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REVIEW

Zinc and the aging brain

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Abstract Alterations in trace element homeostasis could be involved in the pathology of dementia, and in particular of Alzheimer's disease (AD). Zinc is a structural or functional component of many proteins, being involved in numerous and relevant physiological functions. Zinc homeostasis is affected in the elderly, and current evidence points to alterations in the cellular and systemic distribution of zinc in AD. Although the association of zinc and other metals with AD pathology remains unclear, therapeutic approaches designed to restore trace element homeostasis are being tested in clinical trials. Not only could zinc supplementation potentially benefit individuals with AD, but zinc supplementation also improves glycemic control in the elderly suffering from diabetes mellitus. However, the findings that select genetic polymorphisms may alter an individual's zinc intake requirements should be taken into consideration when planning zinc supplementation. This review will focus on current knowledge regarding pathological and protective mechanisms involving brain zinc in AD to highlight areas where future research may enable development of new and improved therapies.

Keywords Zinc · Aging brain · Alzheimer's disease · Diabetes · Nutrigenomics

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Abbreviations

Aβ	Amyloid-beta
A2M	α2-Macroglobulin
AD	Alzheimer's disease
ADAS-cog	Alzheimer's disease assessment scale-cognitive subscale
ApoE	Apolipoprotein E
APP	Amyloid precursor protein
DM	Diabetes mellitus
DM1	Type-1 DM
DM2	Type-2 DM
ERK1/2	Extracellular signal-regulated kinases
GABA	Gamma-aminobutyric acid
IL6	Interleukin 6
IR	Insulin receptor
MCI	Mild cognitive impairment
NFTs	Neurofibrillary tangles
NMDAR	*N*-methyl-D-aspartate-sensitive glutamate receptor
NOS	Nitric oxide synthase
NOX	NADPH oxidase
MMSE	Mini-mental state examination
MT	Metallothionein
NTB	Neuropsychological test battery
PCAD	Preclinical Alzheimer's disease

Introduction

In terms of quality of life and financial burden on society, dementia is the largest health problem facing the world today. In 2010 the World Health Organization estimated that 35.6 million people were affected by dementia (Wimo

2010). Unless preventative or curative treatments are developed this number is expected to triple by 2050 (Wimo 2010). Among the various forms of dementia, Alzheimer's disease (AD) is the most common affecting nearly 10 % of the population in the United States over 70 years of age (Plassman et al. 2007). Disruption of mineral homeostasis has long been suspected as a pathological mechanism in AD and therapeutic strategies are now being aimed at restoring mineral homeostasis. Evidence regarding changes in the brain mineral distribution of AD patients is apparently conflicting (Schrag et al. 2011b), and our understanding of the mechanisms regulating zinc distribution in the brain during normal development, aging, and disease remains incomplete. Nevertheless, preclinical studies and early clinical trials have provided encouragement for mineral targeted therapies in the treatment and prevention of AD (Constantinidis 1992; Ritchie et al. 2003; Lannfelt et al. 2008; Faux et al. 2010). These include zinc supplementation as well as pharmaceutical approaches designed to alter zinc and copper distribution. Zinc supplementation can also improve glycemic control in patients with diabetes mellitus (DM) (Jayawardena et al. 2012) and may benefit a large portion of the aging population (Maylor et al. 2006). However several polymorphisms that affect zinc homeostasis have been identified, future research is needed to understand how these mutations may alter dietary zinc requirements and the efficacy of zinc supplementation to prevent or treat major chronic diseases that affect the aging population (Giacconi et al. 2005; Xu et al. 2012).

Biological functions of zinc

Zinc is an abundant and widely distributed essential trace element. Zinc has structural, functional, and combined roles in numerous proteins including approximately 2,700 enzymes (Andreini and Bertini 2012) such as hydrolases, transferases, oxido-reductases, ligases, isomerases and lyases. Structurally, zinc is present in different protein domains. Among these domains, the key biological relevance of zinc fingers (e.g. regulation of transcription and redox homeostasis) is stressed by the finding that 3 % of the proteins encoded in the human genome contain zinc fingers (Lander et al. 2001). Zinc modulates the activity of proteins such as receptors and enzymes that are involved in the regulation of numerous processes, including the synthesis of macromolecules, the regulation of signaling cascades and gene transcription, and transport processes. In this capacity, a role for zinc as a second messenger of intracellular signal transduction has recently been recognized (Yamasaki et al. 2007). Zinc is also involved in preserving genomic stability through several actions including regulation of redox homeostasis [reviewed in (Oteiza 2012)], DNA repair, synthesis, and methylation (Sharif et al. 2012). Furthermore, zinc can play a role in intercellular signaling as exemplified in the nervous system where zinc functions as a neurotransmitter (Chorin et al. 2011).

Considering the multiple cellular events regulated by zinc, a dyshomeostasis of this metal during aging can have important deleterious effects on this population.

Risk of zinc deficiency in the elderly

Low dietary intake combined with senescence of homeostatic mechanisms contributes to an elevated incidence of zinc deficiency in the aging population, which may contribute to an increased risk of DM and dementia. Low circulating zinc (in plasma or white blood cells) is common among hospitalized elderly patients and has been associated with many diseases including DM and AD (Walter et al. 1991; Prasad et al. 1993; Singh et al. 1998; Pepersack et al. 2001; Kazi et al. 2008; Brewer et al. 2010). However, in some cases (e.g. patients carrying ApoE ε4 alleles) AD may be associated with increased circulating zinc levels (Gonzalez et al. 1999). A variety of socioeconomic factors contribute to insufficient micronutrient intake in the elderly population. Elderly people living alone may have reduced motivation or ability to cook. Lower dietary quality combined with a reduced total caloric intake among many elderly people can contribute to micronutrient deficiencies. As micronutrient deficiencies arise, decreased energy and motivation can further compromise dietary quality in a pathological cycle. For example, dietary zinc deficiency is known to decrease food intake in animal models and zinc supplementation improves taste acuity in elderly subjects (Pepersack et al. 2001; Stewart-Knox et al. 2008; Amani et al. 2010). Inadequate zinc intake certainly contributes to deficiency in many elderly patients (Singh et al. 1998; Pepersack et al. 2001) but effects of chronic inflammation and age-related decline in zinc transport mechanisms may also contribute to a functional zinc deficiency (Turnlund et al. 1986; Wong et al. 2012). For example, senescence of rat vascular smooth muscle cells involves decreased ZnT expression (Patrushev et al. 2012) and an age-related decline in plasma zinc was associated with increased methylation of the ZIP6 promoter and an exaggerated inflammatory response in mice (Wong et al. 2012). Furthermore, zinc supplementation restored plasma zinc levels leading to a reduction in markers of inflammation and oxidative stress in elderly subjects (Bao et al. 2010). While these findings support the notion that zinc deficiency contributes to chronic inflammation, cytokines (e.g. IL6) can lower zinc availability. Therefore, low circulating zinc levels found in patients with DM and AD could contribute

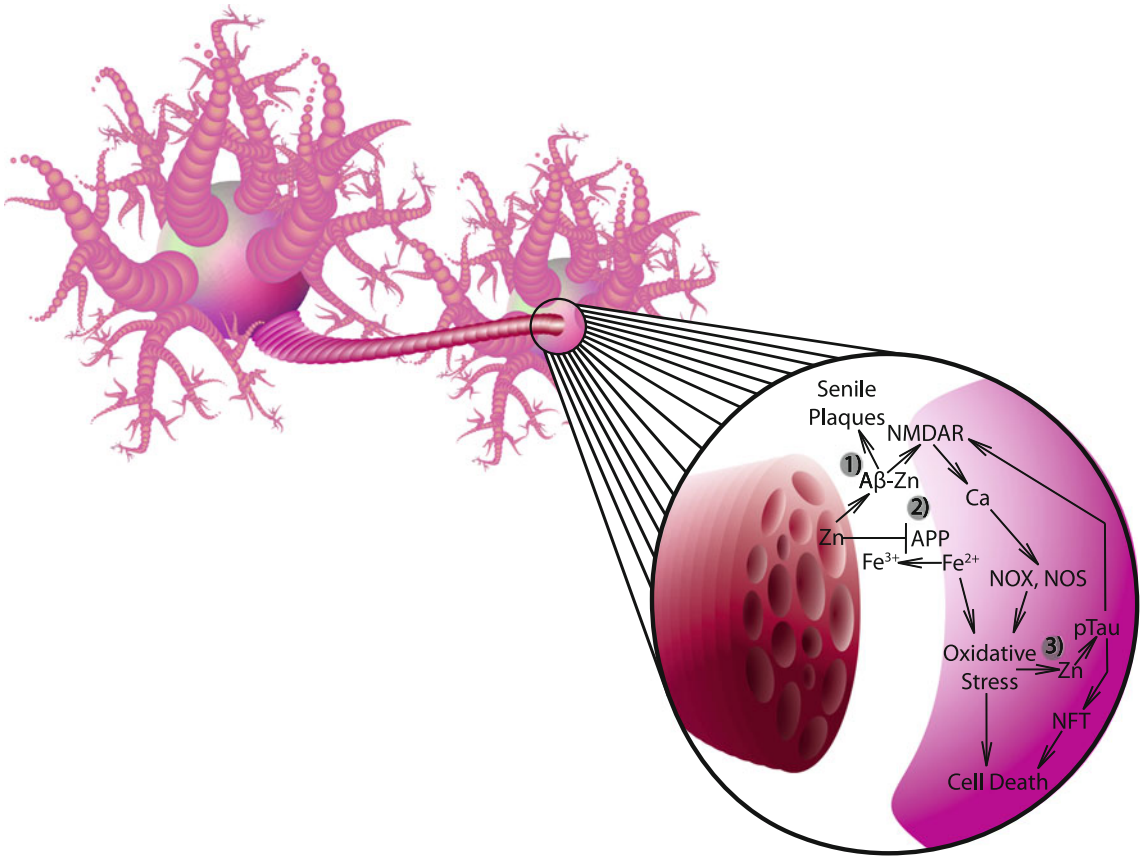

Fig. 1 Potential role of excess zinc in Alzheimer's disease pathology. Zinc is released from synaptic vesicles in response to neuronal activity. Three main mechanisms have been proposed for how excess zinc can contribute to AD. (1) Zinc can accumulate bound to Aβ at zinc-secreting synapses promoting the formation of protease resistant oligomers and fibrils forming senile plaques. Aβ oligomers stimulate NMDAR-dependent increase in cellular calcium, leading to activation of NADPH oxidase (NOX) and nitric oxide synthase (NOS) generating oxidant species (superoxide anion and nitric oxide). (2) Zinc can inhibit the iron export ferroxidase activity of APP, leading to the accumulation of ferrous iron in neurons and potentially to oxidative stress. (3) Zinc stimulates kinases and inhibits protein phosphatases leading to phosphorylation of Tau which promotes the aggregation of Tau in neurofibrillary tangles (NFT) and contributes to a positive feedback loop that further increases postsynaptic calcium influx through NMDARs resulting in neuronal cell death

to or result from the inflammatory background associated with these diseases. However, several studies have found low or marginal zinc intake is common among elderly individuals and the therapeutic effects of zinc supplementation in clinical trials suggests that current intake may be inadequate for many (Constantinidis 1992; Beletate et al. 2007; Bao et al. 2010; Lai et al. 2012).

The role of excess zinc in Alzheimer's disease pathology

Clinical research and mechanistic studies using a combination of techniques support a model of AD pathology involving increased local zinc in cortical gray matter and pathological lesions. However, decreased zinc availability on both the cellular and systemic level has also been implicated in AD pathology.

Increased local zinc concentrations have been implicated in three major pathological mechanisms contributing to AD: (1) synaptic targeting of amyloid-beta (Aβ) oligomers to *N*-methyl-D-aspartate-sensitive glutamate receptors (NMDARs) stimulating excitotoxicity, (2) inhibition of amyloid precursor protein (APP) iron export ferroxidase activity contributing to oxidative stress, and (3) hyperphosphorylation of Tau that contributes to a positive feedback on the NMDAR leading to neuronal cell death and the formation of neurofibrillary tangles (NFTs; see Fig. 1).

A variety of conditions that involve excessive synaptic activity are risk factors for AD (Frederickson et al. 2005). They include medial temporal lobe epilepsy, traumatic brain injury, and conditions that disrupt blood flow to the brain such as arthrosclerosis, hypertension, stroke, and cardiac bypass surgery. In this context, excessive zinc release may play a causal role in excitotoxic cell death by targeting Aβ oligomers to the NR2B subunit of the NMDARs (Deshpande et al. 2009; Solomonov et al. 2012). The accumulation of Aβ oligomers leads to increased

synaptic activity in the APP/PS1 mouse model and direct application of soluble Aβ dimers to CA1 neurons increases synaptic activity in wild type mice measured in vivo by calcium imaging (Busche et al. 2012). Deficiency of the zinc transporter ZnT3 or the brain specific zinc binding protein metallothionein (MT)3 can prevent deposition of Aβ in Swedish mutant APP mice (Lee et al. 2002; Manso et al. 2012), and senile plaques form preferentially in zinc enriched cortical layers of APP/PS1 mice (Stoltenberg et al. 2007). These findings provide further evidence that zinc released from synaptic vesicles could contribute to AD pathology.

Amyloid precursor protein has recently been recognized as a copper dependent ferroxidase, and it has been proposed that excess zinc inhibit this function contributing to AD (Duce et al. 2010). APP likely serves a similar function to ceruloplasmin in exporting iron from neurons. Addition of zinc, as either $ZnCl_2$ or bound to Aβ, inhibits the oxidation of iron by APP but not ceruloplasmin in vitro. Furthermore, addition of a zinc chelator to cortical homogenates from AD patients was able to restore APP ferroxidase activity (Duce et al. 2010). Disruption of iron export could lead to neuronal accumulation of ferrous iron potentially contributing to the oxidative stress condition associated with AD (Cervellati et al. 2012).

Zinc can also stimulate the hyperphosphorylation of Tau through inhibition of protein phosphatases (e.g. PP2A) and activation of kinases (e.g. ERK1/2) (Martin et al. 2012; Nuttall and Oteiza 2012). Mice expressing the human ApolipoproteinE (ApoE) ε4 allele under a neuron specific promoter have increased phosphorylation of ERK1/2 and Tau in areas of the hippocampus and cortex where zinc-secreting neurons are concentrated (Harris et al. 2004). ApoE ε4 is a major risk factor for AD and this may in part be related to its ability to affect zinc homeostasis. For example, zinc stimulated Tau phosphorylation through an ERK1/2 dependent mechanism in neural cell cultures transfected with ε4 more than in cultures transfected with ε3 (Harris et al. 2004). Inhibition of PP2A and activation of ERK1/2 signaling has been proposed as a major mechanism contributing to excitotoxic cell death subsequent to zinc accumulation in conditions such as epilepsy and transient cerebral ischemia (Ho et al. 2008). For example, inhibitors of ERK1/2 signaling reduce infarct size after occlusion of the mid cerebral artery (Nuttall and Oteiza 2012). Furthermore, cell cycle reentry has been identified as an early pathological event in AD, and injection of the PP2A inhibitor okadaic acid into the rat cortex stimulated neuronal death through mitotic catastrophe (Chen et al. 2006). Phosphorylation and dendritic localization of Tau mediates excitotoxicity downstream from amyloid formation in AD pathology and other neurodegenerative diseases involving protein misfolding, such as Creutzfeldt–Jakob disease and frontotemporal dementia (Riemenschneider et al. 2003; Roberson et al. 2007; Asuni et al. 2010). This data is consistent with a model of AD pathology where excitotoxicity increases cellular free zinc concentrations, contributing to Aβ aggregation and Tau phosphorylation, which exacerbates excitotoxicity in a pathological cycle leading to neuronal cell death.

Although excess zinc released during excitotoxicity is likely to contribute to AD, this picture is complicated by the fact that zinc initially plays a protective mechanism during increased synaptic activity. For example, activation of the zinc receptor in the hippocampus increases chloride export through the potassium chloride cotransporter (KCC2) facilitating hyperpolarizing currents through gamma-aminobutyric acid receptors (Chorin et al. 2011). Zinc can also reduce oxidative stress associated with excitotoxicity through a variety of mechanisms including inhibition of the NMDAR and competition with copper for redox active binding sites on Aβ (Cuajungco et al. 2000; Oteiza 2012). Furthermore, infusion of zinc delays the development of seizures in a kindling model of epilepsy (Elsas et al. 2009), and mice with ZnT3 and/or MT3 deficiency have increased susceptibility to kainic acid induced seizures and hippocampal damage (Cole et al. 2000).

In summary, zinc released during increased synaptic activity initially protects against excitotoxicity, but in AD zinc may also contribute to multiple pathological mechanisms resulting in excitotoxic cell death.

Evidence that zinc accumulates in the brain during Alzheimer's disease

While recent reviews have stated that zinc, iron, and copper accumulate in the cortex of AD patients (Bonda et al. 2011b; Greenough et al. 2012), a quantitative meta-analysis found decreased levels of copper and no significant difference in cortical zinc or iron (Schrag et al. 2011b). Furthermore, a citation bias was found for studies reporting increased cortical iron. The belief that trace mineral levels are elevated has justified the use of chelating agents for the treatment of AD. Therefore, it is important to critically analyze the rationale for these interventions. When all available data from valid methods was pooled, cortical zinc levels were not statistically different. However, the zinc concentration of the parietal lobe was significantly higher in AD patients compared to healthy individuals (Schrag et al. 2011a). Standardization of analytical techniques may be required to reduce the variability of future studies (e.g. some studies analyzed an equal mixture gray matter and white matter but others did not specify). Further insight may be gained from compartmental analysis given that

elevated zinc levels in AD patients have been observed in: the cortical gray matter of the temporal lobe (Schrag et al. 2011a), senile plaques (Miller et al. 2006), and synaptic vesicles (Bjorklund et al. 2012).

Analysis of MT and zinc transporter expression provides further evidence suggesting that brain zinc homeostasis is deranged in AD. Brains from AD patients have increased MT1 and MT2 but decreased MT3 levels (Yu et al. 2001). Expression of the vesicular zinc transporter Znt3 normally decreases with age, and in AD they are even lower (Adlard et al. 2010). Decreased ZnT3 expression may be subsequent to an elevation in synaptic zinc, because subjects with preclinical AD (PCAD) have a similar magnitude of elevated zinc in the hippocampal synaptic vesicle fraction as AD patients while ZnT3 levels are not different from age-matched controls (Bjorklund et al. 2012). Interestingly, the total level of soluble zinc in the hippocampus from PCAD subjects was intermediate between controls and AD patients. Considering that soluble Aβ oligomers are associated with the postsynaptic density in AD and not PCAD, it is likely that this difference reflects the accumulation of zinc bound to Aβ oligomers. As zinc bound to Aβ oligomers can disrupt synaptic function and contribute to neuronal cell death, decreased ZnT3 expression may result from the selective loss of zinc-secreting synapses. While Znt1 expression is increased in the temporal lobe of patients with early- or late-onset AD, low levels are associated with PCAD and mild cognitive impairment (MCI) (Lovell et al. 2005; Lyubartseva et al. 2010; Beyer et al. 2012). A recent study found that mRNA levels of several zinc transporters (ZIP 1 and 6 as well as ZnT 1, 4, and 6) increase with AD progression correlating with NFT accumulation (Beyer et al. 2012). Therefore, further analysis of zinc distribution in PCAD and MCI is required to further our understanding of how zinc metabolism changes through AD progression. This knowledge may facilitate interventions targeted at the early stages of the disease to prevent irreversible degeneration. Histological analysis to further analyze the spatial pattern of these changes could provide valuable insight into pathological mechanisms involving zinc in AD. For example, increased expression of ZnT and ZIP genes (which have opposing roles in cellular zinc homeostasis) might seem contradictory from the perspective of cellular homeostasis but histological analysis revealed that Znt1, 3, 4, 5, 6, and 7 accumulate with labile zinc in senile plaques of AD patients (Zhang et al. 2008). Increased ZnT expression in senile plaques could be either a homeostatic response to prevent toxic elevations of zinc (e.g. related to excitotoxicity) from accumulating in the cytoplasm, or a mechanism contributing to the accumulation of zinc in plaques. If zinc accumulation in senile plaques leads to deficiency in surrounding tissue, ZIP1 expression may increase to restore homeostasis. Thus, it remains unclear to what extent changes in zinc transporter expression in AD reflect pathological or homeostatic processes.

The role of zinc deficiency in AD pathology

Although excess zinc most likely participates in AD pathology, decreased zinc at either the systemic or cellular level may also contribute to AD pathology. Despite the protective effects of Znt3 deficiency against accumulation of Aβ, Znt3 knockout mice have age-related memory impairments comparable to AD mouse models (Adlard et al. 2010). For example, these mice have normal learning on the standard form of the Morris water maze when young but impaired performance in old age. Znt3 KO mice also have impaired: reversal learning in a modified Morris water maze, discrimination between familiar and novel stimuli, and fear conditioning responses (Adlard et al. 2010; Martel et al. 2011). Low Znt3 expression in AD combined with zinc sequestration in senile plaques could reduce the pool of readily releasable synaptic zinc creating a situation similar to a genetic Znt3 deficiency. Loss of zinc can contribute to synaptic dysfunction by disrupting the PrSAP2/Shank3 scaffold at the postsynaptic density (Grabrucker et al. 2011b). Zinc deficiency also facilitates calcium influx through the NMDAR leading to activation of NADPH oxidase and nitric oxide synthase (Aimo et al. 2010). Activation of these enzymes combined with mitochondrial dysfunction leads to oxidative stress and subsequent disruption of microtubule stability (Mackenzie et al. 2011) and accumulation of phosphorylated Tau in NFT (Bonda et al. 2011a). Zinc also regulates degradation of Aβ directly through modulation of protease structure and indirectly by increasing protease expression (Grasso et al. 2012). Therefore, decreased zinc availability could contribute to the accumulation of Aβ. Furthermore, zinc deficiency can disrupt energy metabolism and contribute to chronic inflammation (Bao et al. 2010). Together these findings support a model in which zinc accumulates with Aβ, leading to a functional zinc deficiency that contributes to AD pathology despite a net increase in the level of zinc in cortical gray matter.

Zinc and insulin signaling in diabetes mellitus and dementia

Metabolic syndrome and DM are risk factors for dementia (Profenno et al. 2010) and disruptions of zinc and glucose homeostasis may be related to a common pathological mechanism in these conditions. Low plasma zinc concentrations are found in DM patients, and zinc

supplementation improved glycemic control among DM patients in double-blind placebo controlled trials (Jayawardena et al. 2012).

Zinc is involved in insulin processing as well as in signaling downstream from the insulin receptor (IR). Insulin is stored in secretory granules of β-cells in the pancreas as a crystalline hexameric complex containing zinc ions. Znt-8 transports zinc into the secretory granules of β-cells and mice with a conditional deletion of Znt-8 in pancreatic β-cells have reduced islet zinc content leading to impaired insulin processing and glucose intolerance (Wijesekara et al. 2010). On the other hand, zinc has insulinomimetic effects by inhibiting the dephosphorylation of the IR by protein phosphatases (Haase and Maret 2005). Znt7 sequesters zinc into the Golgi apparatus and vesicles in a variety of tissues including skeletal muscle and Znt7 knockout mice display growth retardation that cannot be rescued by dietary zinc supplementation. Suggesting impaired insulin signaling, male Znt7 knockout mice develop insulin resistance on a high fat diet (Huang et al. 2012).

DM is a major risk factor for dementia and impairments of insulin signaling have been implicated in the pathophysiology of dementia. It has been proposed that AD could be type 3 DM after observing impaired insulin signaling associated with decreased mRNA levels of insulin and insulin-like growth factors in the brains of AD patients (Steen et al. 2005). However, the brain IR is functionally distinct from the peripheral receptor in that it does not regulate brain glucose uptake, and the function of insulin signaling in the brain is an area of active research. Mice with brain IR deficits have decreased levels of gonadotropin-releasing and luteinizing hormones associated with impaired gonadal development. Brain IR signaling may also contribute to satiety as supported by findings that mice with IR deficits display increased food intake and adiposity (Bruning et al. 2000). The IR is expressed throughout the brain with the highest levels in the hypothalamus and hippocampus. While it seems likely that the hypothalamus is a major target for insulin regulating sexual development and satiety; insulin may also play a role in mechanisms of hippocampal synaptic plasticity that contribute to learning and memory. In rats, Morris water maze training stimulates IR signaling involving the recruitment Shc52 at the synaptic membrane to activate Ras-ERK1/2 signaling. Suggesting that training can sensitize the IR; insulin stimulated ERK1/2 phosphorylation in hippoccampal membrane fractions taken from maze-trained but not naive or untrained swimming controls (Zhao et al. 2004). It is possible that decreased insulin signaling could contribute to cognitive impairment in AD. Considering that insulin has been shown to improve memory in healthy subjects as well as patients with MCI or AD (Benedict et al. 2007; Craft et al. 2012; Ott et al. 2012) and that zinc also stimulates ERK1/2 signaling (Nuttall and Oteiza 2012); it is possible that insulin- and zinc-based therapies converge on a common mechanism to improve glucose homeostasis and cognition.

The nutrigenomics of zinc homeostasis in AD and DM

Polymorphisms in major genes controlling zinc homeostasis are associated with AD and DM (Table 1) and it may soon be feasible to use this nutrigenomic information to provide optimized recommendations. With accessible genome sequencing, it is now possible to identify individuals with these mutations and in some instances we may be able to treat a functional deficiency with zinc supplementation in order to prevent or treat disease.

A polymorphism in SLC30A8 the gene encoding the ZnT8 transporter that mediates sequestration of zinc in secretory vesicles of pancreatic β-cells, is associated with both DM type 2 (DM2) (Boesgaard et al. 2008; Jing et al. 2011) and DM type 1 (DM1) (Gohlke et al. 2008). It is unclear how the Znt8 polymorphism contributes to DM2 risk (Boesgaard et al. 2008), but autoimmune dysfunction involving antibodies against Znt8 could contribute to DM1 (Wenzlau et al. 2011). Considering that zinc supplementation has clinical benefits in DM patients; research is needed to investigate if this polymorphism affects optimal zinc requirements.

Apolipoprotein E is the strongest genetic risk factors for late-onset AD and altered zinc homeostasis may contribute to this risk. For example, elevated plasma zinc is an independent risk factor for AD among ε4 carriers (Gonzalez et al. 1999) and the risk of AD is greater among DM2 patients that also carry the ε4 allele (Peila et al. 2002). Suggesting that ApoE ε4 disrupts zinc homeostasis, mice expressing human ε4 have decreased tissue MT levels compared to mice expressing ε3 (Graeser et al. 2012). Furthermore, ApoE knockout mice have reduced synaptic zinc and ZnT3 expression (Lee et al. 2010). However, the

Table 1 Polymorphisms potentially affecting zinc homeostasis

Gene	Putative role in zinc homeostasis	Polymorphism	Disease risk
MT1A	Buffering and chaperone	+647A/C	DM2
MT2A	Buffering and chaperone	−209A/G	DM2
SLC30A8	Sequestration in secretory vesicles	R325 W	DM1&2
IL6	Regulates MT and A2 M	−174G/C	AD
A2M	Extracellular transport	−88A/G and 25T/G	AD
APOE	Unknown	C112R	AD

mechanism through which ApoE affects zinc homeostasis is largely unknown. Decreased tissue MT could potentially explain the increased circulating levels of zinc (Gonzalez et al. 1999). However, the total level of zinc in the mouse liver was not effected by ApoE genotype (Graeser et al. 2012). The ε4 allele results from mutation of cysteine 112 to an arginine and it has been proposed that this mutation alters zinc homeostasis by reducing the ability of ApoE to bind zinc (Lee et al. 2010). For example, ApoE attenuated zinc induced Aβ aggregation in vitro, but the ε4 form is less effective than ε3 (Moir et al. 1999). On the other hand, the ApoE ε4 mutation disrupts the processing of ApoE through the secretory pathway leading to decreased circulating ApoE levels and accumulation of cytotoxic fragments in neurons (Mahley et al. 2009). In summary, further research is required to understand how the ApoE allele could affect zinc homeostasis, and determine if this mechanism contributes to the link between ApoE and AD.

The cytokine interleukin 6 (IL6) that is released during the acute phase of an inflammatory response, reduces zinc availability by inducing the expression of the zinc binding proteins MT and α2-Macroglobulin (A2M). While this mechanism is beneficial to the acute immune response, a long-term decrease in zinc availability may contribute to pathological processes in conditions of chronic inflammation (e.g. DM and dementia). IL6, MT, and A2M expression increase in old age and impaired zinc availability contributes to immunosenescence. A2M is the major high affinity zinc binding protein in plasma and requires zinc for its functions that include IL6 binding to prevent its proteolytic degradation (Mocchegiani et al. 2006). A mutation in the IL6 promoter upregulates its expression leading to increased MT, low plasma zinc, impaired innate immunity (Mocchegiani et al. 2007), and increased risk of AD (Licastro et al. 2003). A mutation in the coding region of MT1A is associated with increased expression of IL6 and MT, higher risk of DM2, and shorter lifespan (Cipriano et al. 2006; Giacconi et al. 2008). Furthermore, this mutation may directly interfere with the functions of zinc in cellular signal transduction because it attenuates the release of zinc in response to nitric oxide (Cipriano et al. 2006). Similarly a mutation in the MT2A promoter is associated with low plasma zinc, higher blood glucose levels, and risk of atherosclerosis and ischemic cardiomyopathy among DM patients (Giacconi et al. 2005). The above data suggests that individuals with IL6 and MT mutations may have higher optimal zinc intake requirements. However, it is not clear if AD-associated polymorphisms in the A2M promoter could affect zinc requirements (Song et al. 2010). Considering that zinc supplementation has been proposed as an intervention to treat AD, it will be important to further clarify how these mutations could affect the response to dietary zinc supplements in patients with AD.

Therapies aimed at modulating zinc availability

The "metal hypothesis of Alzheimer's disease," which states that "Aβ-metal interactions potentiate the neurotoxicity of Aβ," has led to the testing of metal binding pharmaceuticals for the treatment of AD (Bush and Tanzi 2008). One of these drugs, clioquinol, was originally taken as an intestinal amebecide and then more generally to treat intestinal infections until being withdrawn for oral use after many patients using it developed subacute myelo-optic neuropathy (Bareggi and Cornelli 2012). Clioquinol is able to cross the blood brain barrier and binds to zinc and copper removing these metals from senile plaques. The metal bound form of clioquinol becomes neutral and crosses cell membranes. Therefore, clioquinol may function as both a chelator to remove toxic zinc accumulation in the brain and as an ionophore to facilitate the delivery of zinc and copper to deficient cells. Although its mechanism of action is still unclear, clioquinol improved cognitive function and prevented Aβ accumulation in APP mutant mice (Grossi et al. 2009). An early clinical trial found decreased plasma Aβ42 and increased zinc after treatment with clioquinol in AD. While scores on the AD Assessment Scale-cognitive subscale (ADAS-cog) improved, this did not reach statistical significance (Ritchie et al. 2003). The first phase two clinical trial with PBT2, an analog of clioquinol more effective as a zinc/copper ionophore, found no significant effect on the mini-mental state examination (MMSE), ADAS-cog, or neuropsychological test battery (NTB) composite, memory or executive scores compared to the placebo (Sampson et al. 2012). However, the highest dose was well tolerated for 12 weeks and resulted in significantly lower cerebrospinal fluid Aβ42 levels, and improved performance relative to baseline values on two executive function tests from the NTB (Faux et al. 2010). While larger trials are required to further test the efficacy of PBT2, several novel compounds aimed at modulating zinc availability including targeted nanoparticles loaded with zinc or coupled to chelators are in the preclinical testing phase (Bush and Tanzi 2008; Liu et al. 2009; Grabrucker et al. 2011a).

Clinical trials have shown therapeutic potential for a variety of strategies aimed at modulating zinc availability in AD patients, but interactions between zinc and other nutrients, especially copper, complicate this picture. Although accumulation of zinc seems to contribute to AD, zinc supplementation may be therapeutic. A small unblinded clinical trial conducted in 1992 found that zinc-aspartate supplementation improved cognitive performance

in eight out of ten patients with AD (Constantinidis 1992). More recently, a 6 month randomized placebo controlled trial of reaZin, a zinc containing formulation designed to avoid the gastrointestinal irritation associated with oral zinc, conducted in sixty AD patients found a significant decrease in serum copper and a prevention of cognitive decline (measured with ADAS-cog, MMSE, and the Clinical Dementia Rating Scale-Sum of Boxes) that did not reach statistical significance. Longer treatment duration and larger sample size are likely to improve results in future trials given that the largest protection was seen in older patients who face more rapid deterioration. Furthermore, post hoc analysis revealed a statistically significant reduction of cognitive decline on two tests (and nearly significant for the MMSE) when analyses were limited to the twenty-nine patients over seventy years old (Brewer 2012). Furthermore, dietary zinc deficiency exacerbated behavioral and histological pathology in an APP mutant mouse (Stoltenberg et al. 2007), and zinc supplementation prevented AD pathology in the 3X-Tg mouse model (Corona et al. 2010). However, another study found impaired memory performance in zinc supplemented APP mutant mice associated with decreased Aβ deposition (Linkous et al. 2009).

Excessive zinc intake relative to copper can lead to copper deficiency and subsequent anemia and degeneration of cognitive function (Penland 2000; Hedera et al. 2009; Railey et al. 2010). Therefore, it is important to monitor copper status to prevent deficiency during zinc supplementation therapy. Nevertheless, the benefits of zinc supplementation are in some instances (e.g. Wilson's disease and possibly AD) related to decreased copper levels, and zinc may provide a safer method than chelating agents for the reduction of circulating copper levels. Zinc supplementation could provide a broad range of benefits for the aging population because clinical trials have also found reduced markers of inflammation and oxidative stress as well as improved mood and memory among elderly subjects (Constantinidis 1992; Beletate et al. 2007; Bao et al. 2010; Lai et al. 2012).

Summary

Both increased and decreased zinc concentrations in the brain have been linked to AD pathology. These apparently opposite findings could be explained by the fact that multiple zinc pools are present in the brain and serve distinct functions. For example, synaptic and cytosolic zinc may play completely different roles. A major challenge for the future is to elucidate which of these alterations are a cause or a consequence of AD pathology. This knowledge is highly relevant to support the use of zinc-targeted therapies in AD. On the other hand, zinc supplementation can be highly beneficial for the elderly in general, and for those with DM in particular. The occurrence of gene polymorphisms in the population, which affect zinc homeostasis potentially contributing to the risk of DM and dementia, can now be taken into consideration when designing future clinical trials for zinc-based therapies.

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