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Zinc(II) Induced Alzheimer's Disease Prevention and Progression With Early, Middle and Lately Stages

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ABSTRACT

Zinc(Ⅱ) induced Alzheimer's Disease (AD) prevention and suppressive progression with early, middle, and lately stages are elucidated, and subsequently zinc binding molecular mechanism on each Aβ peptide and Tau protein in progressing stages is clarified. Zinc homeostasis regulates MCI and AD prevention, in which $ZnCl_2$ could prevent AD pathology by that zinc can reduce β-Amyloid (Aβ) and Tau proteins. Zinc transporters may allow the novel therapies that ZnT-6 functions to a likely site of Aβ generation. At AD progression with early stage, zinc-induced aggregation of Aβ peptides and tau hyperphosphorylation on amyloid and tau aggregation consider the involvement of environmental zinc in Aβ and tau pathology. Zinc can suppress spreading of the Aβ peptide and the Tau protein that elemental zinc 150 mg daily is showed to be evident for an improvement of memory, understanding, communication, and social contact in AD. Zinc induced middle stage AD progression is pathologically characterized by the deposition of Aβ plaques and hyperphosphorylated Tau Proteins (p-tau). Zinc Finger Proteins (ZNFs) regulate the accumulation of tau proteins to affect the Neurofibrillary Tangles (NFTs), resulting in the formation of NFTs, and can inhibit protein phosphatase, promoted abnormal phosphorylation of tau protein. Zinc(Ⅱ) can prevent heavy stage AD with pathological deposits of Senile Plaques (SPs) and NFTs that the tau-zinc interaction will help understanding the zinc-related tau regulation or aggregation processes in both physiological and pathological conditions. Zinc accelerates the fibrillization of human Tau and thereby increases Tau toxicity in neuronal cells with zinc exacerbated tauopathic deficits.

Zinc induced toxic Reactive Oxygen Species (ROS) generation and hyperphosphorylated tau cause oxidative stress and neurotoxicity, leading to hyperphosphorylated tau damages.

Zinc(Ⅱ) binding AD molecular mechanism on Aβ and Tau proteins is that Zn^{2+} ions which having Zn^{2+} ions-centered tetrahedral geometric coordination pattern and Zn-CysHis Ligands complexes with tetrahedral geometry formed, bind with Aβ and Tau proteins in each three AD progressing stages, causing Zn^{2+} ions-each stages protein complex formations and oxidative stress to Aβ and Tau protein cells, leading the Zn-CysHis Ligands complexes to molecular and apoptosis activities of synaptic cells.

Keywords:

Zinc(Ⅱ), Aβ and Tau proteins, SPs and NFTs, Tau hyperphosphorylation, Tau toxicity and tauopathy, ROS and oxidative stress, Zinc-binding molecular mechanism.

Abbreviation

Aβ=Amyloid-β, AβOs=β-Amyloid Oligomers, AD=Alzheimer's Disease, APP=Amyloid Precursor Protein, CNS=Central Nervus System, CSF=Cerebrospinal Fluid, DMN=Default Mode Network, EAD=Early AD, ER=Entorhinal Region, HD=Huntington's Disease, HPG=Hippocampus/Parahippocampal Gyrus, LAD=Late Stage AD, LLPS=Liquid–Liquid Phase Separation, LTP=Long-Term Potentiation, MCI=Mild Cognitive Impairment, MBI=Mild Behavioral Impairment, MBR=Microtubule-Binding Region, NC=Normal Control, Nfts=Neurofibrillary Tangles, NTR=N-Terminal Projection Region, PD=Pick Disease, PET=Positron Emission Tomography, PRR=Proline-Rich Region, PP2A=Protein Phosphatase 2A, ROS=Reactive Oxygen Species, SP=Senile Plaques, TGN=Trans-Golgi Network, TRE=Transentorhinal Region, Znfs=Zinc Finger Proteins, ZnT=Zinc Transport.

Introduction

Alzheimer's disease (AD) is the most common cause of dementia with a brain disorder for a gradual decline in memory, thinking, behavior and social skills. AD is a degenerative brain disease and causes the brain to shrink and brain cells to eventually die. Further, early stage β-amyloid oligomers (AβOs) and late stage β-amyloid peptide (Aβ) plaques are the pathological hallmarks of AD brains. AβOs are known to be more neurotoxic and contribute to neuronal damage [1]. The Aβ deposited in AD is more easily cleared and does not show the same physical and biochemical characteristics as the amyloid found in AD. AD pathogenesis is driven by the production and deposition of the Aβ with amyloid binding ligand that these ligands could be quite useful, provided that their binding site selectivity has been characterized under in vivo imaging-like conditions [2].

The formation of Senile Plaques (SP) and Neurofibrillary Tangles (NFTs) have been considered as the defining pathological features of AD that the deposition of Aβ is the initial pathological event in the disease leading to the formation of NFT, cell death, and ultimately dementia [3]. Aβ, either as plaques, or as nonfibrillar, soluble, oligomeric forms, initiates a pathophysiological cascade leading to tau misfolding and assembly that spreads throughout the cortex, ultimately resulting in neural system failure, neurodegeneration and cognitive decline [4]. Although synaptic loss has been reported in AD brains, mainly due to a structural damage imputable to plaques and tangles in a later stage of the disease, a subtle effect exerted by soluble forms of Aβ and tau at the synapse seems to be the earlier event underlying memory loss [5].

The other, zinc(II) has important role for AD prevention and pathological progressing stages that physiological role of zinc in the brain is important for AD pathology and AD is a devastating neurodegenerative disease with a dramatically increasing prevalence and the contribution of zinc to the formation, aggregation, and degradation of the Amyloid-B (Aβ) peptide and the contribution of zinc to the pathogenesis of AD [6]. Zn(II)-bound peptide to form amorphous aggregates with less entropic penalties than their fibrillar counterparts with a result of zinc binding to the N-terminus and Aβ42 revealed a higher rigidity than Aβ40 at the C-terminus [7]. Zinc binding to the tau protein influences the protein aggregation Kinetics and Oligomer Distribution [8]. The zinc binding to Tau protein results in substantially different effects on the protein aggregation that this is especially relevant when considering recent evidence implicating zinc binding to Tau to the generation of toxic aggregates, independently of phosphorylation, in which the mechanism of zinc-regulated Tau aggregation and toxicity in the AD brain [9].

In this short-review article, zinc(II) induced AD prevention and progression with early, middle, and lately stages are elucidated, and subsequently zinc binding molecular mechanism for AD prevention, Mild Cognitive Impairment (MCI, and each Aβ peptide and Tau protein in progressing stages is clarified.

AD progressing process

MCI at the clinical pre-dementia stages with progressive cognitive deficits incipient Alzheimer's disease

MCI as a pre-existing state of AD was defined by Petersen et al. (1999) as progressive memory loss, a prodrome of Alzheimer's disease, and the other, Mild Behavioral Impairment (MBI) is indicated as a counterpart of MCI as a transitional state between normal aging and dementia that have implications for early detection, prevention, and treatment of patients with late-life dementia [10].

An accurate prediction on the conversion from MCI to AD is of vital clinical significance for potential prevention and treatment of AD. The clinical features of AD vary from stable performance and cognitive health with only a gradual decline in the short-term memory to a serious state of mild cognitive impairment and into different forms of dementia on deterioration of memory, learning, orientation, the other, the pathological features of AD are the accumulation of Aβ and the aggregation of Aβ as the cause of neurodegeneration observed in AD [11].

Early stage; No impairment, Minimal cognitive decline, Lenient decline.

The aggregation of Aβ gives rise to NFTs, neuronal dysfunction and dementia. During the process leading to AD, tau and Aβ first misfold and form aggregates in one brain region. Aβ is a proteolytic product of APP that is highly expressed in neurons and physiologically involved in many functions, regulation of synaptic functions and plasticity, involvement in early nervous system development and in neuroprotection. Tau and Aβ first misfold and form aggregates in one brain region, from where they spread to interconnected areas of the brain spreading of both pathogenic proteins and to avoid their synergistic impact on neuronal networks [12].

A variety of Amyloid-β (Aβ) and tau Positron Emission Tomography (PET) tracers are already available for the clinical diagnosis of AD in primary tauopathies that PET imaging using Aβ and tau tracers has enabled the early and differential diagnosis of AD and the detection of other targets, neuroinflammation and synaptic density at the beginning of AD has the potential for more holistic in vivo diagnostics [13]. Amyloid plaques and NFTs simultaneously accumulate in AD that these two aggregation processes appear to occur independently, while the NFTs are intracellular lesions which develop in neuronal cell bodies and comprise primarily of aggregates of the microtubule (MT)-binding protein tau with the relative stable each Aβ-tau oligomeric complex formation, Aβ and tau oligomers as chemical reactions [14].

Accumulation of amyloid beta and phosphorylated tau within the brain cause disturbances in synaptic function and loss of neuronal cells. Abnormal accumulation and aggregation of phosphorylated tau leads to the disease state in AD and other tauopathies. Phosphatase plays a major role in abnormal phosphorylation, which leads to the aggregation of tau and abnormally hyperphosphorylated tau aggregates occur in neurons, which leads to synaptic loss and neuronal damage in the brain [15]. Synaptic and axonal biomarkers change in earlier and later Alzheimer's disease stages that global amyloid-b deposition would be associated with changes in synaptic markers, memory dysfunction and default-mode network activity, whereas elevated tau PET would be accompanied by more pronounced axonal degeneration, global cognitive decline and para hippocampal white matter damage [16].

Spreadings of Amyloid-β (Aβ) and tau proteins are implicated in memory impairment, MCI. An increases tau phosphorylation that a specific inhibitor of the tau kinase glycogen synthase kinase blocks the increased tau phosphorylation induced by Aβ and prevents Aβ-induced impairment of Long-Term Potentiation (LTP) [17]. Aβ aggregation and Aβ removal progressing, and Tau production and phosphorylation altering and progressing had been elucidated [18]. Progress of tau-targeting therapy in AD with an emphasis on immunotherapy is regulated microtubule assembly and affected the morphology and growth of neuronal axons that the degree of tau pathology is more closely related to cognitive decline in AD patients [19]. Pathological situation tau may be hyperphosphorylated and assembled in an aberrant way that as a consequence of these modifications, neural toxicity supplements, resulting in the appearance of neurological disorders, mainly dementias for Alzheimer's disease, which are

collectively known as tauopathies [20].

Tau structure such as a N-Terminal Projection Region (NTR), a Microtubule-Binding Region (MBR), a Proline-Rich Region (PRR), and Carboxyl-Terminal Region (CTR) domains contain similar structural motifs the length of 18 amino acids that the CTR region of Tau presents an amino acids sequence that is highly conserved across different species [21]. The tau pathology is initially seen in the cerebral cortex in glutamatergic neurons of the Transentorhinal Region (TRE) and then Entorhinal Region (ER) cortices (NFT stages I-II in the lower portion of panel B points to the border between the two), in which the tau pathology is confined predominantly to layer pre-α (inset shows neurofibrillary tangles in pre-α) [22].

Middle stage; Medium Cognitive Decline, Moderately Severe Cognitive Decline

Aβ accelerates the phosphorylation of tau protein that is caused by tau hyperphosphorylation and the interplay between Aβ and tau to promote a better understanding of the roles of these proteins in the pathological process of AD and Aβ plaques facilitate neuritic plaque tau aggregation and propagation [23]. Tau pathology develops in the deeper layers of TRE and ER, in the CA1 sector of the Ammon's horn and in the adjoining temporal neocortex [22]. Tau is regulated during both normal homeostasis and in stress-induced responses by an array of posttranslational modifications. In AD and other tauopathies, however, the phosphorylation level of tau is significantly higher. Tau hyperphosphorylation results from perturbation of cellular signaling, mainly through imbalance in the activities of different protein kinases and phosphatases [24]. Tau protein is characterized by structural variability depending on the crystallization conditions and the formation of pathologic aggregates, in which the molecular structures of Tau tangles have large implications in diagnosis and a new generation of anti-aggregation ligand compounds able to modulate Tau aggregation [25].

Heavy stage; Severe decline, Critical Cognitive Decline

In the advanced stages of the disease central sensory procedures, including the visual system, get affected, AD-associated problems decrease life expectancy, reduce quality of life, cause physical disability, and eventually lead to serious problems in daily life activities such as social and occupational functions [26]. Amyloid-β and tau was associated with the segregation and integration of brain functional connections, and episodic memory. Amyloid-β first accumulates in a set of distributed brain regions that form part of the so-called Default Mode Network (DMN). Conversely, tau pathology begins to accumulate in vulnerable loci, later advancing to local functionally connected regions, possibly following transsynaptic spread along functional connections [27].

Severe AD step status becomes to be abnormal deposited by pathological Aβ and Tau proteins in brain that tau loss of function does not replicate human clinical phenotypes, toxic gain of function has been historically suggested as the cause of tauopathies, accumulation of insoluble tau deposits, and subsequent neuronal loss, in which tau-targeting therapies will eventually play a central role in the treatment of tauopathies [28]. Amyloid Beta and hyperphosphorylated tau-independent mechanisms of synaptic damage, factors affecting tau accumulation, and neurotransmitter abnormalities due to phosphorylated tau accumulations at the synaptic cleft with factors affecting tau accumulation [29]. Tau pathology finally spreads to the secondary and then primary visual, auditory, somatosensory. Rapid tau fibrillation at later stage tau pathology destroys the cellular engine for Aβ production [22].

As critical AD stage, tau-targeting therapy is a progressive neurodegenerative disorder characterized by two pathological hallmark lesions: extracellular plaques composed of β-Amyloid (Aβ) peptide and intracellular neurofibrillary tangles made up of highly phosphorylated tau protein [19].

Zinc(II) induced suppressive AD dementia proceeding for early, middle, severe stages

Zinc induced MCI and AD prevention

Zinc homeostasis regulates MCI and AD prevention due to be very important players in the pathophysiology of neurodegenerative disorders [30]. Progression from MCI leads to Early AD (EAD) with a decline in cognitive function, cognition decline in addition to memory, a clinical dementia rating scale, impaired ADLs, and a clinical evaluation of dementia, and leads to Late Stage AD (LAD) characterized by severe dementia with disorientation, profound memory impairment, global cognitive deficits and immobility that Aβ processing occurs leading to increased generation of oligomeric Aβ species and the promotion of oxidative damage associated with AD. As the disease progresses and extraparenchymal Zn levels normalize, the resulting alterations in multiple ZnT proteins could further promote Aβ aggregation and SP formation [31].

Zinc could prevent AD pathology by that zinc can reduce Aβ and Tau proteins, in which zinc is involved in inducing both Aβ and tau aggregation involved in zinc-mediated tau hyperphosphorylation as well as consider the involvement of environmental zinc in Aβ and tau pathology in AD [32]. Zinc can modulate formations of the Amyloid-β (Aβ) peptide and Tau protein, therefor, zinc ($ZnCl_2$) could prevent AD [33]. Findings on the potential efficacy of zinc therapy for prevention and the improvement of cognitive decline [34]. Zinc and copper interaction with Aβ in the pathophysiology of AD indicate that the CQ class of agents could have therapeutic utility in AD [35].

Zinc transporters (ZnTs) may allow the discovery of novel therapies not only for AD, but also for other neurodegenerative diseases such as PD and Huntington's Disease (HD) on the prevention or treatment of chronic neurodegenerative diseases [36]. ZnT-6 is of particular interest in AD because it functions to sequester Zn in the trans-Golgi network (TGN), a likely site of Aβ generation through cleavage of APP by the proteolytic gamma secretase complex that immunohistochemical analyses of ZnT-6 in the Hippocampus/Parahippocampal Gyrus (HPG) of MCI, AD and Pick Disease (PD) subjects as another tauopathy [37].

There was a statistically significant decrease of serum Zn (11.7 ± 0.5 μM) in men with MCI compared to women with MCI (13.7 ± 0.6 μM) and normal control (NC) men (13.9 ± 0.6 μM). Serum Zn levels due to Zn loss in probable AD patients were comparable to those in NC subjects [38]. Sleep disturbances increase Aβ plaques and tau protein aggregation. Whether zinc plays a role in cognitive impairment, which often co-exists

with sleep disorders, must be investigated. Several clinical trials have confirmed the benefit of zinc supplementation in sleep disorders [39].

Zinc induced AD progression with early stage

AD is pathologically characterized by the deposition of β-amyloid (Aβ) plaques and hyperphosphorylated tau proteins (p-tau) that zinc ion promotes the intermolecular bridging of tau monomers through cysteine and histidine binding with the aggregation process. The molecular interactions can be the dominant origins for the aggregation that new zinc-tau protein chemical interaction and chemical bonding can provide significant signature signals for us to analyze such complex processes [40]. An excessive zinc concentration at the early stages of the formation of conglomerates can negatively affect aggregation, since in systems where zinc ions occupied the 11EVHH14 coordination center and the His6 residue of every Aβ16 monomer, playing an important role in the formation of neurotoxic non-fibrillar aggregates of beta-amyloid peptide Aβ16 [41].

The inhibition of the formation of Aβ oligomers and aggregation is the most promising strategies in the development of disease-modifying therapeutic approaches in AD that inhibition of zinc-dependent oligomerization of the Aβ metal-binding domain and suppression of the zinc-dependent oligomerization of various Aβ isoforms [42]. Zinc ions are sufficient to exert effects on aggregations of Aβ peptides and tau hyperphosphorylation with an especially high level of zinc found around neurofibrillary tangles and Aβ-amyloid plaque [43]. Zinc can suppress spreading of the Amyloid-β (Aβ) peptide and the Tau protein that elemental zinc 150 mg daily is showed to be evident for an improvement of memory, understanding, communication, and social contact, and zinc-hydrogenaspartate can improve memory, understanding, communication and social interaction in AD [44].

Amyloid plaque pathology might be a biomarker of zinc dyshomeostasis that may explain amyloid deposition caused by the slow turnover of synaptic Zn^{2+} released during glutamatergic synaptic transmission. There are many types of ZIPs and ZnTs expressed in neurons, but ZnT^3 is implicated in cognitive loss with aging and amyloid formation in AD. ZnT concentrates Zn^{2+} in glutamatergic synaptic vesicles that is released upon synaptic activity and then is normally rapidly taken up by unidentified energy-dependent mechanisms [45].

In the pathogenesis of AD particularly the amyloid precursor protein and amyloid beta peptide generation and aggregation, low extra-parenchymal Zn early in disease progression may lead to increased levels of brain Zn, in which these elevations of Zn could then become concentrated in subcellular organelles that Aβ processing occurs leading to increased generation of oligomeric Aβ species and the promotion of oxidative damage associated with AD and the resulting alterations in multiple ZnT proteins could further promote Aβ aggregation and SP formation [46].

Zinc induced AD progression with middle stage

Disruption of Zn^{2+} homeostasis is associated with the pathogenesis of a variety of Central Nervus System (CNS) disorders that Zn^{2+} is involved in the synthesis and processing of APP to affect the production of Aβ. Zn^{2+} can influence the digestive efficiency of the 3 secretases through conformational changes. Zn^{2+} can interact with Aβ to regulate the polymerization of Aβ into different forms. At low concentrations by selective precipitation of aggregation intermediates, Zn^{2+} performs a protective effect on resisting the neurotoxicity of Aβ. While at high concentrations, Zn^{2+} binding increases the fibrillar Aβ aggregation, resulting Zn^{2+}-amyloid interactions promote the precipitation of Aβ fibrils [47]. Phosphorylated Aβ species could be significant for the development of late AD that the role of pS8-Aβ42 as a potential quencher of zinc-induced oligomerization of endogenous Aβ species and of pathological effects associated with this process [48].

Zinc Finger Proteins (ZNFs) regulate the accumulation of tau proteins to affect the neurofibrillary tangles, pathological tau protein formation (hyperphosphorylation), resulting in the formation of neurofibrillary tangles typical of AD, and can inhibit protein phosphatase, promoted abnormal phosphorylation of tau protein, play an important role in neurodevelopmental disorder which may contribute to autism, anti-inflammatory and neuroprotective effects [49].

Excessive zinc released from synaptic vesicle activation promotes tau hyperphosphorylation in cells and liquid–liquid phase separation of tau protein. In the AD brain, presynaptic neurons release excessive zinc, which causes oxidase activation in neurons and exacerbates pathological development, leading to neuronal death, in which rapamycin prevents zinc-induced cognitive impairment and protects neurons from tau pathology, oxidative stress, and synaptic impairment [50].

Zinc induced AD progression with heavy stage

Zinc homeostasis with moderating synaptic activity may benefit the AD patients not only through reducing amyloidosis but also through reducing tauopathy that synaptic activity promotes tau hyperphosphorylation. Zinc-induced tau hyperphosphorylation was observed in cultured brain slices incubated with exogenously supplemented zinc that Tau hyperphosphorylation induced by synaptic activity was strongly associated with inactivation of Protein Phosphatase 2A (PP2A) [51].

Removal of zinc binding almost completely abolishes Tau toxicity, suggesting that appreciable Tau toxicity requires both the presence of hyper phosphorylation equally contribute to tauopathy that Zn^{2+} induces Tau protein has a tetrahedral zinc-binding center involving Cys 291, Cys 322, His 330, and His 362, that there could be another pathway where different Cysteine and Histidine groups of different tau monomers bind to the zinc ion, and the aggregation occurs through cross-linking of tau monomers by zinc ion [52]. Zinc binding sites to Tau proteins similar to AD neurodegeneration have four Zn^{2+} binding sites in the protein while using monomer-enriched full-length human Tau. While binding of one zinc to Tau at micromolar affinities has been established in the R1/R3/R4-containing K19 construct and the R3 fragments, in which the aggregation rate of Tau is greatly enhanced by zinc binding, suggesting that processes occur in amyloid assembly [53]. The clinical importance of zinc in tau aggregation paves the way for designing potential therapies for tauopathies [54]. Zinc binding is a substantial contributor to tauopathy and in AD a combination of Aβ plaque and tauopathy,

could accelerate late Tau toxicity development, leading to advanced AD. Zn^{2+} can then accelerate the fibrillization of human Tau, thereby enhancing early and late apoptosis and increasing Tau toxicity in neuronal cells [55].

Thus, zinc regulates Tau aggregation and toxicity, and will be helpful to explain the mechanism of zinc-regulated Tau aggregation and toxicity in the AD brain and an involvement of zinc in the pathogenesis of AD and other tauopathies and provide critical insights into the mechanism of Tau toxicity enhanced by zinc, in which Zn^{2+} binds to full-length human Tau by interacting with Cys-291 and Cys-322, forming a 1:1 Zn^{2+}-Tau complex. Zinc dramatically accelerates abnormal aggregation of human Tau and significantly increases Tau toxicity in neuronal cells mainly via bridging Cys-291 and Cys-322. Pathological zinc regulates Tau aggregation and toxicity associated with Alzheimer disease [56].

Zinc induced ROS generation in AD

Continuous inflammation in the nervous system was regarded as the major cause of neurodegeneration occurring in AD. Increased activation of microglial cells during neuroinflammation causes toxic Reactive Oxygen Species (ROS) generation. There is a vicious cycle formed by excessive zinc, tau, and oxidative stress: elevated levels of zinc raise the production of ROS in mitochondria that excessive zinc and hyperphosphorylated tau cause oxidative stress and neurotoxicity. Hyperphosphorylated tau damages microtubule function and induces oxidative stress. Increased oxidative stress has been indicated to cause tau hyperphosphorylation and aggravate neuronal death [50]. Zinc also induced oxidative stress and ROS generation in AD synapsis cell that AD and oxidative stress appear to go hand in hand, with ROS production being both a cause and consequence of Aβ aggregation and many of the pathological changes that take place during AD appear to be very similar to those observed in injury related to oxidant-induced zinc liberation and downstream apoptosis [57].

Zinc high concentrations were associated with memory and cognitive regions of the brain, including this binding of zinc has a highly ordered conformational state of Aβ, leading to the production of toxic, fibrillary, Aβ aggregates, the immunological/inflammatory response to non-soluble Aβ plaques involves the disruption of zinc homeostasis followed by uncontrolled cerebral zinc release, which is typical for oxidative stress. Thus, the uncontrolled accumulation of zinc or Aβ leads to zinc-induced and Aβ-mediated oxidative stress and cytotoxicity [58].

Zinc binding molecular mechanism on Aβ and Tau proteins during AD progressing stages

Zn(II)-binding to the N-terminus of Ab40, the residues flanking this region become more mobile on the picosecond-to-nanosecond timescale, and the increased rigidity of Ab42 at the C-terminus, zinc(II) can bind to Ab and redirect its assembly from amyloid fibrillar toward less toxic amorphous aggregation [59]. Zn^{2+} ions have a protective effect on Aβ's toxicity at low Zn^{2+} concentrations, whereas higher concentrations may enhance toxicity, in which Zn^{2+} has been reported to inhibit formation of amyloid fibrils. At high Zn^{2+} concentration, amorphous aggregates are formed. Structural Aβ– Zn^{2+} interactions showed that Zn^{2+} binds to the N terminus of 40 residue variant of Aβ (Aβ40) where the first 16 residues are the minimal peptide sequence for Zn^{2+} binding. In Aβ40 the Zn^{2+} ion is coordinated by four ligands, the histidines H6, H13, and H14 and the N-terminal [60]. Zn(II) binding to the Aβ peptide bases on the Zn (peptides) complexes that Zn(II) coordination site to Aβ has been revealed that a tetrahedrally bound Zn(II) ion, in which the coordination sphere is made by two His residues and two carboxylate side chains, in which equilibria between equivalent ligands for one Zn(II) binding position have also been observed, the predominant site being made by the side chains of His, Glu, and Asp [61].

The other, in zinc-binding sites structure on tauopathy, the Tau protein has a tetrahedral zinc-binding center involving Cys 291, Cys 322, His 330, and His 362, in which the aggregation occurs through the β-sheet formation without the direct involvement of the zinc-binding domain in the aggregation that there could be another pathway where different Cysteine and Histidine groups of different tau monomers bind to the zinc ion, and the aggregation occurs through cross-linking of tau monomers by zinc ion [43]. Zinc induced Aβ and tau proteins are involved with zinc dyshomeostasis in promoting both Aβ and tau aggregation and oxidative stress, the effects of lipid membranes on Aβ and tau (co)-aggregation, and the peptide-based inhibitors of Aβ and tau misfolding [62]. Three distinct zinc binding sites on tau are recognized to be located in the N-terminal part, the repeat region and the C-terminal part, where the N-terminal and the C-terminal sites are independent of each other and the clinical importance of zinc in tau aggregation pave the way for designing potential therapies for tauopathies [63].

Thus, Zinc ions are subject to bind proteins that Zinc binds to Aβ plaques and tau proteins in a tetrahedral geometry, binding to two cysteine and two histidine residues that Zn(II) binding to the Aβ/Tau peptide bases of the Zn (peptides) complexes that Zn(II) coordination sites to Aβ/Tau have been revealed that tetrahedrally bound Zn(II) ion, in which the coordination spheres are made by two His residues and two carboxylate side chains. Chemical reactions on the accumulation of (Aβ)/(Tau) proteins are indicated in the following;

(Zn^{2+}) + (Aβ) + (Tau)=Zn^{2+}Tetrahedral {(Aβ)•(Tau) proteins}

Accordingly, zinc(II) induced suppressive AD dementia molecular mechanism is clarified by that zinc ions bind to Aβ plaques and tau proteins and reduce the toxicity with B-Amyloid Oligomers (AβOs) and tau oligomers or hyperphosphorylated tau proteins. Zinc(II) coordinated molecular mechanism has been subsequently elucidated that Zn^{2+} ions which having Zn^{2+} ions-centered tetrahedral geometric coordination pattern formed, bind with each AD processing stages Aβ and Tau proteins, causing Zn^{2+} ions-each three stages protein complex formations and oxidative stresses to Aβ and Tau protein cells, leading the Zn-CysHis Ligands complexes to molecular apoptosis activities of synaptic cells and it could become possible to reduce or remove accumulation of Aβ/Tau proteins due to zinc ion complexes compound formation on the accumulation of Aβ/Tau proteins.

In Summary, as shown in mentioned-above, zinc induced AD prevention and progression with early, middle, and severe stages, and zinc-binding molecular mechanism on Aβ and Tau proteins in progressing each AD stages is represented in Table 1.

Table 1: Zinc induced AD prevention and progression with early, middle, and severe stages, and zinc-binding molecular mechanism on Aβ and Tau proteins in progressing each AD stages.

Zn^{2+} ions	Zinc induced AD prevention and AD progressing for early, middle, and severe stages			
	MCI with pre-dementia and AD Prevention No Impairments	AD Early Stage Minimal Cognitive Decline, Lenient Decline	AD Middle Stage Medium Cognitive Decline, Moderately Severe Cognitive Decline	AD Severe Stage Severe Decline, Critical Cognitive Decline
Zn^{2+} Ions →	→ Zn^{2+}, ROS Zn^{2+}Conc; 50∼100μM •Zinc homeostasis regulates MCI and AD preventions due to neurodegenerative disorders •$ZnCl_2$ therapy for AD prevention •Zinc transporter can prevent AD •Reaction of Zn and Cu with Amyloid-β is effective for AD prevention •ZnT-6 is efficient in MCI, AD, and PD	→ Zn^{2+}, ROS Zinc Conc; 100∼250μM •Zinc can regulate Amyloid-β and Tau pathology in preclinical AD spreads •Zinc-hydrogenaspartate can improve memory, understanding, and communication •Serum Zn (11.7 ± 0.5 μM) in men •ZnT proteins promote Aβ aggregation with SP formation	→ Zn^{2+}, ROS Zinc Conc; 100∼400 μM •Zn^{2+} homeostasis induced complex tau protein aggregation and oxidative stress occur in heavy spreading of tau protein and Aβ peptide •ZNFs regulate accumulation of tau proteins, affect the neurofibrillary tangles, and play an important role in neurodevelopmental disorder	→ Zn^{2+}, ROS Zinc Conc; 100∼500 μM •Zn^{2+} homeostasis could prevent heavy stage AD with SPs and NFTs accumulations •Critical spreading of Tau protein and Aβ peptide and oxidative stress •Zinc increases Tau phosphorylation •Zinc exacerbates Tau pathology and tauopathic deficits •Zn-HisCys-Ligand complexes formation
Zinc(Ⅱ)-binding suppressive AD dementia molecular mechanism; Zinc(Ⅱ) ions-induced the regulated accumulations of the Aβ and Tau proteins occur in AD progressing three stages that zinc ions bind to Aβ plaques and tau proteins and reduce the toxicity with AβOs and tau oligomers or hyper-phosphorylated tau proteins. Zinc(Ⅱ) coordinated molecular mechanism has been subsequently clarified that Zn^{2+} ions which having Zn^{2+} ions-centered tetrahedral geometric coordination pattern and Zn-CysHis Ligands complexes with tetrahedral geometry formed, bind with Aβ and Tau proteins in AD progressing each three stages, causing Zn^{2+} ions-each stages protein complex formations and oxidative stress to Aβ and Tau protein cells, leading the Zn-CysHis Ligands complexes to molecular and apoptosis activities of synaptic cells.				

Conclusions

Alzheimer's Disease (AD) has severe neurodegenerative brain disorder by the accumulation of amyloid-beta plaques, abnormally hyperphosphorylated tau (p-tau) containing intracellular Neurofibrillary Tangles (NFTs) in the brain causing neural disintegration, synaptic dysfunction, and neuronal death leading to dementia.

Zinc induced Mild Cognitive Impairment (MCI) and AD prevention are involved that zinc homeostasis regulates MCI and AD prevention and zinc ($ZnCl_2$) could prevent AD pathology by that zinc can reduce β-Amyloid (Aβ) and Tau proteins. Zinc transporters may allow the discovery of novel therapies that ZnT-6 functions to a likely site of Aβ generation.

Zinc induced AD progression with early stage is involved that zinc-induced aggregation of Aβ peptides and zinc-mediated tau hyperphosphorylation on amyloid and tau aggregation considers the involvement of environmental zinc in Aβ and tau pathology. Zinc can suppress spreading of the Aβ peptide and the Tau protein that elemental zinc 150 mg daily is showed to be evident for an improvement of memory, understanding, communication, and social contact in AD.

Zinc induced AD progression with middle stage is involved that is pathologically characterized by the deposition of Aβ plaques and hyperphosphorylated tau proteins (p-tau). ZNFs regulate the accumulation of tau proteins to affect the NFTs, resulting in the formation of NFTs, and can inhibit protein phosphatase, promoted abnormal phosphorylation of tau protein. Excessive zinc released from synaptic vesicle activation promotes tau hyperphosphorylation.

Zinc induced AD progression with heavy stage is involved that Zinc(Ⅱ) can prevent heavy stage AD with pathological deposits of SP and NFTs that the tau-zinc interaction will help understanding the zinc-related tau regulation or aggregation processes in both physiological and pathological conditions. Zinc accelerates the fibrillization of human Tau and thereby increases Tau toxicity in neuronal cells, in which zinc exacerbated tauopathic deficits in circadian rhythm, nesting behavior.

Zinc induced ROS generation in AD is involved that increased activation of microglial cells during neuroinflammation causes toxic Reactive Oxygen Species (ROS) generation and hyperphosphorylated tau cause oxidative stress and neurotoxicity, leading to hyperphosphorylated tau damages. Increased oxidative stress has been indicated to cause tau hyperphosphorylation and aggravate neuronal death.

Zinc(Ⅱ) binding AD molecular mechanism on Aβ and Tau proteins with progressing stages is clarified that Zn^{2+} ions which having Zn^{2+} ions-centered tetrahedral geometric coordination pattern and Zn-CysHis Ligands complexes with tetrahedral geometry formed, bind with Aβ and Tau proteins in each three AD progressing stages, causing Zn^{2+} ions-each stages protein complex formations and oxidative stress to Aβ and Tau protein cells, leading the Zn-CysHis Ligands complexes to molecular and apoptosis activities of synaptic cells.

Conflicts of Interest

Author declares there is no conflicts of interest.

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