in zinc homeostasis disruption in course of that pathological state. The inhibition of β-amyloid concentration was observed in

brains of ZnT3 gene knock-out animals (Tg2576 mice) (44). However, excessively reduced activity of ZnT3 transporter may affect signal transduction in neurons, which can result in memory difficulties. Beyer et al. (42) demonstrated that the AD severity is connected with the significant loss of ZnT3 expression in the cortical regions of human brain. It was concluded that ZnT3-derived extracellular zinc pool is important for the proper regulation of normal cognitive function by modulation of the synaptic neurotransmission. The observations of ZnT3 gene knock-out mice behavior confirmed that animals exhibit deficits in learning and memory. What is more, the loss of memory functions were age-dependent and it is presumed that the adverse effects could be similar to those observed in AD patients, which underline the importance of proper expression of ZnT3 protein in specific regions for maintaining the brain function (41, 45).

Thus, once disturbed zinc concentration and distribution can influence zinc transporters expression. The altered zinc homeostasis manifested in the elevated extracellular zinc state may in consequence lead to up-regulation of expression of ZnT1 protein, which in turn exports zinc ions outside cells (24, 44). The raised concentration of extracellular zinc can be interpreted as a signal for the enhanced synthesis of this zinc exporter. Finally, it results in the enormous zinc export outside cells and the augmented zinc imbalance. The recent results demonstrated the increased expression patterns of zinc transporting proteins ZnT1, ZnT3, ZnT4, ZnT6, and ZnT7 in brain vessels of mice model APPswe/PS1dE9 (44).

The additional zinc activity connected with AD development is revealed in the hyperphosphorylation of τ protein. This phenomenon promotes polymerization of this protein and generation of neurofibrillary tangles in AD neurons (46). Kim et al. (46) showed that zinc regulates phosphorylation of τ protein through extracellular signal-regulated kinase pathway (MAPK/ERK); τ protein deposits affect microtubule function in neurons and probably may be the important cause of neuronal death in AD.

The regulation tissue-distant metabolic transitions by zinc, such as insulin synthesis and secretion pathways, may influence AD development. The recent experimental reports suggest the dependence between regulation of cells insulin sensitivity and AD pathogenesis, which ultimately qualify to name this disease as "diabetes type 3" (47).

The progressive loss of synaptic connections and the neuronal degeneration lead to the advancement of dementia in AD pathogenesis (21). The

influence of elevated ROS activity on the disease development is consistent with the frequently reported increased ROS formation observed in AD patient neurons. The explanation may be the failure in mitochondria functioning, which lead to the depolarization of mitochondrial membranes and in consequence to the increased ROS activity (48, 49). It is obvious that ROS are especially harmful in CNS because of pro-oxidation of lipids, which are essential for proper nerve membranes function and also for the conductivity and signal transduction pathways. Summarizing, the role of zinc in the pathogenesis of AD may be miscellaneous. Further studies are necessary to understand the complex role of zinc in the AD severity and treatment.

Other CNS disorders connected with zinc imbalance

There are recent clinical evidences that other CNS diseases may be correlated with zinc dyshomeostasis. The main symptoms of Parkinson's disease in human are motoric dysfunctions and a decrease in kinetic abilities. This neurodegenerative disorder is the consequence of dopaminergic neurons damage resulted from the progressive deficiency of neurotransmitter dopamine (23, 47). The biochemical processes affected in PD may be correlated with disruptions of zinc homeostasis. Clinical studies with PD patients suggested significantly decreased zinc status in patient blood serum compared with healthy elders control group. Another meaningful observation concerned protein deposits connected with metal ions disturbances in patient brain compartments, which showed some similarities to those observed in Alzheimer's disease (23). Experiments in vitro on clonal CHO cell line with overexpressed D2 receptors showed that zinc ions may have influence on dopamine receptors modulation and in that way low zinc status could be another factor reducing dopamine activity (50). Additionally, lowered zinc concentration may have influence on pathophysiology of PD by increased inflammation processes, generation of ROS and affected neurotropic factors levels, resulted in the proceeding neuronal degeneration.

As it was mentioned before, in the developing human brain, disrupted trace metal homeostasis may disturb the proper conduct of the process and in consequence affect hippocampus functioning. This, in turn, may lead to the following: affected attention, memory and activity levels in human but especially can correlate with children affected behavior. The epidemiological and clinical studies showed that children with ADHD disorder had decreased level of zinc in blood, hair and urine compared with control groups of children without attention problems (30). Additionally, the relation between effectiveness of methylphenidate and amphetamine derivatives used in ADHD treatment altogether with zinc supplementation was observed (51). Zinc role in ADHD disorder may be correlated with the activity of this biometal as a second messenger in brain cells. In turn, positive zinc action on attention processes may be connected with zinc regulation of dopamine metabolism and transport (47, 51). However, double blind placebo controlled study by Bilici et al. (53) showed that beneficial effects of 150 mg/day zinc sulfate supplementation for 12 weeks on ADHD symptoms were limited and rather comparable with placebo. All these findings indicate necessity of further studies on zinc role in ADHD disorder.

In autism spectrum disorder (ASD) the progress of disease may interfere with adequate supply of trace elements. ASD is a neural development disorder characterized by occurrence of repetitive behaviors and affected social interaction (31). Pathogenesis of this disorder is unknown but genetic, life-style and environmental factors are being under consideration now. It was hypothesized that one of important factors may be early zinc deficiency combined with accumulation of other toxic metals. Preliminary studies showed that most of children exhibiting ASD symptoms had significantly lowered zinc levels in hair (31). Also Faber et. al. suggested the importance of zinc deficiency and the probability of metallothionein detoxification system disturbances in ASD pathogenesis (54). They hypothesized that plasma zinc/copper ratio may be considered as a one of biomarkers of autism susceptibility in children. It was also reported that supplementation of nutrients, including zinc, during infancy development, can reduce severity of ASD symptoms (31). However, the exact mechanisms of beneficial effects of Zn in etiology of this disorder are not proved enough.

On the basis of presented studies, disturbances of zinc balance during human life span seem to be an important factor correlated with development of CNS diseases.

CONCLUSIONS

Zinc plays an essential role in the number of processes crucial for proper cells and organism function. The most important, regulated by this biometal, are gene expression, antioxidation defense and apoptosis. During human growth zinc can influence development and proper function of nervous system and neuronal plasticity. Specific zinc trans-

porters strictly regulate the uptake of this ion into the organism. However, zinc concentration in the diet is important, due to the lack of mechanisms which allow to store this biometal for a long time. The zinc imbalance can result not only from insufficient dietary intake, but also from impaired activity of zinc transport proteins and zinc dependent regulation of metabolic pathways. The crucial role of zinc homeostasis in CNS exhibits influence on proper function of learning, cognition and mood regulation. The adequate zinc levels in specific brain compartments seem to be critical for the proper brain functioning because even slight disturbances in zinc homeostasis may lead to or participate in the development of several disorders.

The exact role of zinc and zinc-binding proteins in CNS pathogenesis processes is being under intensive investigation. Therefore, the pressing issue is to dispel the doubts on the adequate zinc level in specific pools and find out how the concentration changes may be involved in the pathogenesis of diseases and brain dysfunctions. Notably, there is a need to develop reliable methods of determination zinc disturbances in the brain with the potential to use them in diagnosis of neurodegenerative diseases. The crucial issue is also to determinate appropriate zinc supplementation in brain diseases prevention as well as in proper treatment. Many detailed mechanisms of zinc activity in living cells are known to date but further research warrants understanding of complex influence of zinc on human organism.

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