Anatolian Journal of Biology
ISSN: 8726-444X
2022 1:13-17

Research Paper

The Role of Iron, Copper and Zinc Elements in the Pathogenesis of Alzheimer's Disease

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Received 27 April 2022; accepted 26 May 2022
Available online 30 June 2022

Abstract

The clinical syndrome that prevents individuals from living a functional and independent life due to impairments in various cognitive areas is called dementia. The most common cause of dementia is Alzheimer's disease. Alzheimer's disease is very common worldwide and mortality rates due to Alzheimer's disease are very high. Age is the most important risk factor for Alzheimer's disease. In addition to the medical history, laboratory tests and physical examination for the diagnosis of Alzheimer's disease; brain imaging techniques such as positron emission tomography and electroencephalography are used. Alzheimer's disease is a chronic neurodegenerative disease characterized histopathologically by the presence of amyloid-β peptides in extracellular senile plaques and the formation of intracellular neurofibrillary tangles. Trace elements are associated with the formation of amyloid-β plaques and play an important role in the progression of Alzheimer's disease.
It is thought that the deterioration in metal homeostasis may be a cause of Alzheimer's disease. It was determined that amyloid-β misfolding was significantly affected by the presence of metals both in and around the established Alzheimer's disease plaques. The presence of copper, iron, and zinc in amyloid-β clusters has been recently associated with neurotoxicity. In addition, it has been shown that the redox activity of metal ions can trigger cellular cascades that leads to the production of reactive oxygen species. Studies have shown that restoring the proper metal ion balance in the brain can stop amyloid-β aggregation, break up amyloid plaques, and slow down the cognitive decline associated with Alzheimer's disease in affected individuals. In this review, the effect of metal ions on Alzheimer's disease is discussed in the light of current studies in the literature.

Keywords: Alzheimer's disease, copper, zinc, iron.

1. Introduction

Dementia is a clinical syndrome characterized by impairment in various cognitive areas that prevents the individual from living a fully functional and autonomous life [1, 2]. The most common cause of dementia is Alzheimer's disease (AD), accounting for approximately 60 to 80% of all cases [3]. AD is the sixth leading cause of death with an estimated prevalence of approximately 30 million people In the United States. Age is the most important risk factor for AD, with an exponential increase in prevalence from 3% to 32% in the 65 to 85% range [4].
AD is a chronic neurodegenerative disease characterized histopathologically by the presence of amyloid-β (Aβ) peptides in extracellular senile plaques and the formation of intracellular neurofibrillary tangles (NFTs) composed of the hyperphosphorylated, microtubule-associated protein tau [5–7]. It is known that tau pathology in AD brain spreads along a neural network [8].
Since dementia may also result from a range of etiologies that appear or coexist with AD, pathological confirmation at autopsy (or, rarely, biopsy in living individuals) has traditionally been required for definitive diagnosis. However, positron emission tomography (PET) imaging and detection of biomarkers of plaques and NFTs; enabled the detection of these pathologies in living individuals as well. For example, in individuals with mild cognitive impairment, a positive amyloid PET scan or characteristic cerebrospinal fluid levels of Aβ, tau, and phosphorylated tau are sensitive and specific biomarkers of AD that often, but not always, predict the likelihood of progression to dementia [9–11].
It was determined that Aβ misfolding was significantly affected by the presence of metals both in and around

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the established AD plaques [12, 13]. The function of disruption in metal homeostasis as a cause of AD is being investigated. Studies have shown that restoring the proper metal ion balance in the brain can stop Aβ aggregation, break up amyloid plaques, and slow AD-related cognitive decline in both AD patients and AD transgenic mice [14].

1.1. Alzheimer's Disease Pathogenesis

AD is a highly progressive and complex neurodegenerative disease and one of the leading causes of dementia worldwide [15]. Histopathological features of AD; extracellular clusters of Aβ plaques and intracellular NFTs.

Amyloid-β plaques initially develop in the basal, temporal, and orbitofrontal neocortex regions of the brain and later progress through the neocortex, hippocampus, amygdala, diencephalon, and basal ganglia. In advanced cases, Aβ; it can also be found throughout the mesencephalon, lower brain stem, and cerebellar cortex. This concentration of Aβ triggers NFT formation located in the locus coeruleus and transentorhinal and entorhinal regions of the brain. In the critical stage, it spreads to the hippocampus and neocortex. Aβ and NFTs are considered major players in disease progression [16].

The pathogenesis of amyloid begins with the alternative splicing of amyloid precursor protein (APP), an integral protein on the plasma membrane, by β-secretases and γ-secretases to produce insoluble Aβ fibrils. Aβ then oligomerizes; spread to synaptic clefts and interfere with synaptic signaling. As a result, it polymerizes into insoluble amyloid fibrils that aggregate into plaques. This polymerization leads to hyperphosphorylation of the microtubule-associated τ protein and activation of kinases that lead to its polymerization into insoluble NFTs. Aggregation of plaques and tangles is followed by uptake of microglia surrounding the plaques. This promotes microglial activation and local inflammatory response and contributes to neurotoxicity [17].

2. Disruption in Metal Homeostasis and Alzheimer's Pathogenesis

The accumulation of Aβ plaques in the brain is the most important distinguishing feature of AD. The plates consist of clustered Aβ peptides ranging in length from 39 to 43 amino acids. These peptides are produced from the transmembrane precursor APP [18]. Unstable metal ion concentrations can disrupt the normal activity of enzymes that regulate the cleavage of APP, leading to abnormal Aβ formation. Isoforms 1-40 and 1-42 are the most abundant isoforms of Aβ. The second isoform had a greater propensity for fibrillation and thus plaque formation. Amyloid fibrillation is reversible in the early stages [19]. Experiments revealed that oxidative stress in AD pathology can promote apoptotic death of neurons via caspase-3-dependent or independent pathways [20].

The presence of copper, iron, and zinc in Aβ clusters has also been recently associated with neurotoxicity [21]. Studies have shown that these metal ions can interact with Aβ and induce its aggregation. In addition, the redox-active metal ions can trigger a cascade that leads to the production of reactive oxygen species (ROS) [22, 23].

2.1. Alzheimer's Disease and Iron

Copper, which acts as a catalyst for numerous biological processes; it is a potentially toxic element due to its chemical redox potential and participation in free radical reactions that can damage cellular functions [33].

Loosely bound, free-flowing copper in the cytoplasm has been shown to be the main cause of the increased copper content in the blood serum plasma of AD patients [34]. Due to the close link between the deterioration of copper homeostasis and AD, which was established by several meta-analysis studies, studies have begun in this area [35]. The degradation, which causes the copper ion to be loosely released in the cytoplasm from tightly bound to proteins, has important biochemical consequences. Copper has been shown to increase the accumulation of Aβ peptides in AD by specifically increasing APP activity [36].

In addition to its role in Aβ aggregation, copper has also been shown to be involved in tau aggregation. It has been determined that copper induces tau hyperphosphorylation by activating the cyclic dependent kinase 5/p25 complex and GSK-3β kinase [36, 37].

It is known that Cu(I/II) secreted into the synaptic space upon neuronal stimulation can have an effect on extracellular Aβ peptides. Interactions between Cu(I/II)−Aβ complexes and neurotransmitters can affect; the oxidative conversion of neurotransmitters, the pathways associated with aggregation of Cu(I/II)−Aβ and copper transport via the formation of a temporary ternary complex of Cu(II), Aβ4−x, and a neurotransmitter [38].

2.3. Alzheimer's Disease and Zinc

Zinc is an essential component for maintaining the structures of macromolecules, including proteins and nucleic acids, necessary for the human body to maintain its physiological function. At the same time, zinc acts as a cofactor for more than 300 enzymes. It also regulates many cellular processes and pathways, including the nervous system [39]. It has been reported that almost all clinical features of neurological diseases related to learning, memory and emotional stability are associated with zinc deficiency. These diseases are related to dysfunction of normally metal-rich brain regions such as the hippocampus, amygdala, and neocortex [40]. These neocortical regions are also the

regions most prone to AD pathology. For this reason, the hypothesis of disruption of zinc homeostasis has been proposed as the cause of the close relationship between AD and zinc imbalance [41]. Zinc homeostasis has complex effects on various brain processes, which is thought to lead to the onset of chronic pathologies of AD [42].

After the discovery that Aβ is normally secreted by neurons as a soluble peptide [43], studies on the factors inducing Aβ aggregation have begun. It has been found that zinc binds to Aβ and induces its precipitation [44]. The metal binding site on Aβ is not specific for zinc and overlaps with residues coordinating copper and iron [44]. The Aβ-zinc complex is resistant to proteolysis and increases the stability of Aβ aggregates. The rat/mouse homologue of Aβ has a His13Arg residue that reduces zinc binding and zinc-induced precipitation [45]. This helps explain why these rodents do not develop amyloid plaques unless modified to overexpress the human Aβ sequence [46].

There are studies showing that zinc interacts with other main proteins that play a role in AD. It has been found that zinc increases the expression of presenilin 1 [47] and affects the stability of apolipoprotein E (ApoE), especially ApoE4 [48]. Presenilin 1 and ApoE expression have been determined to play an important role in the maintenance of cellular and neuronal zinc trafficking. It was determined that the free ionic form of zinc (Z^{2+}/Z^{3+}) increased tau phosphorylation and aggregation [47].

In the plasma membrane, zinc uptake protein (ZIP) mainly regulates zinc (Zn^{2+}) entry, while zinc transporter (ZnT) regulates Zn^{2+} flux. High Zn^{2+} levels increase Aβ accumulation, tau modification and formation of reactive oxygen species (ROS). Low Zn^{2+} levels and decrease in the bioavailability of Zn^{2+} cause synaptic dysfunction [32].

3. Conclusion

Studies in the literature have shown that imbalances in the homeostasis of intracellular biometals and toxic metal exposure are associated with AD pathology. It has been determined that biometals that increase tau hyperphosphorylation, Aβ aggregation and APP expression accumulate in the brains of AD individuals. Toxic metal exposure can also trigger AD through various mechanisms such as protein modification and neuroinflammation.

It is thought that it will be possible to identify possible solutions and drug targets for AD as a result of the identification of heavy metals and specific genes associated with them by further studies in this area.

Conflict of Interest

The authors declare no conflict of interest.

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