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Brain-Delivery of Zinc-Ions as Potential Treatment for Neurological Diseases: Mini Review

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Abstract

Homeostasis of metal ions such as Zn^{2+} is essential for proper brain function. Moreover, the list of psychiatric and neurodegenerative disorders involving a dysregulation of brain Zn^{2+}-levels is long and steadily growing, including Parkinson's and Alzheimer's disease as well as schizophrenia, attention deficit and hyperactivity disorder, depression, amyotrophic lateral sclerosis, Down's syndrome, multiple sclerosis, Wilson's disease and Pick's disease. Furthermore, alterations in Zn^{2+}-levels are seen in transient forebrain ischemia, seizures, traumatic brain injury and alcoholism. Thus, the possibility of altering Zn^{2+}-levels within the brain is emerging as a new target for the prevention and treatment of psychiatric and neurological diseases. Although the role of Zn^{2+} in the brain has been extensively studied over the past decades, methods for controlled regulation and manipulation of Zn^{2+} concentrations within the brain are still in their infancy. Since the use of dietary Zn^{2+} supplementation and restriction has major limitations, new methods and alternative approaches are currently under investigation, such as the use of intracranial infusion of Zn^{2+} chelators or nanoparticle technologies to elevate or decrease intracellular Zn^{2+} levels. Therefore, this review briefly summarizes the role of Zn^{2+} in psychiatric and neurodegenerative diseases and highlights key findings and impediments of brain Zn^{2+}-level manipulation. Furthermore, some methods and compounds, such as metal ion chelation, redistribution and supplementation that are used to control brain Zn^{2+}-levels in order to treat brain disorders are evaluated.

Keywords

Alzheimer's disease; ion chelators; nanoparticles; postsynaptic density; amyotrophic lateral sclerosis; zinc; nutrition; dietary zinc; epilepsy

1. INTRODUCTION

The metal-ion content in the brain is surprisingly high compared to other tissues [1], with Zn^{2+} and Fe^{2+} as prevalent metals. In particular, since the first discovery in 1955, Zn^{2+} has been known to be highly enriched in the hippocampus [2] and neocortical (150 – 200 μM [3, 4]) region of the mammalian brain [5]. Zn^{2+} is necessary for the maturation and function of the brain and a dysregulation of brain Zn^{2+}-levels is seen in many psychiatric and neurological diseases like Parkinson's [6–8] and Alzheimer's disease [6, 9–11], schizophrenia [12, 13], ADHD [14–16], mood disorders [17–20], amyotrophic lateral

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sclerosis (ALS) [21], Down's syndrome [22], multiple sclerosis [23, 24], epilepsy [25–27], Wilson's disease [28, 29] and Pick's disease [30].

Zinc plays a role in synaptic transmission and serves as an endogenous neuromodulator. Moreover, Zn^{2+} is important for postsynaptic density (PSD) stability, such that PSDs contain a Zn^{2+} concentration of 4.1 nmol per mg protein [31, 32]. Zn^{2+} levels are also important for nucleic acid metabolism and brain microtubule growth [1]. Zn^{2+} is selectively stored in, and released from, glutamatergic presynaptic vesicles [33]. Vesicular Zn^{2+} that is co-released with neurotransmitters elevates Zn^{2+} concentrations in the synaptic cleft from approximately 10 nM to 300 μM [34, 35]. This Zn^{2+} then binds to neurotransmitter receptors [36], such as the NMDA subtype of glutamate receptor (NMDAR) [37, 38] or enters the postsynaptic cell via various routes, including ion channels [39]. Zn^{2+} deprivation affects Zn^{2+} homeostasis in the brain and the reduced levels of Zn^{2+} in the hippocampus lead to brain dysfunctions and learning impairment.

Over the past decades, a vigorous scientific debate has occurred on the role of Zn^{2+} within the healthy brain and especially in neurodegenerative disorders [40–48]. Therapies attempting to regulate Zn^{2+}-levels by preventing release, blocking ion channels, supplementing Zn^{2+} and buffering Zn^{2+} concentration within the brain have played increasingly important roles in the treatment of diverse neurological and neuropsychiatric diseases [41]. Controlled and regional delivery of Zn^{2+} to the brain is highly desirable and an important direction for future research including the delivery of drugs. However, there are only few studies that deliver or delete Zn^{2+} in specific brain areas, and though some methods and compounds are available to achieve this task, the vast majority of studies manipulate Zn^{2+} levels by dietary supplementation or restriction. In the present review, we explore the role of Zn^{2+} in a variety of disorders and highlight recent therapeutic approaches designed to modulate Zn^{2+} levels in the brain. We also review strategies for modulating Zn^{2+} levels and delivery into the brain.

2. DYSREGULATION OF BRAIN Zn^{2+}-LEVELS IN PSYCHIATRIC AND NEURODEGENERATIVE DISORDERS

2.1. Alzheimer's Disease, Parkinson's Disease and Pick's Disease

Alzheimer's disease (AD) and Parkinson's disease (PD) are two neurodegenerative disorders that occur in an age-related manner. AD is characterized by the abnormal intracellular accumulation of the amyloid beta (Aβ) protein [49] and/or its assembly into paired helical filaments and extracellular accumulation in plaques. Possible causes of AD include increased levels of oxidative stress in the AD brain, as well as the sequestration of Zn^{2+} ions within amyloid plaques. Intriguingly, Zn^{2+} can induce Aβ monomers to aggregate in different forms [50, 51], and is known to bind Aβ via its histidine imidazole rings and accumulate within senile plaques [52, 53]. This led Adlard *et al.* to propose that Aβ causes cognitive impairment by trapping synaptic Zn^{2+} rather than through direct toxicity [53]. Functionally, Zn^{2+} trapping by Aβ likely resembles phenotypes observed in loss of function studies of ZnT3 (a vesicular Zn^{2+} transporter) [53]. ZnT3 knockout mice exhibit a complete absence of Zn^{2+} from synaptic vesicles throughout the brain [54], and show dramatic synaptic and memory deficits similar to those seen in APP transgenic mice, a model for AD [53].

Intriguingly, serum Zn^{2+} concentrations were found to be significantly decreased in AD patients compared to control subjects [9]. Moreover, in an AD mouse model, Zn^{2+} supplementation greatly delayed hippocampal-dependent memory deficits and strongly reduced Aβ pathology in the hippocampus [55]. Given that increased brain Zn^{2+}-levels enhance plaque formation, Zn^{2+} was regarded as disease promoting in the past. However, as

clustering of Aβ is mediated by Zn^{2+} ions, drugs with metal chelating properties are expected to produce a significant reversal of plaque deposition *in vitro* and *in vivo* [43]. Yet, there is emerging evidence that Aβ plaques are actually non-toxic deposits within the brain that may even be protective compared to protofilamentous Aβ. Clearly additional research is needed to resolve the role of Zn^{2+} in Alzheimer's disease and more completely explore the potential benefits of Zn^{2+} supplementation.

In Parkinson's disease (PD), α-synuclein aggregates in intracellular inclusions called Lewy bodies, which are associated with the degeneration of dopaminergic neurons in the substantia nigra pars compacta. Patients with PD show a significant decrease in Zn^{2+} levels compared to control subjects [56]. Oxidative stress is implicated as a major causative factor for PD. However, oxidative stress is hard to separate from other facets of the degenerative processes, including mitochondrial dysfunction, excitotoxicity, nitric oxide toxicity and inflammation [57]. Intriguingly, altered production of nitric oxide is thought to directly influence Zn^{2+} levels. Moreover, in a *Drosophila* PD disease model, Zn^{2+} supplementation greatly improves the phenotype of the flies [58].

Pick's disease is a relatively rare form of dementia. Similar to AD and PD, Pick's disease is marked by the accumulation of randomly oriented filaments of tau proteins called "Pick bodies". However, these Pick bodies differ markedly from neurofibrillary tangles associated with Alzheimer's disease [59]. Pick's disease eventually leads to the gradual shrinking of brain cells and is associated with changes in personality, including socially inappropriate behavior, poor decision-making skills and eventually a decline in memory as well as ability to speak coherently. Postmortem studies of patients with Pick's disease revealed that the hippocampus had higher levels of atomic zinc, as well as stronger Timm's staining – a method that detects Zn^{2+} and heavy metals [60], as compared to control or Alzheimer's disease (AD) patients [30, 61]. Moreover, Pick's disease patients have increased Zn^{2+} levels in blood cells and urine. Thus, in contrast to AD and PD, an excess of Zn^{2+} might contribute to the pathogenesis of Pick's disease.

2.2. Depression

A correlation between Zn^{2+} deficiency and clinical depression has been demonstrated in both clinical studies and in animal models [17, 18]. Clinical depression is often accompanied by lower serum Zn^{2+} concentrations [19, 20, 62] and Zn^{2+} deficiency is able to cause depression- and anxiety-like behaviors in humans, whereas Zn^{2+} supplementation has been used to treat depression. Intriguingly, a correlation between Zn^{2+} deficiency and severity of depression has also been shown, such that patients suffering from major depression had significantly lower serum Zn^{2+} levels than non-depressed controls. Furthermore, patients with minor depression had intermediate levels of Zn^{2+} [63]. In a group of depressed female students, serum Zn^{2+} levels were inversely correlated with depression severity [64]. Moreover, severity of depressive symptoms and decreased serum Zn^{2+} concentration were also correlated in women with postpartum depression [65]. Intriguingly, very low doses of Zn^{2+} administered together with very low, otherwise ineffective doses of the antidepressant drugs imipramine or citalopram, enhanced their antidepressant-like effect [66, 67]. Additionally, dietary Zn^{2+} supplementation was shown to be potentially effective in reducing anger and depression based on the evaluation with the Profile of Moods State (POMS) in a group of women who underwent Zn^{2+} supplementation [68].

2.3. ADHD and Schizophrenia

Attention deficit and hyperactivity disorder (ADHD) is, characterized by attention - problems and hyperactivity, with symptoms presenting usually before seven years of age [14]. Although there are many theories about the possible causes of ADHD, one of the

prevalent theories involves impaired dopaminergic signaling. This is supported by the observation of beneficial effects found in patients treated with dopamine agonists like methylphenidate or amphetamines [14]. Intriguingly, many children with ADHD have lower Zn^{2+} levels compared to healthy children [16]. Moreover, Zn^{2+} supplementation, combined with methylphenidate, had favorable affects on the treatment of children with ADHD. Although a dysregulation of brain Zn^{2+}-levels might not be a direct underlying cause of ADHD, the effects of Zn^{2+} supplementation as an ADHD therapy are currently being explored in ADHD children with low plasma Zn^{2+} concentrations.

Schizophrenia is a chronic psychiatric disorder characterized by a disruption in cognition and behavior that is likely caused by a combination of genetic and environmental factors that are not yet understood. In 1973, McLardy observed a 30% deficit of brain Zn^{2+} content in individuals with early onset schizophrenia [69]. Since then, other researchers have obtained similar results from postmortem patient brains showing dramatic decreases in hippocampal Zn^{2+} with up to a 50% reduction in schizophrenic patients [70].

2.4. Epilepsy

Zinc ions appear to play an ambiguous role in epilepsy. There is good reason to believe that excessive intracellular Zn^{2+} contributes to neurodegeneration [25] and that Zn^{2+} entry into neurons is facilitated by synaptic activity and mediates the selective neuronal cell death that occurs following global ischemic insults or prolonged seizures [47]. Indeed, some researchers have noted an increase in brain Zn^{2+} levels following a seizure in rats and mice. However, the contribution of Zn^{2+} to the etiology and manifestation of epileptic seizures is less clear [71]. Zn^{2+} can influence neuronal transmission by multiple mechanisms, such that Zn^{2+} may act to attenuate the GABA response, thereby eliciting hyperexcitability in neurons and ultimately triggering a seizure. Conversely, Zn^{2+} may also act as an inhibitory neurotransmitter decreasing voltage-dependent potassium currents and excitatory neurotransmitter release [72] increasing the likelihood of a seizure [73]. Additionally, intracellular modulatory affects of Zn^{2+} are likely to occur [74]. Not surprisingly, Zn^{2+} has been reported to have proconvulsant [75] as well as anticonvulsant [76] affects, such that seizure susceptibility is decreased by dietary Zn^{2+} supplementation in an epilepsy mouse model, and conversely increased by dietary Zn^{2+} deficiency [77]. Since these mice exhibit significant decreases in Zn^{2+} concentration within the hippocampal dentate gyrus [78], a role for Zn^{2+} dysregulation in the pathophysiology of convulsive seizures was suggested. However, systemic Zn^{2+} supplementation or depletion might lead to brain Zn^{2+} levels that are hard to predict and control, adversely affecting areas outside the seizure foci. Recent studies have elegantly used Zn^{2+} infusion into the hippocampus, hinting towards an anticonvulsant affect of Zn^{2+} in epilepsy [79]. This conclusion is consistent with studies showing that ZnT3 knockout-mice [80] and mice on a Zn^{2+}-deficient diet [81,82] were more susceptible to kainic acid induced seizures. Taken together, a connection between Zn^{2+} and seizures is highly probable, though only a minority of studies suggests a proconvulsant effect of Zn^{2+}. Clearly, additional studies are necessary to tease apart the apparent contradictions.

3. Zn^{2+} DEPLETION FROM AND DELIVERY TO THE BRAIN

3.1. Beneficial Effects of Zn^{2+} Supplementation

Several studies reported beneficial effects of Zn^{2+} supplementation in the treatment of neurodegeneration. Moreover, Zn^{2+} has been successfully employed to treat specific types of schizophrenia and Wilson's disease, a disease characterized by psychosis and hallucinations caused by Cu^{2+} overload [83]. A Zn^{2+} supplement called "Ziman drops" (10% zinc sulfate with 0.5% manganese chloride) was administered to patients suffering

from schizophrenia who had low serum Zn^{2+}-levels [13]. Subsequent studies showed that along with normalizing biochemical abnormalities, the patients demonstrated significant mental and physical improvements [13]. Moreover, Zn^{2+} administration improved the efficacy of antidepressant drugs in depressed patients [84, 85]. Thus, Zn^{2+} supplementation may be important in the treatment of depression [86–91]. Furthermore, individuals with ADHD receiving a dose of 55 mg zinc sulfate per day, which is equivalent to 15 mg Zn^{2+}, in addition to methylphenidate showed beneficial effects of Zn^{2+} supplementation, confirming the role of Zn^{2+} deficiency in the etiopathogenesis of ADHD [15]. However, 15 mg zinc per day is higher than the Recommended Dietary Allowance (RDA) for zinc, thereby raising the question of how much Zn^{2+} is needed to obtain beneficial affects in the treatment of psychiatric and neurodegenerative disorders. Moreover, although systemic Zn^{2+} supplementation was shown to have beneficial effects in the past, there is a fundamental flaw in the approach of dietary Zn^{2+} supplementation. Since the brain is protected from excessive Zn^{2+} and Zn^{2+} uptake into the brain is highly regulated (see discussion below), only patients with a preexisting Zn^{2+} deficiency might benefit from dietary Zn^{2+} supplementation. Thus, the Zn^{2+} status of patients needs to be evaluated if Zn^{2+} delivery into the brain by dietary supplementation is to become an effective therapeutic strategy. Although Zn^{2+} deficiency in humans is generally uncommon, elderly populations often consume insufficient amounts of Zn^{2+} [92], perhaps acting as a modifying factor in neurodegenerative diseases like Alzheimer's and Parkinson's.

3.2. Measurement of Zn^{2+} Levels

The most common approach for assessing Zn^{2+} levels is measuring serum or plasma Zn^{2+}. In humans Zn^{2+} can be found in concentrations of 11 – 23 μM in blood [93] and 0.15 μM in cerebrospinal fluid [4]. Normal plasma concentrations range from about 80 to 120 μg/dL, whereas Zn^{2+} deficiency concentrations are less then 70 μg/dL. Additionally, Metallothionein levels in erythrocytes can be a useful index to measure the Zn^{2+} status in humans [94]. However, measuring serum Zn^{2+} levels does not reveal slight and/or temporally fluctuating alterations in extra- and/or intracellular Zn^{2+} levels in discrete brain areas. This might be a reason for some contradictory results in Zn^{2+} research in the past. For example, determining Zn^{2+} levels in the CSF from the area of abnormality (e.g., seizure focus) during neurosurgery might be a better approach, although it is seldom pursued. Thus, not only a controlled and region specific targeted Zn^{2+} delivery or depletion is desirable, but also a region specific evaluation of existing steady state Zn^{2+} levels.

3.3. Regulation of Zn^{2+} Levels

Several paradigms exist for inducing Zn^{2+} deficiency or supplementing Zn^{2+} in animal models like mice and rats. Zn^{2+} deficiency is usually caused by a dietary Zn^{2+} restriction. While control mice and rats are normally fed diets containing between 25 mg kg and 80 mg/kg Zn^{2+}[95–101], Zn^{2+} deficiency is caused when the diet contains 0.5 mg/kg – 6 mg/kg Zn^{2+} [95, 99, 101]. Zn^{2+} overdoses can be reached at 100 mg/kg – 180 mg/kg [96, 97]. However, though Zn^{2+} overdoses might elevate serum Zn^{2+} levels, this doesn't necessarily lead to elevated brain Zn^{2+} levels in healthy control animals. This is likely a consequence of reduced absorption of Zn^{2+} at higher doses that might occur due to the saturation of Zn^{2+} transport mechanisms [102]. Nonetheless, dietary Zn^{2+} supplementation is considered a treatment in Zn^{2+} deficient rats/mice. Another common method for Zn^{2+} supplementation is tap water, where usually doses between 75 mg to 132 mg $ZnSO_4$ per L water are used [55]. The daily water intake by a 470 g rat is approximately 35 ml/day [103]. Intraperitoneal injection of zinc is used as an additional method in numerous studies, with injections between 3 mg/kg body weight/day – 10 mg/kg/day [95, 104, 105]. Zn^{2+} deficiency early in life can be induced by a Zn^{2+} deficient diet of pregnant animals. For example, female rats

shifted to a Zn^{2+} deficient diet (0.5 mg Zn /kg diet) at day 19 of pregnancy will result in pups being fed Zn^{2+} deficient milk during lactation [106].

The time course of treatment highly depends on the research objective, as a consequence both, acute and chronic treatments have been used. Moreover, Zn^{2+} supplementation and deficiency manifest at different rates in different tissues. Intriguingly, in fasted rats, a single dose of Zn^{2+} containing the daily amount of Zn^{2+} intake led to a rise in plasma Zn^{2+} levels within an hour and a half [107]. However, plasma Zn^{2+} levels and brain Zn^{2+} levels might not directly correlate, for example, hippocampal mossy fiber Zn^{2+} levels were reduced in rats fed a Zn^{2+} deficient diet, but only after 90 days of treatment, not 28 days [108]. The average total brain Zn^{2+} concentration is approximately 150 mmol/l, which is about 10-fold serum Zn^{2+} levels [108]. However, the pool of free Zn^{2+} ions, with about 500 nmol/l in brain extracellular fluids, is very low [110]. Nevertheless, in general, brain Zn^{2+}-levels can be affected by altering dietary Zn^{2+} concentrations [108].

Based on several studies [95, 96, 98, 99, 105, 111–116], we calculated the change in Zn^{2+} levels based on measurements of serum and hepatic Zn^{2+} levels in rats treated for 28–42 days with dietary zinc deficiency versus Zn^{2+} supplementation. Our results revealed a steep increase in serum Zn^{2+} levels that can be observed in response to very low levels of dietary Zn^{2+} (0.57% dietary Zn^{2+} compared to controls with 21.9% serum Zn^{2+} levels and 6.8% dietary Zn^{2+} compared to controls with 70% serum Zn^{2+} levels of control animals) and milder Zn^{2+} deficiency (20% dietary Zn^{2+} compared to controls with 88% serum Zn^{2+} levels of control animals) Fig. (1A). However, at dietary Zn^{2+} levels between 20% and 100% compared to controls, the rate of increase in serum Zn^{2+} levels is much lower. Zn^{2+} supplementation, at 2-fold and 4-fold dietary Zn^{2+} concentrations, increases serum Zn^{2+} levels approximately 25% Fig. (1A). However, toxic side effects and the saturation of Zn^{2+} uptake mechanisms appear to set limits on further increases as seen when dietary Zn^{2+} is increased 6-fold. Here, only a 10% increase in serum Zn^{2+} levels is observed compared to controls. The dietary Zn^{2+} concentration in relation to serum Zn^{2+} levels in rats after 6 weeks of treatment again shows a steeper increase in serum Zn^{2+} concentration between 0.6 and 6 mg Zn /kg diet compared to higher dietary Zn^{2+} levels Fig. (1B).

Regarding treatment of human patients and the validity of animal models, one can calculate that Zn^{2+} supplementation between 70 mg/kg diet – 90 mg/kg diet is at the lower end of Zn^{2+} doses used for Zn^{2+} supplementation in many studies and translates to a human supplementation of 25 mg – 100 mg zinc per day for a 70 kg individual [103]. With a daily recommendation of about 11 mg and an absorption of 20 – 40% of zinc, these doses are within the same range as those used for Zn^{2+} supplementation in many commercial preparations [103] ranging from 15–100 mg zinc per tablet with a recommendation of 1 tablet per day. Since serum levels of less then 70 μg/dL suggest Zn^{2+} deficiency and serum Zn^{2+} levels of animal fed on Zn^{2+} deficient diet reached approximately 50 μg/dL in studies with very low levels of dietary Zn^{2+}, mouse and rat animal models indeed reflect Zn^{2+} deficient states of humans. However, systemic Zn^{2+} supplementation or induced deficiency affects the whole body and local brain Zn^{2+} levels poorly reflect measured serum Zn^{2+} concentrations. This is a disadvantage to many studies on the function of Zn^{2+} within the central nervous system, besides other impediments.

4. IMPEDIMENTS TO Zn^{2+} DELIVERY INTO THE BRAIN

The daily zinc requirements for adult men and women were set at 9.4 mg and 6.8 mg, respectively, while 11 mg and 8 mg were set at RDAs, respectively [117]. This amount can be easily reached by dietary Zn^{2+} supplementation. The rate of absorption can be additionally increased if the Zn^{2+} supplement is taken along with vitamin B6 [118].

Specifically, 71% of dietary zinc was absorbed when rats were given 40 mg of vitamin B6 per kilogram of diet [112] compared to 46% with only 2 mg vitamin B6. Zn^{2+} excess appears to have almost no brain toxicity, although patients show some significant somatic effects [119, 120]. In rats fed 100 mg of zinc oxide (via gastric tube), Zn^{2+} has very little toxicity in the brain [121, 122, 13]. In humans, even massive zinc ingestion (12 grams over 2 days) was reported to produce only reversible lethargy [123] in terms of neurological symptoms. One explanation for this might be that the mammalian brain is protected from systemic factors by the blood-brain barrier (BBB). The BBB is comprised by a layer of specialized endothelial cells [124] and Zn^{2+} enters the brain at a constant rate when within the range of plasma Zn^{2+} concentrations occurring in healthy individuals. However, outside this range, the Zn^{2+} transport rate is significantly altered [125]. Unfortunately, many drugs are unable to cross the BBB [126]. The transmissivity of this epithelial structure is restricted by the presence of tight junctions, connecting the cerebral endothelial and epithelial cells of the choroids plexus. Moreover, glial cells found surrounding the surface of these capillaries cohere the endothelial cells, producing high electrical resistance compared to other systemic endothelia [127]. Studies of sodium and potassium transport by brain capillaries revealed that endothelial cells of the BBB contain distinct types of ion transport systems on the two sides of the capillary wall. This allows ions to be pumped across the capillary against an electrochemical gradient [128]. The BBB is highly restrictive for Zn^{2+}, but transport does not require energy [125]. Thus, although the BBB protects the brain from excessive Zn^{2+}, it creates a problem for the regulation of Zn^{2+} brain-levels with dietary Zn^{2+} supplementation, especially if the desired final Zn^{2+} level is higher than physiological levels restricted by BBB permeability. Additionally, the final Zn^{2+} concentration obtained by dietary Zn^{2+} supplementation is hard to predict given that other dietary factors can influence Zn^{2+} absorption. Inositol hexaphosphates and pentaphosphates present in food exert negative effects on Zn^{2+} absorption, as do iron and cadmium if given together in a supplement. Moreover, the amount of protein in a meal influences Zn^{2+} absorption, though some proteins may act differently. A few amino acids, such as histidine and methionine, as well as organic acids (e.g., citrate), have a positive effect on Zn^{2+} absorption and have been used along with Zn^{2+} supplements [102]. Thus, although dietary Zn^{2+} supplementation has been effective in some studies, a method for more targeted and controlled Zn^{2+} release within the brain is desirable.

Once inside the brain, the mechanisms that modulate the free Zn^{2+} pool are key to health and performance. Transition metals such as Zn^{2+} are maintained at low levels because an excess of free Zn^{2+} has been shown to be neurotoxic. 300–600 μM Zn^{2+} for 15 min induces rapid morphological changes in cultured mouse cortical neurons and leads to cell death of virtually all neurons within 24 h [110, 129, 130, 47]. If the concentration of Zn^{2+} is increased to 1 mM, an exposure time as short as 5 min suffices to destroy many cortical neurons [131]. Since Zn^{2+} is a small, hydrophilic, charged ion, which cannot cross biological membranes by passive diffusion, specialized mechanisms are required for its uptake. Indeed, free Zn^{2+} is distributed across the plasma membrane in a large gradient [132]. Maintenance of this electrochemical gradient requires an active transport system. A group of zinc transporter proteins termed “ZnTs” have been characterized as mediators of Zn^{2+} transport. Among these ZnT3 is important for synaptic vesicle Zn^{2+} uptake [80] and ZnT1, widely distributed throughout the brain, is associated with Zn^{2+} efflux [133, 134]. However, Zn^{2+} also readily enters neurons via glutamate receptors and voltage gated Ca^{2+} channels [132], consequently membrane depolarization substantially enhances the ability of Zn^{2+} to kill neurons [135].

Once inside the cell, a number of conserved proteins are known to bind Zn^{2+}, among them metallothioneins [136, 137], but several other proteins actively buffer Zn^{2+}, including glutathione. Approximately 90% of the total brain Zn^{2+} is bound to endogenous proteins [4].

This binding is reversible, and recent studies have shown that Zn^{2+} is released from metallothioneins in response to nitric oxide (NO) [138] and oxidized glutathione (GSSG). Thus, these intracellular Zn^{2+} stores might be interesting targets for new drug development.

The intracellular bound Zn^{2+} influences many cellular functions and pathways. An astonishing number (over 300) of enzymes require Zn^{2+} for their functions [46] and Zn^{2+} has catalytic, coactive (or cocatalytic) and structural [139, 140] importance. Taken together, Zn^{2+} ions play important roles in regulating biological functions including the activity of transcriptional factors, oxidative stress response, DNA repair and DNA transcription. In the CNS, Zn^{2+} has been additionally found to influence NMDAR mediated signaling [141] and might even mediate higher cognitive functions such as learning and memory and plasticity of emotional networks [41, 142, 143]. Depending on a variety of factors, including protein turnover and Zn^{2+} binding affinity, Zn^{2+} deficiency most likely affects some Zn^{2+} dependent processes more than others, and thus Zn^{2+} deficiency versus Zn^{2+} supplementation will have several outcomes that have to be carefully monitored.

Despite most studies aiming to influence the function of neurons by Zn^{2+} deficiency and supplementation, glial cells might play a modifying role. Little is known about the uptake of Zn^{2+} in glial cells. However, prolonged exposure to high concentrations of free Zn^{2+} causes glial cell death. These cells express ZnT1 transporters and metallothioneins. For future studies on the contribution of glial cells to Zn^{2+} homeostasis within the brain, a mechanism to trigger Zn^{2+} increase in neurons versus glial cells would be desirable.

5. METHODS AND COMPOUNDS SUITABLE FOR REGULATION OF BRAIN Zn^{2+}-LEVELS

5.1. Dietary Zinc Supplementation

Dietary Zn^{2+} supplementation has been the method of choice for years and has been widely used. Zinc can be administered in the form of oral tablets, lozenges or sprays. Common compounds used for Zn^{2+} supplementation include zinc oxide, zinc sulfate, zinc acetate, zinc chloride and zinc gluconate. However, these compounds differ in the amount of Zn^{2+} provided as well as in absorption properties. Zinc oxide for example has 78% Zn but is poorly absorbed [144], Zinc carbonate has 52.1%, zinc chloride 48%, sulfate monohydrate 36.4% and zinc gluconate has only 14.3% Zn. While zinc chloride, zinc sulfate and zinc acetate are all very soluble, zinc carbonate and zinc oxide are fairly insoluble. The tolerable maximum intake level for zinc has been set at 40 mg daily, which is mostly restricted by side effects caused by the resulting copper deficiency [145]. Gastric irritation is another common side effect. Zinc acetate is one of the best-tolerated Zn^{2+} preparations by the digestive system. All Zn^{2+} supplements should be taken on empty stomach, without simultaneously consummation of other mineral supplements. The main site of absorption of Zn^{2+} found in dietary supplements is the proximal small intestine, most likely the jejunum. Zn^{2+} is absorbed into enterocytes by carrier - mediated processes. Several endogenous substances are thought to serve as ligands for Zn^{2+} that can enhance absorption. Such substances include citric acid, picolinic acid, prostaglandins and amino acids like histidine and cysteine [146]. Glutathione may also serve as ligand. Amino acid ligands help to maintain the solubility of Zn^{2+} in the gastrointestinal tract. Once absorbed, Zn^{2+} passes into portal blood and is transported while loosely bound to albumin or immunoglobulin G until it reaches the BBB [146]. However, uptake through the BBB is mediated by an active transportation-process and therefore final Zn^{2+} concentrations reached in the brain are hard to control or predict. This is the major disadvantage of dietary Zn^{2+} supplementation and future studies will have to consider alternative ways of Zn^{2+} delivery to the brain. Unfortunately, to date, no drug that selectively increases brain Zn^{2+}-levels is available.

However, a study by Czerniak and Haim revealed that phenothiazine derivatives like chlorpromazine, thioridazine and perphenazine are able to increase the total brain Zn^{2+} uptake in Zn^{2+} supplemented rats and mice [147]. Interestingly, dietary Zn^{2+} supplemented with L-histidine improved short-term memory function in Zn^{2+} deficient animals more efficiently than dietary Zn^{2+} chloride supplementation alone [148]. Histidine may be involved in Zn^{2+} transport across the BBB and mediate Zn^{2+} increase by binding to Zn^{2+} from plasma proteins [149]. Furthermore N-acetyl cysteine, a FDA approved precursor of glutathione might increase glutathione levels [150]. Glutathione together with glutathione disulfide enhances delivery of Zn^{2+} to cells.

5.2. Alternative Ways of Zinc Supplementation

For a more targeted Zn^{2+} delivery to the brain, systemic Zn^{2+} supplementation by dietary application is an inadequate method. Alternative methods can achieve Zn^{2+} level regulation by intracranial delivery of therapeutic compounds via implanted cannulas, devices or drug-releasing polymers. A recent study used Alzet® pumps implanted in rat brains, releasing up to 1 mM $ZnCl_2$, at a rate of 0.25 μl/h continuously into the hippocampal hilus for 4 weeks [79]. Furthermore, guide cannulae can be implanted bilaterally into the dorsal hippocampus or lateral ventricle to deliver Zn^{2+} or Zn^{2+} chelators [151]. Another strategy for a more targeted Zn^{2+} delivery is intralumbar injection or of Zn^{2+}-supplements directly into the cerebrospinal fluid (CSF). Thus, immediate high CSF drug concentrations can be reached. The CSF freely exchanges molecules with the extracellular fluid of the brain parenchyma [152]. However, this delivery method faces some difficulties like slow rate of substance distribution within the CSF and increased intracranial pressure [152]. Although these techniques are available, they are unfortunately seldom used in the field of Zn^{2+} supplementation.

Recently, novel nanoparticulate systems were developed that might be used to deliver Zn^{2+} ions through the BBB and thus directly into the brain [130]. This approach dramatically improves control of desired Zn^{2+} concentration in the brain and makes it possible to increase Zn^{2+} levels above those restricted by physiological BBB uptake. Nanoparticle injection is a non-invasive method for drug delivery to the CNS that has a high rate of efficiency (13–15% of the injected dose) [153]. Nanoparticulate drug carriers made of Polylactide-co-glycolide (PLGA) or polylactide (PLA) polymers are biodegradable, biocompatible and FDA-approved. They can be specifically modified with ligands and have been demonstrated to cross the BBB, thereby representing an important tool for future treatment of neurological diseases [154]. Moreover, nanoparticles can be targeted to specific antigen-representing cells, which are subsequently taken up by these cells [130]. Once endocytosed, these nanoparticles were found to degrade constantly over time releasing their content into the cell soma. This strategy thus provides a new opportunity to delivery Zn^{2+} to specific cells within the brain, though their usefulness *in vivo* has yet to be proven. Nanoparticles themselves are not toxic to cells *in vitro*, even at concentrations higher than those used for delivering Zn^{2+} [130] in *in vitro* studies. Thus, the properties of these Zn^{2+} loaded Nanoparticles should provide a new therapeutic strategy for altering Zn^{2+} levels in patients with neuropsychological disorders.

5.3. Zn^{2+} Chelation

Recent studies have focused on the treatment of patients with metal chelating drugs [155–157]. Therapeutic benefits from chelation of Zn^{2+} ions might result from an impairment of their ability to mediate protein folding, clustering or a reduction of redox processes. Brain delivery of Zn^{2+} chelators can be achieved by oral ingestion or by intravenous infusions, i.e. of EDTA, as some Zn^{2+} chelators can directly penetrate cell membranes or be enticed to do so by esterification or by acquisition of a nonpolar state following complex formation with

metals [158]. For example, the zinc-binding 5-chloro-7-iodo-8-hydroxyquinoline (clioquinol) is a chelator that is able to cross the BBB when given at doses of up to 80 mg/day to patients [159]. It also markedly reduced synaptic targeting of Aβ oligomers [160]. PBT2, a derivative of clioquinol, is currently under investigation as a potential treatment for AD. Similarly, it was shown that N,N,N′,N′-tetrakis-(2-pyridylmethyl)-ethylenediamine (TPEN) and bathocuproine disulfonic acid (BC) are able to dissolve Aβ deposits in postmortem AD brain samples [161]. However current research hints to a higher toxicity of fibrillary Aβ compared to Aβ plaques. Thus, a major application for Zn^{2+} chelators like pyrithione, inositol hexakisphosphate and CaEDTA might be after traumatic brain injury and seizures, where chelation of excessive neuronal Zn^{2+} might decrease neurotoxicity [162]. However, CaEDTA is cell impermeable and studies by Lavoie *et al.* suggest that only intracellular but not extracellular Zn^{2+} chelators might influence seizure-induced Zn^{2+} accumulation [74].

The use of Zn^{2+} chelators in general is experiencing difficulties. Although there are high affinity Zn^{2+} chelators available, all Zn^{2+} chelators show additional affinity for copper ions and less for calcium and magnesium ions. Thus, side effects caused by the chelation of other important divalent metal ions in the brain and body tissues are unavoidable. Thus, similar to Zn^{2+} supplementation, a controlled release within specific brain areas is highly desired.

6. CONCLUSIONS

Based on the studies presented above, Zn^{2+} deficiency is surprisingly prevalent in patients with psychiatric and neurodegenerative disorders. However, in most cases, the mechanisms that lead to the decrease in Zn^{2+} levels remain elusive. Moreover, it is likely that the observed deficiencies do not share a common pathway and might occur in discrete brain areas. Unfortunately, most findings in Zn^{2+} research are based on the measurement of serum Zn^{2+} levels that are inefficient to detect slight and/or temporally fluctuations of Zn^{2+} in specific brain areas and more sensitive and direct approaches to detect brain Zn^{2+} levels should be considered for future studies. Thus, it is hard to predict how the brain responds to systemic Zn^{2+} supplementation on a cellular level in each clinical case discussed above.

Moreover, dietary Zn^{2+} supplementation might only be useful in restoring Zn^{2+} levels to those of control subjects. Thus it might not be effective if Zn^{2+} levels within specific brain regions are impaired due to shifts of zinc ions between different pools: i.e. aberrant proteins with Zn^{2+} binding sites. Clearly, the evaluation of Zn^{2+} levels in patients will be necessary to assess the possibility of Zn^{2+} delivery to the brain. Importantly, it is not entirely impossible that at least some of the studies in Zn^{2+} brain-research have been poorly designed and analyzed, creating ambiguous results. However, new methods like implanted osmotic pumps or BBB crossing nanoparticle carriers might allow researchers to increase brain Zn^{2+} above levels restricted by BBB uptake and help to evaluate existing data and the often contradictory results in the light of a more directed approach of brain Zn^{2+}-level regulation.

Although Zn^{2+} supplementation has been shown to be useful on its own, a combination of drug treatment with Zn^{2+} supplementation might be more promising. Zn^{2+} chelation on the other hand should only be considered in cases where toxic Zn^{2+} brain-levels are expected to cause cell death. In Alzheimer´s disease for example, restoring Zn^{2+} balance in a narrow range might lead to beneficial effects. While Zn^{2+} chelators will dissolve Aβ plaques, they might create more toxic protofibrillary Aβ and cause memory problems on their own. Zn^{2+} supplementation however might face difficulties in early stages of the disease since Zn^{2+} ions shift from synaptic stores towards Aβ, but are not depleted from the brain. Only in late stages of Alzheimer's disease, the demand of Aβ for Zn^{2+} ions might generate a measurable

Zn^{2+} deficiency. Although this deficiency might be compensated by Zn^{2+} supplementation, one should be cautious to supplement only equimolar amounts of Zn^{2+} to the loss caused from uptake by Aβ since higher Zn^{2+}-levels might promote surplus generation of Aβ. Thus, controlled and region specific targeted Zn^{2+} delivery to the brain is highly desirable and will be an important goal in future research for drug delivery to the brain.

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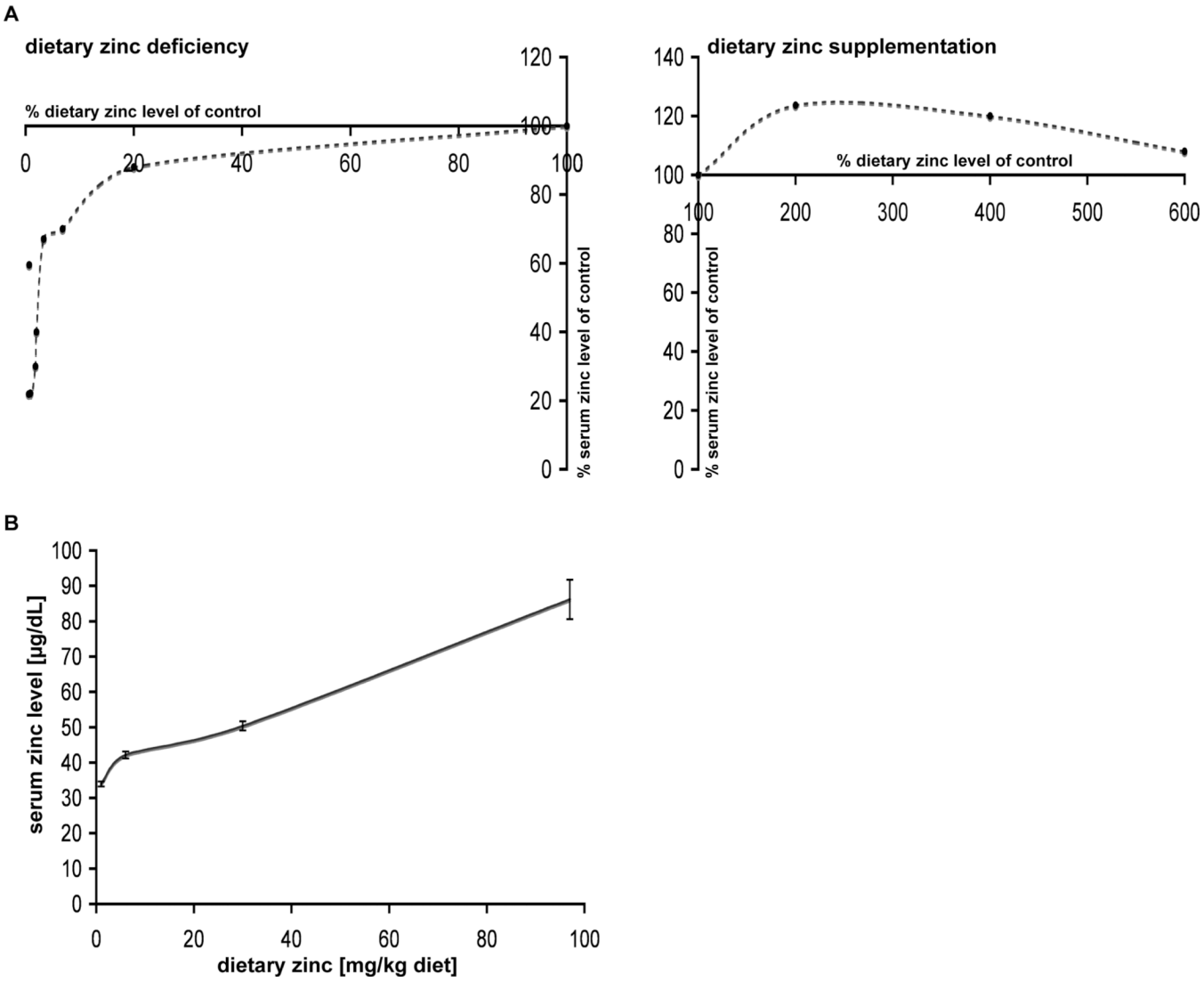

Fig. (1).

Dietary zinc-concentration dependent increase or decrease in serum Zn^{2+} levels. **A**) Changes in serum Zn^{2+} levels induced by dietary zinc deficiency (left panel) or zinc supplementation (right panel) are calculated based on several studies (14–16,18, 22–28). Left panel: A steep increase in serum Zn^{2+} levels can be observed between very low levels of dietary Zn^{2+} and milder Zn^{2+} deficiency. In contrast, between 20% and 100% of dietary zinc compared to controls, the rate of increase in serum Zn^{2+} levels is much lower. Right panel: Zn^{2+} supplementation with 2-fold, 4-fold and 6-fold dietary zinc increases Zn^{2+} levels approximately 25% (2-fold and 4-fold) and decreases slightly with 6-fold (only 10% increase in serum Zn^{2+} levels compared to controls). **B**) Based on several studies, the dietary zinc concentration in relation to serum Zn^{2+} levels in rats after 6 weeks of treatment is shown. Between 0.6 and 6 mg Zinc/kg diet a steeper increase in serum Zn^{2+} concentration is seen.