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Zinc in the central nervous system: From molecules to behavior

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Abstract

The trace metal zinc is a biofactor that plays essential roles in the central nervous system across the lifespan from early neonatal brain development through the maintenance of brain function in adults. At the molecular level, zinc regulates gene expression through transcription factor activity and is responsible for the activity of dozens of key enzymes in neuronal metabolism. At the cellular level, zinc is a modulator of synaptic activity and neuronal plasticity in both development and adulthood. Given these key roles, it is not surprising that alterations in brain zinc status have been implicated in a wide array of neurological disorders including impaired brain development, neurodegenerative disorders such as Alzheimer's disease, and mood disorders including depression. Zinc has also been implicated in neuronal damage associated with traumatic brain injury, stroke, and seizure. Understanding the mechanisms that control brain zinc homeostasis is thus critical to the development of preventive and treatment strategies for these and other neurological disorders.

Keywords

zinc; brain; zinc finger; neurogenesis; neurotoxicity; Alzheimer's disease; depression; traumatic brain injury; stroke; seizure

1. Introduction

Zinc, an essential trace element, plays a key role in maintaining human health throughout the lifespan. In the central nervous system (CNS), the biofactor zinc is second only to iron in trace metal abundance and its prevalence is a reflection of its widespread functions. Alterations in brain zinc status can lead to the pathogenesis of diseases related to development, mood disorders such as depression and anxiety, and neurodegeneration and dementia, such as that observed in Alzheimer's disease. Alterations in brain and neuronal zinc associated with trauma, stroke, and seizures play a role in neuronal damage and death. The development of zinc-based therapies will depend on an understanding of the role of zinc in the brain under normal and pathological conditions.

Homeostasis of protein-bound and free zinc is critical to normal brain function. Zinc provides structural stability for a variety of transcription factors, and in doing so plays an important role in the regulation of gene expression. Zinc plays key roles in enzymatic activity, cell signaling, and the modulation of neurotransmitter activity. Most recently it was

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discovered that adult neurogenesis in the brain is dependent on zinc, a finding that has widespread implications for hippocampal function including learning and memory and control of emotion and mood. Thus, this review will outline these and other CNS functions of the trace element zinc and discuss the relationship between the cellular and molecular functions of zinc to a variety of clinically relevant disorders of the brain and CNS.

2. Zinc finger transcription factors and gene regulation

Zinc is responsible for the DNA-binding ability of many transcription factors through a unique ability to form molecules known as zinc finger (ZnF) proteins. These ubiquitously expressed proteins directly regulate gene expression. They also appear to interface with RNA and function to facilitate protein-protein interactions. While several classes of ZnF proteins are known to exist, by far the most common form is the classical ZnF, consisting of 2 cysteine and 2 histidine (C2H2) or 1 cysteine and 3 histidine (C1H3) residues centralized around a zinc ion with a short b-hairpin and an a-helix incorporated into the structure. The conformation of ZnFs centers around the coordinated zinc ion and provides the molecule with the potential to form a finger-like structure that is capable of binding tightly with specific DNA sequence domains [1].

Ubiquitously expressed zinc finger transcription factors regulate much of the gene expression in the CNS. Transcription factors such as Sp1 regulate basal levels of many genes, while other immediate early genes such as c-fos play a role in gene expression changes in acute activity and stress. While these functions are essential throughout the life span, recent research has defined an important role for ZnF proteins in brain development. Not only is there a role for these proteins in directing embryonic stem cell fate and neurogenesis during brain development [2], but select zinc finger proteins have been linked to region-specific development. For example, the zinc finger proteins Fezf1 and Fezf2 have been implicated in the development of the olfactory region of the brain [3], while Zac1 is involved in the development of neuronal subsets in the cerebellum [4] and Zbtb20 plays a role in the development of the CA1 region of the hippocampus [5].

Other zinc finger transcription factors that are clearly involved in neuronal function include the thyroid hormone receptor that plays a role in neuronal growth and development, and both retinoic acid receptors and vitamin D receptors that participate in neuronal differentiation.

3. Zinc transporters and metallothioneins

Zinc transporters and binding proteins are primary regulators of zinc homeostasis in neurons. An *in vitro* model used to assess the response of the blood-brain-barrier to moderately increased levels of zinc showed an increase in both zinc-specific transport and binding proteins which served to protect the brain against altered zinc homeostasis by sequestering and exporting excess zinc into intracellular vesicles [6].

Detailed descriptions of the functional characteristics of zinc transporter proteins have been extensively reviewed by Levenson et al. [7]. Briefly, two main families of zinc transporters, the ZnT and Zip families of proteins, function to regulate intracellular zinc levels. ZnT and Zip proteins have reciprocal actions. ZnT proteins are responsible for decreasing intracellular zinc by either increasing efflux or via vesicular uptake of zinc, whereas Zip proteins increase cytoplasmic zinc by ushering extracellular and vesicular zinc into neurons and glial cells. One member of the ZnT family, ZnT3, plays a particularly important role in neuronal zinc regulation. ZnT3 is responsible for the accumulation of free zinc in glutamate-containing vesicles found in the hippocampus and cortex [8].

In addition to ZnT and Zip proteins, metallothioneins, a family of proteins first discovered in the 1950s, have a high binding affinity for zinc and not only play a role in the homeostatic regulation of zinc, but also in cellular protection against oxidative stress. Zinc-specific binding sites on MTs are highly sensitive to redox activity. Under conditions of reactive oxygen species production, MT has been shown to increase free zinc abundance by releasing zinc ions [9]. Conversely, under reducing conditions MT sequesters free zinc through an increased binding affinity. A recent review of the ability of MT to buffer free zinc in the brain in response to dopamine-associated oxidative stress hypothesized that initial shifts in MT-mediated zinc release may act as a cell sensor mechanism to minimize neurotoxicity [10].

4. Zinc in development and neurogenesis

4.1. Development

Zinc is essential for normal development of the central nervous system and is required for the formation and function of a variety of proteins, enzymes, hormones, and growth factors that direct stem cell proliferation and differentiation during neurodevelopment. We have known for some time that zinc is needed for key enzymes in the developing brain such as DNA polymerase, a critical enzyme in DNA synthesis [11]. Therefore it is not surprising that even mild zinc deficiency during gestation resulted in learning and memory abnormalities in pups. It should be noted that these deficits persisted into adulthood long after zinc nutriture had been reestablished [12]. More recently, rat pups born of dams receiving pre- and postnatal zinc supplementation showed significant improvements in memory as well as an increase in serum zinc levels compared to controls, indicating that zinc supplementation positively impacts early cognitive development [13]. Furthermore, there is some evidence to suggest that rats fed a zinc-supplemented diet after birth may be more resistant to subsequent diet-induced zinc deficiency [14].

There are also data showing the roles of zinc during brain development are complex. Apoptotic cell death contributes to periods of developmental pruning and plasticity of neurons. Chelation of CNS free zinc in the early neonatal period led to a decline in the normal proapoptotic pathways and associated neuronal apoptosis with a simultaneous increase in expression of antiapoptotic proteins such as Bcl-2. These data suggest that free zinc may be a key factor in controlling programmed apoptotic neuronal pruning during developmental periods [15].

4.2. Neurogenesis

Stem cells and neuronal progenitor cells play important roles in the developing brain by giving rise to the neural tube, the first brain structure to form during gestation, and eventually to the neural crest by way of asymmetric proliferation and migration [16,17]. These neuronal stem cells then differentiate into mature neurons, forming synaptic connections throughout the developing brain. Zinc balance is not only important for neural tube formation and neuronal pruning, but it also governs the process of stem cell proliferation and neurogenesis in the CNS during development. The neuronal stem cell marker nestin was significantly decreased by prenatal and early postnatal maternal zinc deficiency in developing mouse brains. This disturbance in neurogenesis during early brain development is thought to lead to the neurological abnormalities associated with zinc deficiency [18].

Neurogenesis is not, however, confined to the developmental period. A landmark study by Eriksson et al. [19] shed light on the ongoing process of adult neurogenesis by demonstrating for the first time that the human brain contains stem cells capable of proliferating throughout the entire lifespan. Beyond this, research has shown that following

asymmetric proliferation, hippocampal cells in the subgranular zone (SGZ) of the dentate gyrus and the subventricular zone (SVZ) of the lateral ventricles could differentiate into fully functional postmitotic neurons and integrate into the existing circuitry [19,20].

Not only is the hippocampus one of the primary brain regions supporting adult neurogenesis, it has also been shown to contain high concentrations of zinc [21]. Research assessing the impact of diet-induced zinc deficiency on adult male rats showed a 50% reduction in proliferating neuronal precursors in the SGZ and granular cell layer of the dentate gyrus as well as a significant increase in apoptotic cell death among cells in the SGZ compared to control animals. *In vitro* confirmation of these results led to the discovery that mechanistically, zinc deficiency-induced reductions in neuronal precursor proliferation and increases in cell death were a result of p53-dependent alterations in cell cycle progression, mitochondrial ROS production, and elevated caspase-3 expression [22]. Similar results were observed following dietary zinc deficiency in rats, which led to a decline in both progenitor cells and immature neurons that was corrected by switching these animals from zinc deficient to zinc adequate diets for 2 weeks. Furthermore, chelation of free zinc in the hippocampus of rats also led to decreased neural progenitor cell abundance. These data were confirmed by showing that ZnT3 knockout mice lacking hippocampal free zinc had significantly fewer proliferating neuronal precursor cells following hypoglycemia-induced neurogenesis [23].

5. Zinc in neurotransmission

5.1. Synaptic zinc

Most of the zinc in the central nervous system (CNS) is tightly bound to zinc-dependent enzymes and other proteins such as transcription factors and metallothioneins discussed in previous sections. However, ~10% of zinc in the brain is not ligand-associated and is thus characterized as “free” or “chelatable” zinc. In normal neurons, free zinc is largely localized to the presynaptic vesicles of glutamatergic neurons [24], but it has also been seen colocalized to GABA containing neurons [25]. Regions rich in vesicular free zinc include the mossy fibers of the hippocampus, the amygdala, and the olfactory bulb. “Zincergic” neurons are also abundant in the cortex [26].

The primary function of the free zinc in synaptic vesicles appears to be the modulation of a variety of postsynaptic receptors. Upon neuronal excitation, zinc is released into the synaptic cleft where it binds to zinc-specific allosteric sites on these receptors. For example, zinc inhibits GABAA receptors, reducing their inhibitory action [27]. The effect of zinc on excitatory glutamate receptors, however, is more complex. First, zinc acts as an inhibitory neuromodulator of glutamate release [28]. Initially, it was thought to inhibit activity of NMDA glutamate receptors [27]. However, it now appears that zinc regulation of both NMDA and AMPA/kainate glutamate receptors is likely to be biphasic and cell-specific [29,30]. Furthermore, zinc potentiates glycine-mediated currents [31] and regulates voltage-gated calcium channels [32], and sodium, potassium, and chloride channels [33].

5.2. Zinc neurotoxicity

Under pathological conditions, neurotoxic levels of free zinc can accumulate in neurons. The source for this excess zinc not only includes zinc released from synaptic vesicles, but also from other intracellular pools of zinc that can be liberated to form free zinc. The strongest case for the presence of nonvesicular pools of free zinc comes from a report showing that free zinc accumulates after seizure activity in ZnT3 knock-out animals that lack vesicular zinc [34]. When excess zinc floods the synaptic cleft, it enters post-synaptic neurons via glutamate receptors (NMDA and AMPA/kainate) and voltage-gated calcium channels [35]. While exact mechanisms responsible for what happens next is the subject of

intense debate, there is general agreement that excess zinc accumulation leads to neuronal damage. There are three main hypotheses that are currently being explored, namely that excess zinc causes excitotoxicity [29], induces oxidative stress [36], and impairs the generation of cellular energy [37]. The fact that there is convincing evidence for all three of these mechanisms suggests that they are not mutually exclusive and that all three actions of zinc may be acting synergistically to cause neuronal damage and death.

6. Zinc and disorders of the central nervous system

6.1 Alzheimer's disease

Over 37 million people world-wide suffer from dementia in the form of Alzheimer's disease (AD), which is characterized by both cognitive and behavioral decline. The underlying pathology appears to involve the accumulation of amyloid plaques and tau-containing neurofibrillary tangles leading to neuronal degeneration of the hippocampus, amygdala, and neocortex [38].

Among the many factors involved in the pathology of AD, dyshomeostasis of trace metals, including zinc, copper, and iron, has been suggested as a potential, albeit controversial, culprit [39]. Historically, conflicting evidence over whether zinc levels are elevated, depressed, or unchanged among AD patients has emerged. Several recent studies have identified decreased levels of serum zinc in AD patients compared with age- and sex-matched controls, suggesting that subclinical zinc deficiency, likely due to nutritional deficits, exists among this disease population [40,41].

At the mechanistic level, a role for zinc in the tau theory of AD pathogenesis has been suggested. Hyperphosphorylation of tau proteins, a hallmark feature of this theory, was demonstrated by zinc-mediated phosphorylation of serine 214 in tau protein and subsequent initiation of the ERK pathway, leading to the signature decrease of microtubule stability in neurons [42]. A more recent theory related to AD pathology that is gaining recognition is the idea that cytotoxicity arises from amyloid oligomers (early stage Aβ aggregates), rather than mature fibrillary plaques. Transgenic mice expressing Aβ oligomers, but not plaques (APP^{E693Q}), developed AD-related deficits in spatial learning and memory. When these mice were bred in a bigenic model, however, such that the oligomers developed into plaques ($APP^{E693Q} \times PSI\Delta E9$), they showed no greater impairments than mice with oligomers alone [43]. Studies also suggest that free zinc found in synaptic vesicles of glutamatergic neurons can associate with toxic Aβ oligomers, causing stabilization and subsequent accumulation of these peptides [44].

Consistent with these observations, Bjorklund et al. [45] detected increased levels of both synaptically releasable and extracellular zinc in hippocampal tissue from AD patients compared to age-matched control tissue. Kozin et al. [46] recently identified the primary Aβ zinc recognition site responsible for binding zinc ions and inducing dimerization and subsequent oligomerization and aggregation of Ab. Guarding this binding site from zinc ions could potentially inhibit the initiation and subsequent development of AD.

High levels of zinc (100 mg/kg daily) given chronically (4-10 months) in the drinking water of Tg2576 transgenic mice, a model for amyloid β-protein (Aβ) and tau deposition, showed no significant differences in deposition of either Aβ or tau when analyzed using immunohistochemical methods. Soluble Aβ and the oligomer Aβ*56 also remained unchanged among groups according to both ELISA and immunoblot techniques, suggesting that chronic excess intake of zinc does not exacerbate the progression of AD in transgenic mice modeling Aβ and tau aggregation. This refutes the idea that high oral intake of zinc is a risk factor for AD [47]. In fact, increased neuronal proliferation as well as prevention of

AD-related cognitive deficits and mitochondrial dysfunction in the transgenic mouse model, 3xTg-AD, further demonstrates the potential benefits of dietary zinc supplementation in attenuating AD [48].

6.2. Depression

Major depression is an extremely prevalent disorder, affecting over 22 million people in the United States alone at some point during their lives [49]. Not only are the symptoms of depression potentially debilitating, but ~80% of patients with major depression also suffer from comorbid anxiety. Furthermore, an estimated 20-40% of patients diagnosed as clinically depressed are resistant to antidepressant drug treatment [50]. An inverse relationship between serum zinc concentrations and severity of depression has been noted in a number of studies. A study assessing Guatemalan children in grades 1-4 revealed that higher serum zinc concentrations were associated with a lower rate of symptoms related to depression and anxiety [51]. Likewise, low zinc intake was correlated with higher depression scale scores while higher intakes of zinc tempered the interactions between stress and depression in pregnant women [52]. Additionally, women appear to have almost twice the risk of developing depression as men and a recent study confirmed lower serum zinc levels in conjunction with depressive symptoms in women, but not men [53].

In addition to these correlational studies in humans, animal studies have demonstrated a causative role for dietary zinc deficiency in the onset of depression-like behaviors including anorexia and anhedonia, as well as comorbid anxiety. Reductions in serum zinc induced by feeding rats a zinc deficient diet for two weeks produced anxiety-like behaviors that were accompanied by elevated serum corticosterone concentrations [54]. Zinc deficiency-associated anxiety-like behaviors were prevented by antidepressant drug administration [55]. Furthermore, zinc administration (ip injection) 45 min prior to behavioral testing had an anxiolytic effect, suggesting that zinc may be useful in augmenting traditional anxiolytic therapies [56].

Treatment with the antidepressant fluoxetine showed decreased behavioral despair in the forced swim test of rats fed either zinc adequate or zinc supplemented diets, but not in those fed zinc deficient diets, suggesting that zinc is required for the efficacy of antidepressant drugs [57]. This is particularly interesting because not only is serum zinc decreased in depressed patients, but a greater severity of zinc deficiency has also been reported in a subpopulation of treatment refractory patients, identifying serum zinc as a reliable biomarker for antidepressant resistance [58].

Supplementation of this population with zinc as an adjunct to antidepressant medication appears to be an effective approach to therapy. Antidepressant-refractory patients diagnosed with major depression who were treated with 140 mg imipramine supplemented with 25 mg zinc daily for 12 weeks showed significant improvements in depression scores and treatment outcomes compared to those given imipramine supplemented with a placebo [59]. It is interesting to note that in a follow-up to this study, the authors identified a gradual increase in serum zinc levels among all groups after 12 weeks of imipramine treatment compared with baseline measurements, including those supplemented with either zinc or a placebo, further supporting the involvement of zinc in antidepressant drug action [60].

Several theories attempting to explain the mechanisms governing the role of zinc in the onset of depression and subsequent pharmacotherapy have been proposed. Irregularities in zinc balance among neurons may lead to alterations in neurotransmission, which have been implicated in depression. Recent work has demonstrated that subclinical doses of 2.5 mg/kg zinc in combination with either 15 mg/kg citalopram or 5 mg/kg fluoxetine significantly reduced immobility time in the forced swim test compared with control animals and zinc

supplementation or either drug given alone. Furthermore, pretreatment with either p-chlorophenylalanine to inhibit serotonin synthesis or 5HT-$2_{A/C}$ or 5HT-1A receptor antagonists eliminated a decline in immobility time in the FST of mice supplemented with a clinically effective dose of 5 mg/kg of zinc. Taken together, these data support an interaction between the antidepressant actions of zinc and the serotonergic system in preclinical models of depression [61]. There is also evidence showing that zinc influences glutamate signaling in the brain. Ineffective doses of zinc coupled with low-doses of either NMDA antagonists or AMPA potentiators improved the antidepressant activity of zinc in the FST in mice, while pretreatment with NMDA significantly reduced improvements in immobility time brought about by effective doses of zinc [62].

Increasing evidence points to zinc deficiency as a potential generator of mitochondrial reactive oxygen species (ROS) in the brain, which in elevated levels have also been linked to depression [22,63]. Clinically depressed patients were recently found to have increased serum levels of the zinc-dependent antioxidant enzyme superoxide dismutase, which were normalized in response to antioxidant and zinc supplementation [64]. Additional theories supporting the role of zinc in the pathophysiology of depression include the apparent requirement of neurogenesis, which is impaired by zinc deficiency, for the efficacy of antidepressant therapy and the impact of zinc on neurotrophic factors such as BDNF in rats [54,65].

6.3. Traumatic brain injury

Traumatic brain injury (TBI) affects more than 1.5 million Americans annually and is a contributing factor to ~30% of all injury-related deaths [66]. Secondary effects of TBI can include long-term impairments in cognition and behavior, including memory loss, as well as depression and anxiety, with an estimated 40% of patients hospitalized for TBI developing major depression [67,68]. Falls, motor vehicle-traffic injuries, and strikes are the top three causes of TBI, and nearly 20% of armed forces currently returning from active duty in Iraq and Afghanistan have fallen victim to TBI [63,69].

Elevated urinary zinc excretion and declines in serum zinc levels have been documented among brain injured patients, defining a link between TBI and zinc [70]. Controversy exists over whether zinc's role in TBI is neurotoxic or neuroprotective. A study designed to address this debate analyzed the effects of free vesicular zinc, classically thought to intensify neuronal damage following injury, in an animal model of TBI. Chelation of free zinc following TBI in wild type (WT) mice exacerbated cellular damage within the first 24 h as exhibited by increased necrosis and apoptosis compared with control animals. Neuronal damage in these mice appeared almost identical to that observed in ZnT3 KO mice, a transgenic model in which free vesicular brain zinc is eliminated. These data imply that declines in free zinc during the first 24 h post-TBI are more damaging than excess levels of free zinc that have been observed in areas surrounding acute brain injury [71]. This observation has been confirmed in an *in vitro* model by Li et al. [72].

These data are consistent with reports showing that supplementation with zinc can have a positive impact in the aftermath of TBI. Zinc supplementation in rats given a TBI resulted in cognitive resiliency in the Morris Water Maze task, used to measure spatial learning and memory, as well as behavioral resiliency to anhedonia, an indicator of depression. Zinc supplementation given as a treatment after TBI also effectively reduced the cognitive impairments associated with TBI. Administration of zinc after TBI, however, was not as effective as chronic pretreatment at reducing stress-induced adrenal hypertrophy or anxiety-like behaviors [73].

6.4. Stroke

Stroke, which blocks oxygen flow and leads to injury of the brain, is the fourth leading cause of death in the United States [74]. While multiple pathological forms of stroke exist, one common thread among them appears to be altered levels of zinc. Clinical studies of patients diagnosed with stroke have revealed some interesting observations regarding zinc levels.

A recent study by Munshi et al. [75] found that stroke patients had significantly lower serum zinc concentrations compared to healthy age and sex matched controls. Interestingly, there were no significant differences in calcium, copper, or iron levels among stroke patients and healthy control subjects. On the basis of their observations, this group hypothesized that low serum zinc levels may be a risk factor for stroke suggesting that, like TBI, ischemic stroke could be a condition that would benefit from preventative zinc supplementation.

The observations by Munchi et al. were confirmed by another group of researchers who found that patients diagnosed with ischemic stroke had low levels of zinc upon hospitalization. In this study, lower levels of zinc were associated with increased stroke severity. Additionally, decreased zinc status was associated with poor functional status at discharge, independent of other confounding variables such as age, sex, NIH Stroke Scale score at admission, and other potential comorbidities including hypertension, diabetes, atrial fibrillation, or cognitive heart failure [76].

A number of studies using preclinical models have also demonstrated that zinc dysregulation plays a role in neuronal damage and death after ischemic brain injury. For example in a rodent model of transient forebrain ischemia, zinc was released from presynaptic terminals and accumulated in postsynaptic neurons. This translocation was associated with degeneration of neurons in the hippocampus, cerebral cortex, thalamus, striatum, and amygdala. An intracerebral injection with the membrane impermeant zinc chelator Ca-EDTA prior to ischemia was neuroprotective and significantly decreased neuronal death [77]. Administration of Ca-EDTA 30 min prior to mild focal ischemia reduced infarct size 3 days after injury. Unfortunately, at 14 days-post stroke there were no apparent reductions in infarct size even when Ca-EDTA was continuously perfused [78].

6.5. Epilepsy

Epilepsy, a brain disorder identified by the occurrence of spontaneous seizures, is preceded by alterations in neuronal signaling and synaptic excitability [79]. Seizures can be triggered in various ways, including illness, brain damage, abnormalities in brain development, neurotransmitter imbalance, or even several of these conditions coexisting at once.

While epilepsy remains an incurable disease, antiepileptic drugs do provide protection against seizure induction, with the use of either pharmacological or surgical interventions being effective in up to 80% of patients. Areas of ongoing research involve the study of neurotransmitter imbalance, identification of genes driving epilepsy, stem cell transplantation, MRI, and dietary intervention. Epileptics are at increased risk of life-threatening status epilepticus in which patients undergo acute recurrent seizures lasting 5 min or greater without recovery of consciousness and sudden unexplained death. This accounts for 7-17% of deaths among the epileptic population [80].

Research on the role of zinc in seizures has revealed both pro- and anticonvulsant effects. The ability of zinc to be both neuroprotective and neurotoxic in the context of epilepsy appears to be dose-dependent. Recent work has highlighted this dual action of zinc by testing the effects of pre-treatment with the antiepileptic drug valproic acid and zinc supplementation both alone and in combination on the latency and severity of seizures in

rats injected with pilocarpine to model temporal lobe epilepsy, the most common form of adult epilepsy [81]. At high doses of 60 mg/kg daily for 3 weeks, zinc exacerbated seizures, and decreased zinc concentrations and activity of superoxide dismutase, while increasing markers of inflammation, apoptosis, and neuronal damage in the hippocampus of male Wistar albino rats following seizure induction with pilocarpine. These results mimicked those seen in animals given pilocarpine without pharmacological intervention. Zinc administered in moderate levels (3 mg/kg daily for 3 weeks) however, showed marked declines in both latency and severity of pilocarpine-induced seizures as well as increases in zinc concentrations and superoxide dismutase activity and decreases in markers of inflammation and cell death. Combinatorial treatment with both valproic acid and moderate levels of zinc showed an even greater therapeutic benefit than either intervention alone [82]. Although ongoing debate exists over whether treatment with antiepileptic drugs such as valproic acid causes secondary zinc deficiency, the aforementioned work by Baraka et al. [79] supports this controversial theory [83]. Moderate dietary zinc supplementation therefore may act synergistically when ingested in combination with classical antiepileptic treatment.

7. Summary

The effects of zinc manifest throughout the entire lifespan, from neonatal brain development to the progression of neurological disorders, such as Alzheimer's disease, that primarily target the elderly population, serving as a reminder that zinc is an essential component of life. While zinc's scope of function in the central nervous system is quite diverse, a common thread among its many actions can be summarized in one word: homeostasis. When systems involving zinc go awry, it is most often a result of challenging the boundaries of the precise homeostatic control of this trace element. Research investigating the tight regulatory balance of bound, and more notably labile, zinc is ongoing and has the potential to affect a wide array of molecular functions and pathologic outcomes.

While nanoparticle delivery probably offers the most promising future for restoring imbalances in neurological zinc, methods for therapeutically manipulating zinc levels in the brain are lacking due to complicating factors such as serum zinc measurements being nonindicative of brain zinc concentrations, efficacy of supplemental zinc absorption and transport, and most importantly challenges presented by the brain-barrier system in directing either supplementary or chelating compounds towards necessary brain regions. Great strides have been made in elucidating the mechanisms underlying zinc metabolism and function, however there is still much to be discovered in the frontier of zinc neurobiology.

Acknowledgments

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