Chapter 2

Zinc Deficiency

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Additional information is available at the end of the chapter

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Abstract

Zinc is an essential trace element for humans and plays a critical role both as a structural component of proteins and as a cofactor in about 300 enzymes. Zinc deficiency was, for example, reported to affect the immune response and the endocrine system and to induce and modify brain disorders. Besides hereditary zinc deficiency, zinc deficiency – at least in mild forms – is nowadays a very abundant health issue. Today, an estimated 20% of the population worldwide is at risk of developing zinc deficiency with a high number also in industrialized countries. The major risk factors to develop zinc deficiency in industrialized nations are aging and pregnancy. Mechanistic and behavioral studies on the effects of zinc deficiency have mainly been performed using animal models. However, in combination with the few studies on human subjects, a picture emerges that shows importance of adequate nutritional zinc supply for many processes in the body. Especially the immune system and brain development and function seem to be highly sensitive to zinc deficiency. Here, we provide an overview on the effects of zinc deficiency on different organ systems, biological processes, and the associations of zinc deficiency with pathologies observed in humans and animal models.

Keywords: Zn, immune system, brain, homeostasis, synapse, biometal, trace metal, zincergic

1. Introduction

In 1933, zinc was reported for the first time to be essential for the growth of rats. Thirty years later, the first studies in human subjects from the Middle East showed that this was also true for humans [1,2]. To date, many studies have been performed investigating the influence of zinc deficiency on human well-being and mental performance.

While zinc deficiency is commonly caused by dietary factors, several inherited defects of zinc deficiency have been identified. Among them, *Acrodermatitis enteropathica* (AE) is the most common form of inherited zinc deficiency in humans [3]. Inherited AE is an autosomal recessive disorder where in many of the cases mutations in hZIP4 (a member of the SLC39 gene family encoding a membrane-bound zinc transporter) are found [4]. Mutations in other members of this family or in different zinc homeostasis genes may account for other cases of AE in the absence of hZIP4 mutations [5]. Clinically, AE is characterized by impaired intestinal zinc absorption, resulting in a triad of symptoms: dermatitis, alopecia, and gastrointestinal (GI) problems such as intractable diarrhea. However, neuropsychological disturbances such as mental depression, irritability, loss of appetite, behavioral problems, and reduced immune function frequently occur.

The body of an adult human (70 kg) contains about 2–3 g of zinc, which is absorbed from our dietary sources in the proximal small intestine, either the distal duodenum or proximal jejunum [6,7], and released from there into the blood. However, the supply of zinc by our diet is dependent on its amount and bioavailability. It has been estimated that in a western mixed diet, this bioavailability is about 20–30% of total contained zinc [8]. Various agents can decrease zinc absorption [9]; among them are phytates [10,11] and other metals such as copper and, to a lesser extent, calcium and iron [12–15]. Based on average bioavailability, the recommended daily intakes of zinc range from 10 to 15 mg in adults but may be higher under certain circumstances, such as pregnancy and during lactation, where an extra 5–10 mg may be required.

Within the body, two pools of zinc were identified. The majority of zinc (about 90%) is relatively slowly exchanged with the blood plasma and, for example, concentrated in the bones. The remaining 10% of zinc however is rapidly exchanged and it is this pool of zinc that needs daily replenishment and that is therefore especially reactive to the amount of zinc absorbed in the GI system. Exchange of zinc across membranes is mediated by two solute-linked carrier (SLC) families, the SLC30A (ZnT-1 to ZnT-10) and the SLC39A (Zrt, Irt-like protein ZIP1 to ZIP14) family. These transporters show tissue-specific expression and localize to distinct subcellular compartments, where, in general, ZnT proteins transport zinc out of the cytosol and Zip proteins move zinc into the cytosol.

Unfortunately, the clinical diagnosis of a zinc deficiency in humans currently faces major limitations [16]. Although measuring zinc concentrations in blood plasma or serum is currently the most commonly used method, this provides only a snapshot of the zinc status of an individual, and given that serum zinc concentrations may fluctuate by as much as 20% during a day [17], a single blood drawing has low validity. Alternatively, assessment of zinc levels in hair or nail samples might be a preferable method as an average of zinc levels over a longer period of hair or nail growth will be evaluated. The lack of generally accepted biomarkers of zinc status complicates the assessment of zinc deficiency. Thus, zinc deficiency in humans is probably commonly overlooked, especially if only mild or transient and the exact prevalence is currently unknown [18]. In addition, the symptoms of mild zinc deficiency are much less dramatic and more diffuse than those observed in AE. Mild zinc deficiency, for example, might

not cause typical skin lesions. Nevertheless, current estimates are that about 17.3% of the global population is at risk of developing zinc deficiency [19].

Given this relatively high number of potentially affected individuals, in the following, on the background of nutritional deficiencies, we will provide a more detailed discussion of the role of zinc in the body and its association with specific pathologies.

2. The role of zinc in the body

2.1. Zinc and the endocrine system

The endocrine system is comprised of a number of glands in the body and includes the ovaries, the testes, and the thyroid, parathyroid, adrenal, and pituitary glands. Further, the pineal body, the pancreas, and specific cells releasing hormones in the GI tract, kidney, heart, and placenta are part of this system. Zinc has manifold influences on the endocrine system (**Figure 1**). Among them, a role in the metabolism of androgen hormones, estrogen, and progesterone, together with the prostaglandins, a role in the secretion of insulin, and a role in the regulation of thymic hormones have been reported.

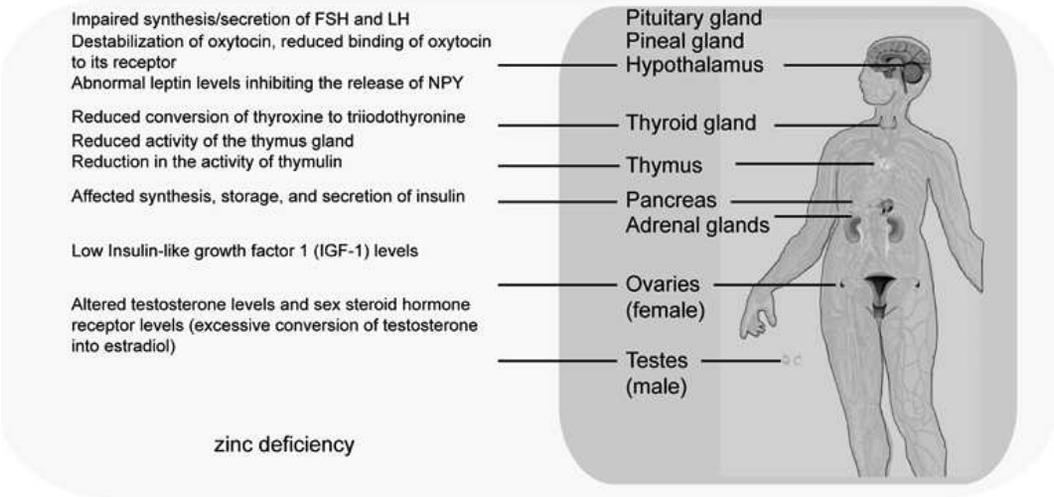

Figure 1. Overview of the major effects of zinc deficiency on the endocrine system. FSH, follicle-stimulating hormone; LH, luteinizing hormone; NPY, neuropeptide Y.

An involvement of zinc in the regulation of sex hormones in males and females can be concluded indirectly, as zinc deficiency in pregnancy is associated with disruption of the estrous cycle, frequent spontaneous abortion, extended pregnancy or prematurity, inefficient labor, and atonic bleeding [20,21]. On a molecular level, zinc deficiency in the female can lead to impaired synthesis/secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Moreover, the nuclear receptors for sex steroids contain zinc finger motifs in their protein structure that might explain zinc dependency of these hormonal systems. In addition, zinc deficiency alters testosterone levels and modifies sex steroid hormone receptor levels [22].

Zinc deficiency affects the enzyme complex aromatase that is normally inhibited by zinc. The increased activation results in an excessive conversion of testosterone into estradiol. Further, zinc deficiency and the depletion of testosterone result in an inhibition of spermatogenesis [23] in males.

Hypogonadism is a major manifestation of zinc deficiency. Although steroids might play a role, it was speculated that the hypogonadism is due to a hypothalamic dysfunction and associated with low insulin-like growth factor 1 (IGF-1) levels. Testicular development can be rescued by zinc supplementation [24].

Zinc also improves the stability of oxytocin, and the stabilization effect is correlated with the ability of the divalent metal to interact with oxytocin. Zinc is essential for the binding of oxytocin to its cellular receptor [25,26].

Zinc plays a key role in the synthesis, storage, and secretion of insulin. Zinc is able to stimulate the action of insulin and insulin receptor tyrosine kinase. A low zinc status has been associated with diabetes (types 1 and 2) [27] and zinc supplementation was reported capable of restoring insulin secretion [28].

In mammals, insulin is synthesized in islets of Langerhans, made of four different cell types in the pancreas. The majority are insulin-producing β cells. There, insulin is stored in a zinc-containing hexameric form. Zinc deficiency can affect the ability of β cells to produce and secrete insulin [29]. ZnT-8 (*SLC30A8*), a specific zinc transporter found localized at insulin secretory granules in β cells, was identified [30,31]. ZnT-8 knockout mice show impaired insulin secretion [32], and *SLC30A8* variants, reducing ZnT-8 activity, increase type 2 diabetes risk in humans [33].

Zinc also plays an important role in the regulation of nutrition. In humans and animals models, marginal zinc deficiency has been shown to result in decreased appetite and low body mass [34], features that can not only be observed in zinc deficiency but also in anorexia nervosa patients [35]. Although the underlying mechanisms are currently not well understood, changes in neurotransmitter concentrations and synaptic transmission at the hypothalamic level might be associated with decreased appetite. Recent studies have also shown a relationship between zinc and leptin [36]. Leptin is a hormonal protein, involved in features such as satiety and energy balance, but was also reported as anti-obesity factor. The major target organ for leptin is the hypothalamus, where leptin controls food intake through its receptors, inhibiting the release of neuropeptide Y (NPY) which has an augmentative effect on food intake [37]. However, leptin also plays a role in immunity [38].

Further, a correlation between zinc deficiency in geriatric patients and reduced activity of the thymus gland and thymic hormones has been reported [39]. Zinc promotes the conversion of thyroid hormones thyroxine to triiodothyronine and zinc deficiency can result in hypothyroidism, a common disorder of the endocrine system characterized by decreased production of thyroid hormone.

Finally, in animal models, zinc deficiency leads to a reduction in the activity of thymulin. Thymulin is a nonapeptide produced by thymic epithelial cells that requires zinc for its

biological activity [40]. Zinc is bound to thymulin in a 1:1 stoichiometry [41], which results in a conformational change generating the active form of thymulin [42]. Thymulin is required for maturation of T-helper cells, leading to a decrease in T-helper 1 (Th(1)) cytokines in zinc deficiency [40]. This last example for a role of zinc in the endocrine system already hints toward its additional involvement in regulatory processes in the immune system. There, zinc ions play a role by binding to specific proteins but also as a second messenger regulating signal transduction in various kinds of immune cells [39].

2.2. Zinc and the immune system

The zinc status of an individual affects the majority of immunological events such as hematopoiesis, immune cell function and survival, humoral immunity, and cytokine secretion [43–45]. This results, for example, in an increased susceptibility to infections with a decreasing zinc status as reported from animal models and human studies [46]. Similarly, in AE, one hallmark symptom is a reduced immune function [47] that is visible through the atrophy of the thymus, functional impairment and reduced numbers of lymphocytes, and increased susceptibility to infections [48]. In contrast, beneficial effects of zinc supplementation have been found regarding the incidence and duration of acute and persistent diarrhea [49–51], incidence of acute lower respiratory infections [52], and duration of the common cold [53].

The immune response can be divided into two major mechanisms: innate and adaptive immunity [54]. Zinc is involved in virtually all aspects of innate and adaptive immunity and it is therefore not surprising that it has been reported that zinc deficiency results in a depressed immune system (**Figure 2**). The effects of zinc on both mechanisms are based on the myriad roles for zinc in basic cellular functions such as DNA replication, RNA transcription, proliferation and differentiation, and immune cell activation.

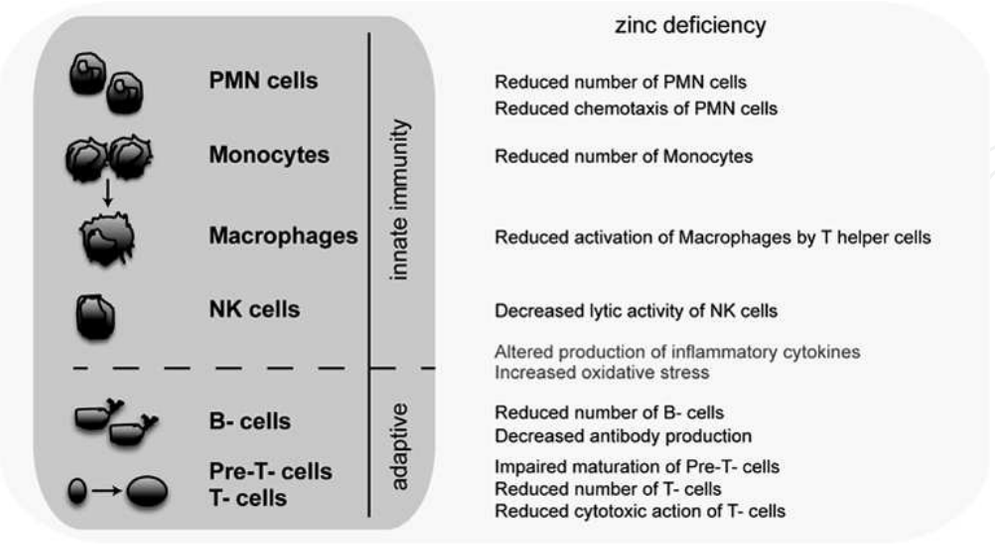

Figure 2. Overview of the major effects of zinc deficiency on the immune system. PMN, polymorphonuclear; NK, natural killer.

Under physiological conditions, the normal response of the body against pathogens is initiated by the activation of the complement system, macrophages, natural killer (NK) cells, and polymorphonuclear (PMN) cells. Under zinc-deficient conditions, all these defending mechanisms are affected [55–58]. For example, PMN are the first cells to actively enter an infected tissue and their chemotaxis is reduced under zinc deficiency [59]. Moreover lytic activity of NK cells is decreased during zinc deficiency.

During the acute phase, profound changes in zinc homeostasis occur, which may serve multiple purposes. For example, altered zinc levels may serve as signaling factor, but zinc redistribution that leads to a decrease in plasma zinc levels might also be used actively by the immune system to attack certain intracellular pathogens. In addition reduced zinc levels lead to a shift of leukopoiesis toward the generation of myeloid cells [44] and reduced extracellular zinc may increase monocyte differentiation [60].

Adaptive immunity is mediated by T and B cells. Zinc deficiency was reported to alter the number and function of neutrophil granulocytes, monocytes, and NK, T, and B cells [39]. In particular, the vulnerability to infections is associated with an impaired T- and B-lymphocyte development and activity [61–63]. T-cell progenitors mature in the thymus and zinc deficiency causes thymic atrophy (see Section 2.1). During maturation, pre-T cells have been reported to be most susceptible to zinc deficiency, which resulted in a loss of up to 50% of these cells in a mouse model [44]. Mature T-helper cells promote the functions of other immune cells. For example, T-helper cells play a role in the activation of macrophages. Cytotoxic T cells, in turn, have a more direct role in the immune response by eliminating virus-infected cells and tumor cells.

In addition, zinc deficiency leads to a reduction of premature and immature B cells and decreases antibody production [64].

Further, zinc plays a role in the inflammatory response and in particular in the termination of this process. Inflammatory processes, in particular sepsis, are associated with major changes in zinc metabolism and homeostasis and accompanied by a redistribution of zinc between tissues. This is underlined by data showing that zinc deficiency leads to aggravated inflammation, increased bacterial burden, organ damage, and mortality in a mouse model of sepsis [65,66]. Similarly, in human patients belonging to a group with elevated risk for zinc deficiency, a high incidence of sepsis has been reported [67].

Zinc is able to downregulate the production of inflammatory cytokines mediated via the NF-kB (nuclear factor "kappa-light-chain enhancer" of activated B cells) pathway [68]. NF-kB mediates the expression of pro-inflammatory cytokines, including TNF-α and IL-1b. Zinc inhibits the I kappa B kinase (IKK) complex member IKKβ [69] and thus prevents downstream translocation of NF-kB dimers into the nucleus [70], where they can increase gene expression by binding to kB sites located within the promoter region of, for example, interleukin 6 (IL-6) [71]. In monocytes, NF-kB activation depends on zinc. Under zinc-deficient conditions, this anti-inflammatory feature is absent possibly contributing to prolonged or chronic inflammation. However, there might be cell-type-specific responses of NF-kB signaling to zinc [39]. Moreover, immune cells contain a vast number of different zinc-dependent enzymes / proteins

that, so far, have not been studied in detail but are likely involved in the immunomodulatory functions of zinc.

There is a close relation between inflammatory processes and oxidative stress [43]. Under physiological conditions, zinc itself is not an antioxidant, because it does not participate in redox reactions, but is considered a "proantioxidant" [72] since it protects cells from the damaging effect of oxygen radicals generated during immune activation [73]. For example, zinc release from thiolate bonds can prevent lipid peroxidation [74] and release from metallothioneins (MTs), major zinc-buffering proteins in cells, may reduce membrane damage by free radicals during inflammation. Zinc deficiency causes an elevation of oxidative stress and zinc supplementation was shown to decrease markers of oxidative stress [43].

Intriguingly, changes in immune function similar to those seen during zinc deficiency were observed in immunosenescence [75]. For example, thymic atrophy, increased inflammation, impaired cellular and humoral immune responses, and recurrent infections were observed [76]. These observations suggest that age-dependent zinc deficiency could be a contributing factor to the age-related decline in immune system function.

2.3. Zinc and the brain

Zinc is one of the most abundant trace metals in the brain. There, different pools of zinc can be found. More than 80% of brain zinc is bound to proteins regulating their protein structure, participating in signaling, or acting as cofactor of enzymes. Free (aqueous) zinc exists predominantly within synaptic vesicles of presynaptic terminals of glutamatergic (zincergic) neurons mostly in the hippocampus, amygdala, and cerebral cortex serving as signaling ion and neuromodulator. During development, brain zinc concentration constantly rises until adulthood where zinc levels remain constant at around 200 μM total brain zinc [77]. During neonatal development the highest zinc levels can be found in the cerebellum, which is accompanied by the rapid growth due to the necessity for motor skills acquisition during this developmental stage. In the adult brain, zinc is especially enriched in the hippocampus and cerebral cortex. On cellular level, in neurons, zinc is diffusely distributed in the cytoplasm and nucleus [78] mainly bound to proteins. However, zinc is also found in neuronal processes [78] and in vesicles of presynaptic terminals [79,80].

The brain zinc homeostasis is tightly controlled by transporters at the blood-brain barrier (BBB) and by intracellular regulatory system. In order to cross the BBB, an active transport of zinc is required. So far the mechanism behind zinc uptake is not fully understood but zinc transport might be mediated by L-histidine [81] and the membrane transporter DMT1 (divalent metal transporter 1) [82]. Further, the export of zinc into brain extracellular fluid remains to be deciphered. In brain cells, zinc homeostasis is controlled by zinc transporters and small zinc-binding proteins. Proteins of the ZnT family transport zinc out of the cytoplasm into organelles or out of the cell, and ZIPs transport zinc into the cytoplasm. Further, intracellular zinc homeostasis is regulated by small zinc-binding proteins like the MTs. Among them MT3 is brain specific.

Brain development is a tightly controlled and highly concerted succession of processes including proliferation, differentiation, apoptosis, maturation, migration, myelination as well as synaptogenesis, and pruning. Animal experiments have shown that zinc is involved in all these processes and that zinc deficiency during early embryonal development has teratogenic effects and affects all organ system but the brain seems to be particularly vulnerable. It is noteworthy that consequences of zinc deficiency strongly depend on the degree of severity as well as the time of onset during development. For example, severe zinc deficiency during early developmental stages is associated with neural tube closure deficits [83,84] and brain malformations. Marginal zinc deficiency during the whole course of pregnancy in turn affects the proliferation of neural progenitor cells, the expression of N-methyl-D-aspartate receptor (NMDAR), and growth and transcription factors which in turn affect the regulation of signaling pathways involved in brain development and function in the offspring of zinc-deficient mothers [85–87]. If zinc deficiency occurs during postnatal development, pups showed a decreased brain size; reduced brain DNA, RNA, and protein concentrations [88] as well as decreased numbers of neurons and impaired dendritic arborization in the cerebellum of Purkinje, basket, stellate, and granule cells [89–91]; and decreased numbers of progenitor cells in the dentate gyrus.

The number of stem cells is reduced in the offspring of zinc-deficient animals [92]. Further, in vivo and in vitro studies have shown that zinc deficiency leads to a decrease in progenitor cell proliferation, most likely due to the arrest of the cell cycle whereby cell proliferation is inhibited. In addition, the amount of spontaneous apoptosis is increased under zinc-deficient conditions [87,93,94]. Similarly, knockdown of the zinc transporter Zip12 leads to disturbances in neuronal differentiation affecting neurite sprouting and outgrowth, neurulation, and embryonic development [84]. These features were accompanied by a reduced tubulin polymerization that was observed in Zip12 knockdown mice as well as in pups of zinc-deficient mothers [84,95,96]. Given that transcription factors like nuclear factor of activated T-cells and NF-kB need a functional cytoskeleton for nuclear shuttling [86,97], it is not surprising that prenatal zinc deficiency leads to a deregulation of transcription factors in neurons that are crucial for brain development through regulating the expression of genes that are involved in proliferation, differentiation, and synaptic plasticity [86].

Even if the zinc deficiency occurs only during pre- or early postnatal development and zinc levels are completely restored at adulthood, long-term effects can be observed in the offspring of zinc-deficient mothers. Prenatal zinc-deficient mice showed impaired maternal behavior, impaired auditory discrimination, alterations in ultrasonic vocalizations of adult males to female urine, increased aggressiveness and emotionality [98–101], severe learning deficits and memory impairments [102–105], and enhanced stress response [106,107] when they were tested as adults. Given the fact that these behavioral alterations observed in prenatal zinc-deficient animals resemble behavioral patterns of people suffering from neurodevelopmental and neuropsychiatric disorders like autism spectrum disorders, schizophrenia, and depression, a role of zinc deficiency in the etiology of these disorders is possible (see below).

Zinc is not only needed during brain development but also to maintain proper brain function. As already mentioned, free zinc is stored in presynaptic vesicles together with gluta-

mate in zincergic neurons of the hippocampus, amygdala, and cerebral cortex. During synaptic activity, zinc is released and serves as signal ion. Enriched in the synaptic cleft, zinc can modulate synaptic signal transduction via the modulation of glutamate receptors, ion channels, cell adhesion molecules, and the pre- or postsynaptic uptake of calcium [82] or may directly act as neurotransmitter via metabotropic GPR39 receptor (GPR39) [108] that is involved in glutamatergic transmission [109]. For example, zinc can allosterically inhibit NMDA receptors through binding to a subunit at low levels or inhibit NMDAR in a voltage-dependent manner at high levels [110] and therefore modulate the signal transduction at the postsynaptic site. Additionally, zinc is also able to modulate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor properties [111,112]. Through the mentioned receptors and voltage-dependent calcium channels, zinc can also enter the postsynaptic neuron and increase the intracellular zinc concentration, which might serve as additional signal. For example, the availability of zinc within the postsynaptic neuron is necessary for, and modulates the assembly of, the postsynaptic scaffold where receptors are anchored [98,113]. Furthermore, the increase of intracellular zinc concentration affects and sometimes is necessary for the induction of long-term potentiation (LTP) through the modulation of kinases and neurotrophic factors activity [114,115]. LTP is believed to be the molecular process underlying memory formation indicating that the increase of cytosolic zinc plays an important role in learning and cognitive performance [116]. However, zinc is not only taken up by the postsynaptic neuron but also by the presynaptic neuron where it might act in a negative feedback mechanism preventing further glutamate release [117,118].

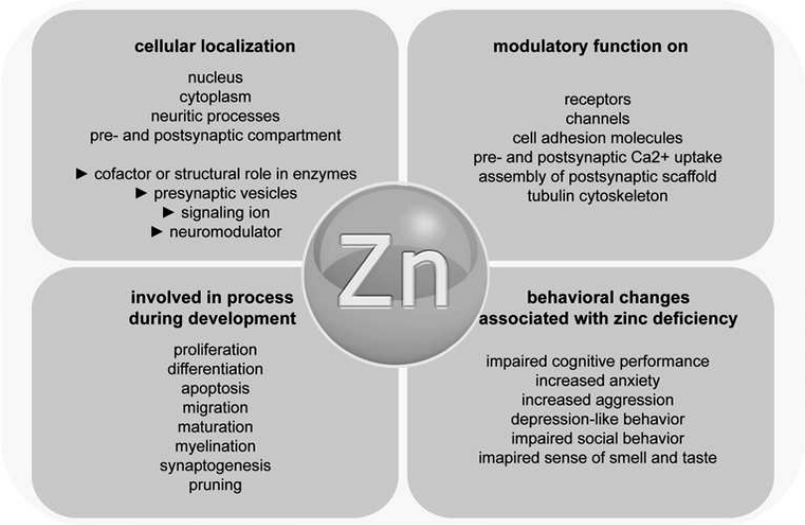

Figure 3. Overview of the major functions of zinc in the brain and effects of zinc deficiency.

Given the multifaceted action of zinc in the brain (**Figure 3**), it is not surprising that zinc deficiency leads to alterations in cognitive performance and behavior in animal models and possibly humans. Acute zinc-deficient animals demonstrated impaired learning and memory behavior [119–122], increased aggressiveness [123] and hyperreactivity/irritability [98], and

anxiety as well as depressive-like behavior [109,124]. Additionally, neurosensory functions like smell and taste are impaired through zinc deficiency [125].

The dysregulation of zinc homeostasis is a common and well-investigated feature in neurodegenerative disorders like Alzheimer's disease (AD) or Parkinson's disease (PD), but only little is known about the role of zinc in the normal aging process of the brain although elderly people frequently suffer from zinc deficiency [126,127] that might be due to lower dietary intake, chronic inflammation, and an age-related decline in zinc transport mechanisms [128,129]. A decrease in histochemically reactive zinc has also been reported in aged animals [130]. Additionally, in a rodent model of aging, zinc was less distributed in the hippocampus, and the expression of ZnT3, a zinc transporter responsible for the transport of cytosolic zinc into synaptic vesicles, was significantly reduced [131]. Given that zinc is important in synaptic plasticity, the underlying cellular mechanism of learning and memory and a lower availability of zinc in the aging brain might affect this feature.

Taken together, zinc has a pivotal role in the brain during all stages of life. Zinc deficiency during brain development leads to persistent deficits in cognitive functions and behavior. In adults, zinc deficiency results in disturbed behavior and may contribute to the age-dependent decline of cognitive performance. Therefore, alterations in zinc homeostasis are intensively investigated in brain disorders but zinc deficiency affects all organ systems of the body and therefore can lead to a plethora of disorders.

3. Zinc deficiency and associated disorders

Zinc deficiency itself is associated with several clinical signs. For example, marginal zinc deficiency may result in depressed immunity, impairment of memory, neurosensory problems such as impaired taste and smell as well as onset of night blindness, and decreased spermatogenesis in males [46,132]. Severe zinc deficiency is characterized by a more severely depressed immune function resulting in frequent infections, dermatitis, diarrhea, alopecia, and mental disturbances [46].

In 1961 it was hypothesized for the first time that human nutritional zinc deficiency of environmental origin might be associated with a disorder in the form of adolescent dwarfism. Patients found in Iranian villages that consumed a severely restricted (inadequate) diet consisting mainly of wheat bread with animal protein food sources largely absent displayed growth retardation and hypogonadism and were iron deficient [133]. Dwarfism and absent sexual maturation were assumed to be caused by zinc deficiency. Likewise in 1967 zinc deficiency was reported as the etiological factor responsible for retarded sexual development and growth in adolescents from rural Egypt with similar dietary habits [1,2,134]. Zinc supplementation resulted in the subject's growth and in the development of their genitalia.

In these cases, zinc deficiency was based on nutrition. It is known from congenital defects like mutations in the zinc transporter ZIP4 that severe zinc deficiency can even become lethal.

However, zinc deficiency is also associated with specific disorders. Few of them will be briefly discussed here exemplarily. Alterations in zinc homeostasis have been implicated in various neurodegenerative, neurological, and neuropsychological disorders such as mood disorders, autism spectrum disorders (ASD), AD, PD, Huntington's disease (HD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS) [135,136].

Probably the strongest association of acute zinc deficiency and a brain disorder is found regarding depression. Therefore, this topic is discussed in a separate chapter in this book.

Zinc deficiency during brain development in turn seems to result in a different clinical picture, arguing for multiple roles of zinc in brain development and adult brain function. For example ASD, a group of neurodevelopmental disorders characterized by the core features of impairments in social interaction and communication as well as repetitive and restrictive behavior [137] might develop influenced by both a genetic component and non-genetic factors such as zinc deficiency during development and early in life [138,139]. Accordingly, investigation of zinc levels in autistic children using hair samples revealed a high prevalence rate for zinc deficiency especially in the youngest age group (0–3 years) [140,141]. Rodent animal models of embryonic zinc deficiency display depending on the severity of zinc deficiency autism-like behavior as well as behavioral symptoms associated with common comorbidities of ASD [98]. Besides memory and learning deficits as well as impaired social behavior in prenatal and perinatal zinc-deficient mice and rats [142], in mouse models of acute and prenatal zinc deficiency, hyper-responsiveness, seizures, and impaired ultrasonic vocalization were observed.

However, besides zinc deficiency causing or contributing to the etiology of a disorder, zinc deficiency that can be systemic or local can also be the consequence. In AD, for example, the most common form of dementia that is characterized by extracellular amyloid plaques consisting of amyloid-β (Aβ) polymers and intracellular neurofibrillary tangles composed of tau protein, zinc is sequestered by the zinc-binding Aβ peptides into extracellular senile plaques. Due to the importance of zinc for proper brain functionality and high prevalence of zinc deficiency among elderly people, the potential role of zinc as a contributing and modifying factor in the course of AD moved into the spotlight of research. While there has been emerging evidence of abnormalities in AD regarding brain zinc, copper, and iron homeostasis, there seems to be a lack of consensus regarding alterations in peripheral zinc status [143]. While several studies reported a significant decrease in serum zinc level of AD patients, others detected a significant increase while some found no difference between patients and controls [144]. One of the possible roles of zinc in AD is its involvement in Aβ accumulation. In plaques both copper and zinc are able to bind Aβ directly. Thus, analysis of Aβ plaques of postmortem AD brain reveals high concentrations of accumulated zinc and copper [143]. Since Aβ is proteolytically cleaved from the amyloid precursor protein (APP), a possible role of zinc in APP synthesis and processing was investigated. APP is cleaved in its Aβ region by α-secretase leading to the production of soluble amyloid precursor peptide (sAA) [145] before by cleavage with β- and γ-secretase, the Aβ peptide is formed [144,146]. In APP's ectodomain, which includes the position of the cleavage site of α-secretase, the enzyme responsible for the first processing step, a zinc-binding site is localized [147] suggesting a possible influence

of zinc on the secretase's activity [144]. In case of zinc deficiency, not only APP cleavage but also synaptic transmission and plasticity might be impaired by sequestration of zinc [148,149].

Besides the brain, high concentration of zinc compared to other tissues can be found in pancreatic tissue, suggesting a role in endocrine and exocrine function of the organ [150,151]. Most importantly, zinc plays a role in synthesis, secretion, and signaling of insulin [152]. Due to its various functions in the pancreas, alterations of zinc homeostasis have been implicated in the pathogenesis of diabetes and in impaired insulin sensitivity [151,153]. Furthermore, hyperzincuria and hypozincemia are frequently diagnosed in diabetic patients [151,153]. Assessment of serum zinc levels in a set of type 1 and type 2 diabetic patients in comparison to healthy controls revealed significant lower mean serum zinc levels in the diabetic groups [154]. db/db mice, an animal model for obesity and diabetes, exhibit hyperglycemia, hyperinsulinemia, hyperleptinemia, and obesity. After dietary zinc supplementation they showed an attenuated fasting hyperinsulinemia and hyperglycemia and elevated pancreatic zinc levels. In db/db mice on a zinc-deficient diet, an opposite effect was observed indicating a possible connection between glycemic control and zinc [155]. Likewise in human studies, beneficial effects of zinc in diabetes type 1 and type 2 have been described [156,157].

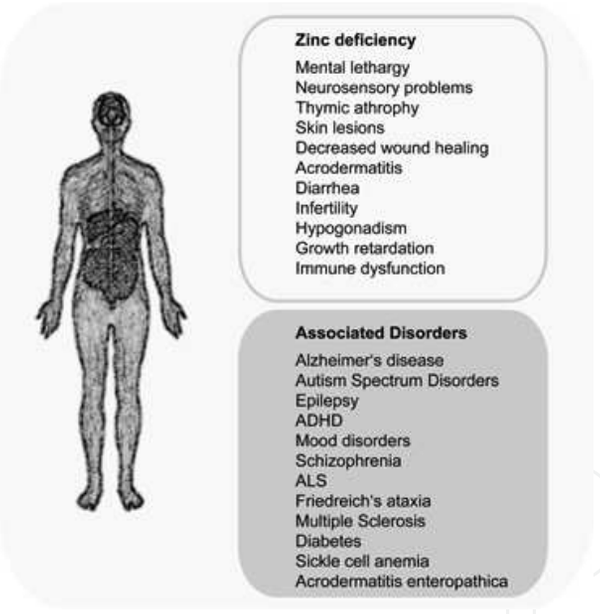

Figure 4. Symptoms of zinc deficiency and associated disorders. ADHD, attention deficit hyperactivity disorder; ALS, amyotrophic lateral sclerosis. Intriguingly, a high number of brain disorders seem to be associated with zinc deficiency.

Taken together, due to the manifold roles of zinc in various organ systems as a key structural component of enzymes and proteins but also signaling ion, zinc deficiency, depending on the time of onset, duration, severity, and systemic or tissue-specific nature, can result in a variety of symptoms with different severities. Further, zinc deficiency is associated with several disorders, probably acting as trigger, modifier, or even cause (**Figure 4**). However, the

molecular mechanisms how zinc deficiency contributes to specific phenotypes are currently not well understood.

4. Conclusions

Although only recently recognized, the importance of zinc as essential trace metal in the body and in particular as signaling molecule is substantiated greatly. Zinc is a trace element with various roles in physiological processes (Kaur et al., 2014). It has been used as a drug in the prevention and treatment of some diseases and new strategies for more targeted delivery or modification of zinc signaling are promising future therapeutic approaches, especially in brain disorders (Ayton et al., 2015; Lee et al., 2015). In addition, the present knowledge about zinc signaling in the various processes and involved pathways seems to be disconnected by specific types of zinc signal used, with different kinetics and sources of zinc. However, most likely, an interplay between the different systems described above may exist by common underlying principles of zinc signaling.

The high rate of the world's population that is at risk for inadequate zinc supply underlines the need for further research on zinc signaling and the need for public health programs to control zinc deficiency.

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