ISSN 2689-8268 | Volume 8

American Journal of Surgery and Clinical Case Reports

Semi-Review Article Open Access

Zinc(II)-Modulated Clearance and Cleavage for Aβ Peptide and Tau Protein in Alzheimer's Disease

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Received: 18 Sep 2024
Accepted: 25 Oct 2024
Published: 30 Oct 2024
J Short Name: AJSCCR

Keywords:

Zinc(II): Aβ and Tau proteins; IDE: Degradation clearance and cleavage; MMPs: Bioactive compounds; NEP: ZEP-TFs: Zinc-binding molecular mechanism

Citation:

Tsuneo Ishida. Zinc(II)-Modulated Clearance and Cleavage for Aβ Peptide and Tau Protein in Alzheimer's Disease. Ame J Surg Clin Case Rep. 2024; 8(3): 1-8

1. Abstract

Zinc(II) can prevent on pre-stage, mild cognitive impairment (MCI) and pathological AD for AD MCI and prevention that antibodies prevent MCI, zinc homeostasis, ZnCl2, zinc transporter (ZnT) prevent MCI and AD, ZnT-6 prevents MCI and AD that ZnT-6 is a likely site of Aβ generation through cleavage of amyloid precursor protein (APP), and insulin degrading enzyme (IDE) with zinc-metalloendopeptidase prevents AD. Clearance and cleavage stage to AD Aβ peptide aggregation is involved that Matrix metalloproteinases (MMPs, MMP2, MMP9) can degrade fibrillar Aβ peptide, Neprilysin (NEP) with MMPs (MMP-2, MMP-3, MMP-9) belonging to the family of zinc- dependent enzymes can be cleared Amyloid-Beta Protein Clearance and Degradation (ABCD), and insulin degrading enzyme (IDE) having a zinc-endopeptidase can cleave a variety of small peptides. Clearance and cleavage stage to AD Tau protein aggregation is involved that Zinc finger protein, Zinc finger protein transcription factors (ZFP-TFs) can reduce persistent repression of tau. Bioactive compound-clearance can be performed, Zinc-BDNF deprivation provokes AEP activation and cleaves Tau, and Zinc ions could be cleaved in tau proteins. Clearance and cleavage stage to AD Aβ toxicity dependent on misfolded Tau is involved that Zinc metalloproteinases, Dietary bioactive compounds can be cleared and cleaved on Aβ and Tau, Zinc-Microglia provide neuroprotection through Aβ and tau cleared and cleaved, and Aβ and Tau degradation clearance is shown by using zinc 150 mg daily. Zinc induced toxic reactive oxygen species (ROS) generation leading to hyperphosphorylated tau damages and increased oxidative stress has been indicated to cause tau hyperphosphorylation and aggravate neuronal death. Zinc(II) binding AD molecular mechanism of clearance and cleavage for three stages to Aβ and Tau proteins is clarified that Zn2+ions which having Zn2+ ions-centered tetrahedral geometric coordination pattern and Zn-CysHis Ligands complexes with tetrahedral geometry formed, bind with Aβ and Tau proteins in each three stages of clearance and cleavage that zinc ions bind to Aβ plaques and tau proteins and reduce the toxicity with β-amyloid oligomers (AβOs) and tau oligomers or hyper-phosphorylated tau proteins, causing Zn2+ ions-each stages protein complex formations, protein cleavage sites having such as APP Aβ40,Aβ42 and Tau H14,H299, H362, and oxidative stress to Aβ and Tau protein cells, leading the Zn-CysHis Ligands complexes to molecular and apoptosis

activities of synaptic cells.

2. Introduction

Zinc(II) has important role for AD prevention and pathological progressing stages that in regulating immune response and synaptic transmission and intracellular concentration of zinc ion is highly regulated due to its involvement in different cellular processes [1]. Furthermore, zinc(II) also can be removed by degradation and clearance on Aβ peptide and Tau protein aggregation that the Aβ and tau levels in brain depend not only on Aβ production and tau protein, but also on its removal via different clearance pathways and enzymatic degradation and phagocytosis by microglia followed by lysosomal degradation and perivascular drainage along basement membranes into the Cerebrospinal fluid（CSF） contributes to Aβ removal from brain [2]. Recent zinc binding enzyme as Aβ-degrading enzymes (ADEs) is also importantly involved that the accumulation of the small 42- residue long peptide Aβ has been proposed as a major trigger for the AD development [3].

Zinc-induced degradation clearance is involved that ABCD pathway, Angiotensin converting enzyme (ACE), Plasmin, and Matrix metalloproteinases (MMPs) have been identified and some have even been successfully evaluated in animal models. Several studies also have demonstrated the capacity of -secretase inhibitors to paradoxically increase the yield of Aβ and we have recently established that the mechanism is by skirting Aβ degradation. This review outlines major cellular pathways of Aβ degradation to provide a basis for future efforts to fully characterize the panel of pathways responsible for Aturnov [4]. The zinc-degrading enzymes of Aβ peptide and Tau proteins are involved that Using Insulin induced degrading enzyme, degradation of Alzheimer's amyloid-β is carried out that insulin-degrading-enzyme (IDE) plays a crucial role in the clearance of Aβ. The cysteine-free IDE mutant (cf-E111Q-IDE) is catalytically inactive against insulin, but its effect on Aβ degradation is unknown, on Proteolysis of Aβ (1-40) by cf-E111Q-IDE, Aβ(1-40) degradation by cf-E111Q-IDE and short Aβ(1-40) fragments cleaved by cf- E111Q-IDE [5]. The insulin-degrading enzyme (IDE) is a Zn2+ peptidase originally discovered as the main enzyme involved in the degradation of insulin and other amyloidogenic peptides, such as the β-amyloid (Aβ) peptide. Therefore, a role for the IDE in the cure of diabetes and Alzheimer's disease (AD) has been long envisaged. Anyway, its role in degrading amyloidogenic proteins remains not clearly defined and, more recently, novel non-proteolytic functions of the IDE have been proposed. From a structural point of view, the IDE presents an atypical clamshell structure, underscoring unique enigmatic enzymological properties. A better understanding of the structure–function relationship may contribute to solving some existing paradoxes of IDE biology and, in light of its multifunctional activity, might lead to novel therapeutic approaches [6]. The brain's clearance systems are related to removal of toxic accumulation of proteins in AD. Degradation clearance is defined broadly as the removal of any substance, such as Aβ, from the brain. Focusing on Aβ given its ability to form aggregates within the extracellular space, but also briefly cover tau, which needs to be investigated in parallel with Aβ and tau [7].

Zinc induced cleavage also is involved that the amyloid precursor protein (APP) neurotoxic cleavage product Aβ are key players in the development of Alzheimer's disease and Proteolytic processing of APP is influenced by metal ions, protein ligands and its oligomerization state [8]. In this semi-review article, zinc(II)-modulated AD prevention, and three stages of clearance and cleavage to Aβ peptide and Tau protein aggregations, and interaction of both Aβ peptide and Tau protein for suppressive progression are elucidated, and subsequently zinc-binding molecular mechanism of clearance and cleavage for degrading-both each Aβ peptide and Tau protein is clarified.

Zinc(II) can suppress AD dementia proceeding by three stages of clearance and cleavage to Aβ peptide, Tau protein aggregations, and interactions of both Aβ and Tau proteins

(1) Zinc(II) can prevent on pre-stage MCI and pathological AD

Antibodies having prevent Pre-dementia mild cognitive impairment (MCI), promote cerebral clearance of Aβ might enhance the ability of monoclonal antibodies to lower brain Aβ. Antibodies having prevent MCI, promote clearance of Aβ from the brain by multiple mechanisms, offering possibilities for increasing this process. The extent to which antibodies which target Aβ are able to slow the progression of early AD may depend not only on their ability to reduce brain levels of Aβ aggregates, but also on their ability to decrease downstream pathological processes [9]. Zinc homeostasis regulates MCI and AD prevention due to be very important players in the pathophysiology of neurodegenerative disorders [10]. As the disease progresses and extraparenchymal Zn levels normalize, the resulting alterations in multiple ZnT proteins could further promote Aβ aggregation and senile plaques (SP) formation [11]. Zinc can modulate formations of the amyloid-β (Aβ) peptide and Tau protein, therefor, zinc (ZnCl2) could prevent AD [12] and Findings on the potential efficacy of zinc therapy for prevention and the improvement of cognitive decline [13]. Zinc transporters 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 [14]. ZnT-6 also 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 [15]. AD is pathologically characterized by the extracellular deposition of amyloid-β (Aβ) protein as senile plaques and the intracellular accumulation of neurofibrillary tangles containing the microtubule-associated protein tau, in which Tau depletion preventing tau pathology has become a main research avenue for AD therapy development [16]. Zinc-binding degrading enzyme as preventing pathological AD is that insulin-degrading enzyme (IDE) has an 110-kDa thiol zinc- metalloendopeptidase that cleaves small proteins of amyloid -protein (Aβ), insulin, glucagon, amylin, atrial natriuretic factor, and calcitonin, in which IDE is the major enzyme responsible for insulin degradation in vitro, but the extent to which it mediates insulin catabolism in vivo has been controversial, with doubts expressed that IDE has any physiological role in insulin catabolism [17]. Zinc and copper interaction with Aβ in the pathophysiology of AD and indicate that the CQ class of agents could have therapeutic utility in AD [18]. 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 [19]. (2) Zinc(II) modulated clearance and

cleavage stage to Aβ peptide in AD progression; MMPs, NEP, IDE Zinc（II） can recovery by removal of Aβ plaque and tauopathy from severe AD that zinc can inhibit Aβ by their degradations, in which Zinc metalloprotein may be able to degrade Aβ peptide that Zinc metalloprotein can downregulate Aβ generation and enhance its degradation [20]. Matrix metalloproteinases (MMPs) are a family of nine highly homologous Zn2+-dependent endopeptidases that are capable of cleaving a wide range of extracellular matrix (ECM) proteins under health and disease conditions [21]. that Matrix metalloproteinases (MMPs, MMP2, MMP9) can degrade fibrillar Aβ peptide [22]. Zinc(II) can degrade Aβ aggregation that Zinc binding to Aβ peptides at their N-terminal region contains Aβ peptides causing Aβ oligomerization, aggregation, and plaque formation, in which zinc enrichment is found in amyloid deposits, especially within and around compact core amyloid plaques, and the abundant zinc around and within apoE/Aβ complexes may block the access or activity of Aβ-degrading antibodies or proteases, supporting the plausibility of chelation strategy aiming at reducing amyloid pathology [23].

Neprilysin (NEP) is a membrane-bound zinc endopeptidase that has been demonstrated to degrade Aβ efficiently and to retard development of amyloid pathology and MMPs (MMP-2, MMP-3, MMP-9) belonging to the family of zinc-dependent enzymes, have been implicated in Aβ degradation [24]. Insulin-degrading enzyme (IDE) having a zinc-endopeptidase can cleave a variety of small peptides, in which zinc and thiol- dependent metallopeptidase and a member of the invercinzin family of metalloendopeptidases, which are usually found in other metalloenzymes [25]. The IDE shows a broad expression into the central nervous system (CNS), in which the IDE is the main enzyme involved in Aβ clearance in the cytosol of human brain lysates. Moreover, the IDE is the main enzyme involved in Aβ clearance and regulates Aβ level in vivo and factors that alter IDE expression and activity can lead to an increase [26]. According to the amyloid cascade hypothesis, called amyloid-β (Aβ), its accumulation, and aggregation in insoluble forms in the senile plaques are thus key early events in AD pathogenesis, additionally the amyloid plaques and rich in Aβ aggregates are detected in AD patient's brains that a tetrahedrally bound Zn(II) ion, in which the coordination sphere is made by two His residues and two carboxylate side chains [27]. Zinc also induced oxidative stress and toxic reactive oxygen species (ROS) generation in AD synapsis cell that the uncontrolled accumulation of zinc or Aβ leads to zinc-induced and Aβ-mediated oxidative stress and cytotoxicity [28]. (3)Zinc(II) modulated clearance and cleavage stage to tau protein aggregation; ZFP-TFs, Zinc finger protein, BDNF Zinc(II) can degrade Tau protein that zinc finger protein transcription factors (ZFP-TFs) can reduce ｐersistent repression of tau, in which can produce potent, specific, and well-tolerated knockdown of endogenous neuronal tau with ZFP-TFs as a therapeutic platform for the treatment of tau protein–related disorders in the human brain [29]. Zinc dyshomeostasis contributes to the development of AD and the molecular and cellular mechanisms are affected by zinc under both normal and disease situations [30]. Zinc (Zinc sulfate 300 mM) leads to tau hyperphosphorylation, oxidative stress, and synaptic impairment that Rapamycin

ameliorates zinc-induced tau hyperphosphorylation, oxidative stress damage, and synaptic impairment and rescues spatial learning deficits by downregulating mTOR/P70S6K activities and upregulating Nrf2/HO-1 activities. That rapamycin prevents zinc-induced cognitive impairment and protects neurons from tau pathology, oxidative stress, and synaptic impairment by decreasing mTOR/p70S6K hyperactivity and increasing Nrf2/HO-1 activity [31]. Tau degradation clearance by selected bioactive compounds can be removed clearance of misfolded tau and tau protein degradation, in which bioactive compound-clearance of misfolded Tau is involved by protein degradation system [32]. 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 [33]. Excessive zinc released from synaptic vesicle activation promotes tau hyperphosphorylation in cells and liquid–liquid phase separation of tau protein. Rapamycin prevents zinc-induced cognitive impairment and protects neurons from tau pathology, oxidative stress, and synaptic impairment by decreasing mTOR/p70S6K hyperactivity and increasing Nrf2/HO-1 activity [34]. C-terminal tau cleavage promotes neurodegeneration that zinc ions could promote tau protein cleavage [35]. Zinc induced Brain-derived neurotrophic factor（BDNF）deprivation provokes asparagine endopeptidase (AEP) activation via reducing δ-secretase (AEP) T322 phosphorylation by Akt, and subsequently cleaves Tau at N368 residue and enhances its binding with TrkB receptors, blocking the neurotrophic signals. AEP-cleaved Tau N368 interacting with TrkB might account for BDNF reduction-triggered AD pathologies [36]. Zinc ion promotes the intermolecular bridging of tau monomers through cysteine and histidine binding with the aggregation process. 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 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 [37]. 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 apoptosis [38]. (4) Zinc(II) modulated clearance and cleavage stage to Aβ toxicity dependent on misfolded tau by protein degradation system; Zinc metalloproteinases, Dietary Bioactive Compounds, RAP Zinc can recovery by removal of Aβ plaque, Tau protein, and tauopathy from severe AD that zinc can inhibit Aβ and tau by their degradations, in which zinc metalloprotein may be able to degrade Aβ and Tau protein that zinc metalloprotein can downregulate Aβ generation and enhance its degradation [39]. Zinc(II) can degrade AD aggregation of both Aβ peptides and Tau proteins that amyloid gradation Aβ degradation [40], The other, tau degradation clearance by selected bioactive compounds can be removed clearance of misfolded tau and tau protein degradation [41]. Zinc-binding sites on microtubules partially overlap with the microtubule binding sites of tau that intraneuronal Zn2+ regulates axonal transport and microtubule-based processes by interacting with microtubules, in which Zn2+ increases induce fast and reversible dissociation of tau in Microtubule-associated protein 2C (MAP2C) from microtubules and Zn2+ via direct interactions with microtubules acts as a brake for axonal transport and redistributes tau in neurons [42]. Aβ accelerates the phosphorylation of tau protein that extracellular amyloid plaques and intracellular NFTs, which are 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 [43]. Alzheimer's disease (AD) is amyloid-b (Ab) plaques and neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau that Zinc-Microglia, the primary innate immune cells of the central nervous system (CNS), provide neuroprotection through Ab and tau clearance but may also be neurotoxic by promoting neuroinflammation to exacerbate Ab and tau pathogenesis in AD [44]. Zinc can suppress spreading of the amyloid-β (Aβ) peptide and the Tau protein that elemental zinc 150 mg dailis 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 [45]. Zinc is involved in inducing both Aβ and tau aggregation that the zinc-mediated tau hyperphosphorylation considers the involvement of environmental zinc in Aβ and tau pathology in AD. Subsequently, zinc ions are sufficient to exert effects on aggregation of Aβ peptides and tau hyperphosphorylation on amyloid and tau aggregation [46]. At heavy stage of AD, thick aggregations and accumulations of Aβ peptides and tau proteins occur that main pathological features include the abnormal deposition of extracellular amyloid-β plaques and the intracellular neurofibrillary tangles of tau proteins and

that the pathological processes in AD and other common neurodegenerative diseases, in which the positron emission tomography (PET) probes that target amyloid-β plaques and tau proteins for diagnosing AD. According to the A/T(N) research framework, combined targeted amyloid-β and tau protein detection via PET to further improve the diagnostic accuracy of AD [47]. 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, abnormal tau protein folding has been thought to lead to cytotoxic tau aggregation, accumulation of insoluble tau deposits, and subsequent neuronal loss that correlates with the clinical features of tauopathies [48]. Although these positive lesions receive a great deal of attention, the loss of neuronal synapses is the best correlate of cognitive decline with cognitive AD severity. 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 [49]. In AD, receptor-associated protein (RAP) plays an important role in the accumulation and aggregation of Aβ that low RAP levels are associated with high Aβ and tau (soluble and insoluble tau protein) pathologies, suggesting that RAP may play a role in the disease process [50]. Thus, zinc regulates Tau aggregation and toxicity, 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 that zinc dramatically accelerates abnormal aggregation of human Tau and significantly increases Tau toxicity in neuronal cells mainly via bridging Cys-291 and Cys-322 and pathological zinc regulates Tau aggregation and toxicity associated with Alzheimer disease [51]. 3. Zinc-modulated molecular mechanism of clearance and cleavage on Aβ peptide and Tau proteins during AD progressing Zinc binding enzyme as Aβ-degrading enzymes (ADEs) molecular mechanism is importantly involved that the accumulation of the small 42-residue long peptide Aβ has been proposed as a major trigger for the AD development [3]. Structural Aβ–Zn2+ interactions showed that Zn2+ binds to the N terminus of 40 residue variant of Aβ (Aβ40), to the increased rigidity of Ab42 at the C-terminus, where the first 16 residues are the minimal peptide sequence for Zn2+ binding. In Aβ40 the Zn2+ ion is coordinated by four ligands, the histidines H6, H13, and H14 and the N-terminal [52, 53]. 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, and 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 [54]. In zinc-binding sites structure on tauopathy, restoration of zinc-binding ability to Tau by introduction of a zinc-binding residue (His) into the original Cys positions restores zinc-responsive toxicities in proportion to zinc-binding affinities [55]. The other, 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, in which three distinct zinc binding sites on tau, located in the N-terminal part (H14, H32, H94, and H121), the repeat region (H299, C322, H329 and H330) and the C-terminal part (H362, H374, H388 and H407) in tau peptide [56]. Thus, zinc(II) 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 degradation clearance and cleavage stages of (Aβ)/(Tau) proteins are indicated in the following; (Zn2+) + (Aβ) peptide + (Tau) protein ⇒ Zn2+Tetrahedral {(Aβ) peptide} + Zn2+Tetrahedral {(Tau) protein} ⇒ 2 {Zn2+ [cleaved-Aβ peptide] + [cleaved Tau Protein]}. Accordingly, zinc(II) induced suppressive AD dementia molecular mechanism of clearance and cleavage is clarified by that zinc ions bind to Aβ plaques and tau proteins and reduce the toxicity with β-amyloid oligomers (AβOs) and tau oligomers or hyperphosphorylated tau proteins. Zinc(II) coordinated molecular mechanism has been subsequently elucidated that Zn2+ ions which having Zn2+ ions-centered tetrahedral geometric coordination pattern and Zn-CysHis Ligands complexes with tetrahedral geometry formed, bind with each AD processing stages Aβ and Tau proteins, causing Zn2+ ions-each three stages protein complex formations, protein cleavage sites having such as APP Aβ40, Aβ42 and Tau H14, H299, H362, and oxidative stresses to Aβ and Tau protein cells, leading the Zn-CysHis Ligands complexes to molecular apoptosis activities of synaptic cells, in which it could become possible to reduce or remove accumulation of Aβ/Tau proteins due to zinc ion complexes compound formation on the Aβ/Tau proteins. In summary, as mentioned-above, zinc(II)-modulated AD MCI, prevention, and clearance and cleavage stages to Aβ peptide and Tau protein aggregations, and interaction of both Aβ and tau proteins for suppressive progression, and subsequently zinc-modulated molecular mechanism of clearance and cleavage for degrading-both each Aβ peptide and Tau protein are represented in Table 1.

Table 1: Zinc(II)-modulated MCI, prevention, and clearance and cleavage stages to Aβ peptide and Tau protein aggregations, and interaction of both Aβ and tau proteins, and zinc-binding molecular mechanism of clearance and cleavage for degrading-both each Aβ peptide and Tau protein.

Zn^{2+} Ions	Zinc(II)-modulated AD MCI, prevention, and three stages of clearance and cleavage to Aβ peptide and Tau protein aggregations, and interaction of both Aβ peptide and Tau protein for AD suppressive progression			
Zn^{2+} Ions →	AD MCI and Prevention	Clearance and cleavage stage to Aβ peptide aggregation	Clearance and cleavage stage to Tau protein aggregation	Clearance and cleavage stage to Aβ toxicity depends on misfolded Tau
	→ Zn^{2+}, ROS	→ Zn^{2+}, ROS	→ Zn^{2+}, ROS	→ Zn^{2+}, ROS
	•Antibodies prevent MCI •Zinc homeostasis, ZnCl2, ZnT prevent MCI and AD •ZnT-6 prevents MCI and AD •IDE with zinc-metalloendopeptidase prevents AD	•MMPs (MMP2,MMP9) can degrade fibrillar Aβ peptide •NEP with MMPs (MMP-2, MMP-3, MMP-9) belonging to the family of zinc-dependent enzymes can be cleared ABCD •IDE having a zinc-endopeptidase can cleave a variety of small peptides	•Zinc finger protein, ZFP-TFs can reduce persistent repression of tau •Bioactive compound-clearance can be performed •Zinc-BDNF deprivation provokes AEP activation and cleaves Tau •Zinc ions could be cleaved in tau proteins	•Zinc metalloproteinases, Dietary bioactive compounds can be cleared and cleaved on Aβ and Tau •Zinc-Microglia provide neuroprotection through Aβ and tau cleared and cleaved •Aβ and Tau clearance is shown by using zinc 150 mg daily

Zinc(II) binding AD molecular mechanism of clearance and cleavage on Aβ and Tau proteins is clarified that Zn2+ ions which having Zn2+ ions-centered tetrahedral geometric coordination pattern and Zn-CysHis Ligands complexes with tetrahedral geometry formed, bind with Aβ and Tau proteins in clearance and cleavage of each 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, causing Zn2+ ions-each stages protein complex formations, protein cleavage sites having such as APP Aβ40,Aβ42 and Tau H14,H299,H362, and oxidative stress to Aβ and Tau protein cells, leading the Zn-CysHis Ligands complexes to molecular and apoptosis activities of synaptic cells.

3. Conclusions

Zinc(II) can be removed by degradation, clearance, and cleavage of Aβ and Tau proteins in the extracellular deposition of amyloid plaques consisting of Aβ peptides, abnormally hyperphosphorylated tau (p-tau) containing intracellular NFTs, and neuronal cell death. Zinc(II) can prevent on pre-stage MCI and pathological AD for AD MCI and Prevention that antibodies prevent MCI, zinc homeostasis, ZnCl2, ZnT prevent MCI and AD, ZnT-6 prevents MCI and AD that ZnT-6 is a likely site of Aβ generation through cleavage of APP, and IDE with zinc-metalloendopeptidase prevents AD. Clearance and cleavage stage to AD Aβ peptide aggregation is involved that MMPs (MMP2, MMP9) can degrade fibrillar Aβ peptide, NEP with MMPs (MMP-2, MMP-3, MMP-9) belonging to the family of zinc- dependent enzymes can be cleared ABCD, and IDE having a zinc-endopeptidase can cleave a variety of small peptides. Clearance and cleavage stage to AD Tau protein aggre-

gation is involved that Zinc finger protein, ZFP-TFs can reduce persistent repression of tau, Bioactive compound-clearance can be performed, Zinc-BDNF deprivation provokes AEP activation and cleaves Tau, and Zinc ions could be cleaved in tau proteins.

Clearance and cleavage stage to AD Aβ toxicity dependent on misfolded Tau is involved that zinc metalloproteinases, dietary bioactive compounds can be cleared and cleaved on Aβ and Tau, Zinc-Microglia provide neuroprotection through Aβ and tau cleared and cleaved, and Aβ and Tau clearance is shown by using zinc 150 mg daily. Zinc induced toxic reactive oxygen species (ROS) generation leading to hyperphosphorylated tau damages and increased oxidative stress has been indicated to cause tau hyperphosphorylation and aggravate neuronal death. Thus, Zinc(II) binding AD molecular mechanism of clearance and cleavage for three stages to Aβ and Tau proteins is clarified that Zn2+ ions which having Zn2+ ions-centered tetrahedral geometric coordination pattern and Zn-CysHis Ligands complexes with tetrahedral geometry formed, bind with Aβ and Tau proteins in each three stages of clearance and cleavage that zinc ions bind to Aβ plaques and tau proteins and reduce the toxicity with β-amyloid oligomers (AβOs) and tau oligomers or hyper-phosphorylated tau proteins, causing Zn2+ ions-each stages protein complex formations, protein cleavage sites having such as APP Aβ40,Aβ42 and Tau H14,H299,H362, and oxidative stress to Aβ and Tau protein cells, leading the Zn-CysHis Ligands complexes to molecular and apoptosis activities of synaptic cells.

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