Copper Toxicity and Alzheimer's Disease

Subjects: Others

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Alzheimer's disease (AD) is an irreversible, age-related progressive neurological disorder, and the most common type of dementia in aged people. Neuropathological lesions of AD are neurofibrillary tangles (NFTs), and senile plaques comprise the accumulated amyloid-beta (Aβ), loaded with metal ions including Cu, Fe, or Zn. Some reports have identified metal dyshomeostasis as a neurotoxic factor of AD, among which Cu ions seem to be a central cationic metal in the formation of plaque and soluble oligomers, and have an essential role in the AD pathology. Cu-Aβ complex catalyzes the generation of reactive oxygen species (ROS) and results in oxidative damage. Several studies have indicated that oxidative stress plays a crucial role in the pathogenesis of AD. The connection of copper levels in AD is still ambiguous, as some researches indicate a Cu deficiency, while others show its higher content in AD, and therefore there is a need to increase and decrease its levels in animal models, respectively, to study which one is the cause. For more than twenty years, many in vitro studies have been devoted to identifying metals' roles in Aβ accumulation, oxidative damage, and neurotoxicity. Towards the end, a short review of the modern therapeutic approach in chelation therapy, with the main focus on Cu ions, is discussed. However, some recent reports of genetic-regulating copper transporters in AD models have shed light on treating this refractory disease. This study aims to succinctly present a better understanding of Cu ions' current status in several AD features, and some conflicting reports are present herein.

Keywords: Alzheimer's disease ; amyloid plaques ; copper ; oxidative damages ; protein modification ; neurodegeneration

1. Introduction

In 1907, Alois Alzheimer was the first to identify a mental decline with amyloid plaques and neurofibrillary tangles found in most dementia symptoms [1][2]. This disorder's main risk factor is old age, because the elderly are more prone to diseases, affecting 10% of people aged 65, and this proportion rises by about three times for people aged 85 and older [3][4] AD typically destroys neurons, and their connection with the brain regions such as the entorhinal cortex and hippocampus area, the parts of the brain essential in forming memories [5]. This disorder disrupts processes necessary for healthy neurons, such as communication, metabolism, and repair [6][7]. Ultimately, the disease is fatal. It is one of the leading causes of death [8] that we are currently unable to stop or cure because the underlying etiology is poorly understood at present [8][9].

Unfortunately, the treatment of AD has often been delayed in general because it is diagnosed only after prominent signs of cognitive deterioration [10], and this is all due to the lack of awareness of cognitive problems on the part of patients and patients' families [11]. Clinical detection of this disorder is only possible when the symptoms are advanced enough to show visible behavior or cognitive changes [12]. There could be enough time to halt or slow this disorder's development with early AD identification before complete onset [12]. Indeed, currently, there is no such treatment for AD [13], and approved drugs that have insignificant effects at altering the pathophysiological course of this disorder [14][15], due to the disease developing from a combination of lifestyle, environment, and genetic risk factors that affect the brain over time [16][17].

One of the most common neuropathological hallmarks of AD is the misfolding and aggregation of amyloid plaques-extracellular insoluble deposits of the β-amyloid peptides [18], and the intracellular formed NFTs (neurofibrillary tangles) [19], leading to the loss of communication between nerve cells, causes brain damage and shrinkage [20]. Posterior cingulated cortex (PCC) [21], entorhinal cortex (EC) [22], hippocampus (HIP) [23] (the first part to be affected by AD), middle temporal gyrus (MTG) (role in cognitive functions such as language processing), and superior frontal gyrus (SFG) (helps in memory) [24][25] are the regions affected in this multifactorial neurological disorder. Some studies have identified the impaired function of the middle temporal gyrus [26] and superior frontal gyrus in AD [27].

Extracellular deposits of Aβ peptides in Alzheimer's are the main pathological events in AD [28][29][30][31]. Senile plaques or amyloid plaques mainly consist of small amyloid beta-peptides (Aβ) (up to 42 or 43 amino acids long) [32]. These are β amyloid precursor protein (APP) metabolites, derived by proteolytic sequential cleavage, first through β-secretase and then with γ-secretase, in the amyloidogenic pathway of producing peptides (Aβ), which contain 39 to 43 amino acids [33].

The APP (main isoforms, APP(695), APP(751), and APP(770)) is a type 1 transmembrane glycoprotein, which is essential for neurogenesis, neurite outgrowth, neuronal guidance, synapse formation, and repair [34][35][36]. The reason for neuritic plaques (senile plaques) forming in AD is due to irregularity between the production and removal of the beta-amyloid protein that accumulates [4]. Hence, the amyloid cascade hypothesis postulates that aggregation and accumulation of Aβ is the first pathological event in AD onset and initiates a cycle of adverse physiological changes that lead to neurodegeneration.

Another study has investigated Aβ aggregations in the senile plaques and co-localization of adenosine receptors in the AD [37]. Recently, some investigations have been done on adenosine, a purine ribonucleoside, because of its neuromodulator and neuroprotection function in neurological disorders [38][39]. It is present in all cells containing glia and neurons, initiates its biological process by four G-protein coupled receptors (GPCRs), namely, the A1, A2A,…A2BAR [40][41]. It has a role in regulating and integrating neuronal excitability, affecting many essential brain activities like sleep, memory, and neural plasticity [42][43][44]. Much research has analyzed adenosine effects via its receptors A1 and A2A in AD [45]. Nonselective blockage or modulation of these two receptors could protect cognitive impairment, making them innovative feasible therapeutic agents for AD [46]. Hippocampus, a brain region important for memory, learning, and neurogenesis [47][48][49], is one of the earliest affected brain regions that tends to exhibit the most rapid volume loss in the disease progression, and its pathology was found to be central to AD [47][50][51].

The hippocampus is a sensitive part of the brain to the dysfunctional homeostasis of transition metals, more so than any other brain region. Much research has also identified another brain part, the cortex, which is damaged by AD [52][53][54], linked with motor function, planning, organization, argumentation, feeling, and language processing [55]. NFTs are mainly composed of the microtubule-associated protein tau, predominantly expressed in the neurons under physiological conditions. This protein is mis-sorted into the somatodendritic compartment due to the tau sorting process's failure, which is another essential factor that aggregates in AD [56]. Microtubules are essential components of a neuron's cytoskeletal system, required for several fundamental cellular and dendritic processes, such as neuronal migration, polarity, axonal production, and differentiation [57][58]. Abnormal Aβ production might lead to the activation of tau mis-sorting, inducing tau pathology [59][60].

Multivalent metal ions such as copper (Cu) [61][62][63], zinc (Zn) [64][65], and iron (Fe) [66][67] are reported to be at higher levels in Alzheimer's senile plaques [68][69]; while the connection of these metal ions with Aβ aggregation is still not well known. Indeed, some evidence from transgenic animal studies shows that Cu accumulates in senile plaques in the brains of 5 × FAD and Tg-SwDI/NOS2−/− mice models with neurodegeneration, as compared to PSAPP, where no Cu deposition has been seen among the mice with less neurodegeneration [70]. Much research has accumulated on Zn and Cu ions' altered homeostasis as the central pathological hallmark [71][72][73] and shows the link of proteins related to Cu metabolism with this multifactorial AD [74].

Considerable research has suggested that Cu dyshomeostasis contributes to the onset of the most common neurodegenerative disorders besides AD, including Parkinson's disease, prion-mediated encephalopathies, Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) [75][76][77][78]. Hence, circumstances leading to a higher or lower copper concentration can be hazardous to health, such as Menkes diseases, a genetic disorder of Cu deficiency [79][80]. Furthermore, an autosomal recessive disorder, Wilson disease (WD), caused by defects of the ATP7B gene with excessive copper deposition in the body and patients' brain examinations have shown copper concentration eight times greater than the controls [81].

Contradicting reports about the Cu concentration in AD has been reported. Some researches indicate a copper deficiency [82][83][84][85], while the majority show its higher level in AD, and therefore, reducing its level is required [86][87][88][89][90][91][92]. Investigations have grown exponentially in the neurodegenerative disorder fields over the past two decades. However, AD's exact etiology is still not well understood, and as such, there is no successful therapeutic option available for this disorder to date [93][94].This literature review aims to present current knowledge regarding Cu's role in AD. Towards the end, a short review of feasible therapeutics/strategies recommended for solving the problems associated with the metal's implication in AD has also been discussed.

2. Contradictory Results about Copper Level in AD

In the body cells, Cu is absorbed through a high-affinity copper transporter Ctr1, incorporating cuprous (Cu^{+}) ions from the intestinal microvilli's surface. Little is known about Cu^{2+} absorption, which is probably absorbed by divalent metal transporter 1 (DMT1) or other shared metal transporters [95]. Ctr1is responsible for the majority (~70%) of Cu import into mammalian cells, from which Cu is passed to glutathione, which carries Cu through the cytoplasm [96]. The absorbed copper ions will be targeted to Cu-binding chaperones and enzymes in different cell compartments such as cytosolic,

mitochondrial, and Golgi. In the cytosol, Cu chaperone for superoxide dismutase 1 (SOD1), CCS, mediates Cu^{+} loading. A recent study suggested that the direct transfer of copper from Ctr1 to chaperones and then passing it to SOD1 is via forming a Ctr1-CCS-SOD1 complex [95]. Besides CCS, soluble copper chaperones such as Atox1 and Cox17 can also escort Cu^{+} from Ctr1 in the cytosolic pool to facilitate copper supply to their specific target compartments [97].

Consequently, in the absence of Ctr1, other pathways to absorbed Cu ions are unavailable to the organism because of the sequestration of copper in the sub-apical vesicles. This has been confirmed by making the intestinal epithelial cell-specific knockout of the Ctr1 (Ctr1int/int) mice, which manifested severe Cu deficiency, and the majority died within three weeks of post-birth [98]. A considerable portion of ingested cuprous ions are passed into circulation in enterocytes to reach different tissues by Atox1/ATPase routes. The mouse model with inactivated ATOX1/ATP7A routes showed defects in Cu distribution, which leads to pathological variations in many organs, especially the brain[99].

In the CNS, Cu deficiency has been found in the hippocampus and amygdala regions of Alzheimer's patients, which causes severe histopathologic alterations in AD. Additionally, scientific research has put forward that the frontal cortex tissue of Alzheimer's patients had an increased susceptibility for exchangeable copper (CuEXC), which is associated with the overproduction of free radicals (ROS) in AD [100].

In the CSF of the AD patients, there is no significant change in Cu concentration as compared to that of the healthy cases (HC) [101]. Furthermore, within peripheral fluids, abnormal homeostasis of copper ions has been intensively investigated. The relevant data point to increased [101][102], decreased [85][103], or unchanged [104] serum or plasma Cu in Alzheimer's patients. Many other scientific analyses have also reported excessive free or diffusible copper in serum [101][103][105]. However, Rembach (2013) has suggested the possibility of decreased non-CP copper levels-copper that is not bound to ceruloplasmin in mild cognitive impairment (MCI) and AD, which leads to a decline of copper-dependent biochemical activities in AD [106], such as reducing SOD1 activity of erythrocytes [85].

Cu association for AD is ambiguous as some substantial researches showed Cu deficiency in AD and, hence, it is required to increase Cu levels [83][84][85]. In contrast, many different scientific pieces of evidence demonstrated Cu overload, and thus it is necessary to reduce it [87][88][89][90][91][92]. The main updated explanation so far is that the abnormal Cu homeostasis is due to an increment in the labile Cu ions and a reduced attachment to proteins [107][108].

Until 2012, the published contradictory scientific researches fueled the debate of copper concentrations in AD. So far, to check Cu levels in various biological specimens of AD patients, such as serum, plasma, and CSF, six meta-analyses have been done during the past six years. Studies published from 1984 to 2017 have been included in these meta-analyses [101][109][110][111][112][113], which give unambiguous results: overall and unbound Cu both are present in higher concentrations in the serum-plasma samples of the AD patients compared to that in the healthy cases [111]. According to the very recent meta-analysis, which includes a total of 35 pieces of research: eighteen report an increase, fourteen show no change, and one reports a decrease in Cu level in the serum-plasma of this disorder [113]. Subsequently, three more studies have been published, stating increased Cu^{2+} ions level in Alzheimer's compared to that in the healthy controls [114][115][116].

These recent researches have contributed considerably to the explanation of the previous controversy. In blood, a higher level of free plasma Cu, which has been identified in 50–60% of Alzheimer's patients, can explain the higher level of serum Cu in AD [108][114][117][118]. Another earlier research also observed an increased concentration of serum copper ions in a special kind of AD (Alzheimer's disease epsilon four apolipoprotein E allele carriers) [119]. According to some scientific investigation, a genetic basis may be the reason for this particular type of AD [119][120][121][122].

3. Therapeutics to Tackle Copper Ions in AD

Despite the exponential growth of scientific literature published in the neurodegenerative disorders area, especially for AD, the exact etiology of AD is still not well understood. To date, there is no successful therapeutic option available for this disorder [93][123]. While there is no cure, there are five FDA-approved medications to cope with the symptoms of AD, which may prevent this disease from getting worse over time [124].

In vitro, removal of Cu^{2+} from Aβ prevents its accumulation [125][126][127], leads to its degradation, stops hydroxyl radical (•OH) production and oxidative damage, and finally reduces cell death [127]. For the effects as mentioned above, researches have suggested potential metal chelation therapy for AD [128][129][130][131][132][133][134]. Nevertheless, the challenge is to build selective and specific metal chelators, as metal ions play crucial roles in Alzheimer's brains. The first metal chelator made for arsenic toxicity in the 1940s was 2,3-Dimercaptopropanol (BAL) [135][136]. Much later, followed by the same approach, the first-generation of metal chelator, a lipophilic small molecule clioquinol (5-chloro-7-iodo-8HQ or CQ) was introduced at the end of the 1990s [126][137]. Transgenic mouse models treated with CQ showed promise by

reducing Aβ accumulation by 50%. CQ reduced Aβ aggregation during Phase II trials and improved cognitive behavior, but failed to provide sufficient evidence of a positive clinical benefit in a larger clinical trial [138][139]. Furthermore, patients exhibited some severe side effects, including neurotoxicity and mutagenicity; therefore, further clinical trials of CQ were stopped.

The most progressive chelator so far is PBT2 (5,7-dichloro-2-((dimethylamino)methyl)) [140], a second-generation of scaffold-based chelator, which has been inspired by CQ and also showed excellent antioxidant properties [141][142][143]. It is a more effective Zn/Cu ionophore than CQ, which could decrease H_2O_2 formation, have greater BBB (blood-brain barrier) permeability, higher solubility, and could also inhibit Cu and Zn induced Aβ accumulation in vitro [143][144]. PBT2 treatment targets metal-induced damage [145], and most importantly, it prevents the loss of necessary metal ions from the body such as the kidney, liver, lungs, and brain [123][146]. It also shifts the Alzheimer's phenotype within days by reducing insoluble Aβ levels by ~30% [143] and alters tau and synaptophysin protein levels' phosphorylation. Interestingly, a lowered level of insoluble total and elevated levels of the soluble total tau has been shown in the treatment with PBT2 [141]. Despite the effects mentioned above, the results of human clinical trials are not up to the mark according to some studies [123][147]. However, some scholars have denied this idea [148]. Results from the phase IIb, the randomized clinical trial, were not as promising even though phase Ib/IIa preclinical trials demonstrated significant reductions in Aβ levels and improvement in various aspects of cognitive functioning.

The research in the Tg 2576 transgenic mice model has shown parenchymal plaque [149][150], indicating that metal chelators help slow disease progression and remove Cu ions only helpful in the initial stages of the AD [151]. While PS1 and PS2 play roles in Cu^{2+} uptake, tissue-specific knocking down of the single presenilins ortholog *(PSN*) in *Drosophila* reduces Cu^{2+} levels and increases its susceptibility to oxidative insult [152]. It was observed that the silencing of *PSN* in flies had less sensitivity to excess dietary Cu due to the reduced copper uptake. BLOC-1 physically interacts with ATP7A, and disruption of the *Drosophila*'s dysbindin/BLOC-1 complex affects copper homeostasis in both mammalian cells and *Drosophila* [153].

Different approaches have been used to treat the pathological hallmarks of the multifactorial AD due to Cu dyshomeostasis, including the metal chelation therapy [143][154][155][156]. Restoring the intracellular copper decreases β-amyloid production, which was found through a mechanism that depends on the activation of phosphatidylinositol 3-kinase (PI3K)/PI3K-Akt pathway, and JNK (Jun N-terminal kinase) [157][158]. Moreover, lately, studies have observed increased intracellular Cu inhibited AD-causing Aβ peptide by direct targeting of presenilin (PS1 or PS2) subunits and nicastrin (NCT) in the γ-secretase complex [61][158][159]. Hence, higher intracellular Cu levels can improve cognitive function as well, by preventing β-amyloid aggregation and tau phosphorylation [160][161][162]. There is proof of the bis(thiosemicarbazone) copper(II) complex having the immunomodulatory potential [163][164], and greater BBB permeability. It inhibits microglial as well as astrocytic inflammatory responses and also has a role in the decrement of bacterial lipopolysaccharide (LPS) induced inflammation [165]. Some researchers have suggested that excess dietary Cu intake increases AD risks, and diets with measured copper should be supported. Additionally, a study conduct with a small amount of Cu in drinking water results in rising levels of amyloid peptides in the brain [166][167], a process that appears to be linked with dysfunction of LRP1-mediated efflux of Aβ from the brain [168] in vascular smooth muscle cells [169][170]. The median intake of copper from food among children and adolescents aged 2–19 years, the recommended daily allowance (RDA) ranges from 800 to 1000 mcg/day. In adults aged 20 and older, 1400–1700 mcg/day is recommended. Despite the difficulties, balancing Cu homeostasis has numerous advantages, and can be a potential drug target for this progressive, neurological disorder. [86][171][172][173],.

4. Conclusions

Collectively, studies strongly advocate that dyshomeostasis of Cu, leads to the onset and progression of AD. Earlier researches have recognized amyloid plaques as toxic factors in AD. Though 20–40% of healthy cases have amyloid plaques, as illustrated by some studies [174]. Furthermore, cell death often leads to amyloid plaque formation in the brain. While mounting evidence implicates *ROS* in the *AD* etiology, loosely bound copper ions are very efficient catalysts for ROS generation by a copper-amyloid complex [175][176].

Some studies indicate an increased liable pool of Cu in the brain [111][176] responsible for Cu deficiency. The reason of Cu deficiency seems to be an essential factor in AD. Copper deficiency leads to Cu enrichment in lipid rafts, so maybe an elevation in lipid raft domains could be the reason for Cu deficiency in the brain; thus, lipid raft domains could be an efficient drug target. Studies indicated that the disrupted lipid rafts (by omega-3 fatty acids) slowed the progression of AD [177][178]. Another direction for research depends on the feasibility of developing novel therapeutic approaches to work against this disease.

The proposal for direct chelation therapy of Cu ions to work in this disorder is still in discussion [147]. Support for the lowering cellular Cu levels comes from the *Drosophila* model of AD, where although copper chelation or genetic knockdown of copper transporters (Ctr1C) decreased the expression of Aβ degrading proteases but rescued the toxic phenotype [179]. Similar results were also observed by silencing the expression of Ctr1B, or when copper exporter DmATP7 [179] and dMTF-1 or MtnA [91] were overexpressed in the nervous system of the Aβ transgenic flies. These flies exhibited improved neurodegeneration, locomotion, longevity, and a reduction in Cu-Aβ complex-induced oxidative stress.

Furthermore, in parallel, antibody-based treatment for Aβ aggregation is now developing and providing safe results as well [180]. Research organizations should come to the same standpoint regarding the experimental requirements and procedures to be used, to avoid different and ambiguous results for such serious matters. In this context, all the struggles for a better understanding of AD pathology's molecular mechanisms and developing innovative therapeutic approaches should be appreciated.

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