Metals in Parkinson’s and Alzheimer’s Diseases

Subjects: Chemistry, Inorganic & Nuclear

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Metal ions are fundamental to guarantee the regular physiological activity of the human organism. They are involved in several biological processes such as electron transfer, oxygen transport, the maintenance of osmotic pressure, and the regulation of DNA transcription. Metals such as iron, cobalt, selenium, copper, zinc, and manganese are essential for human life and are usually required in trace amounts. On the other hand, aluminum, mercury, arsenic, and others are considered non-essential metals since they possess no biological function. The importance of metals in the human organism is so fundamental that several pathologies, among which are neurodegenerative diseases (NDs), are related to a common phenomenon known as metal dyshomeostasis.

metal ions Alzheimer’s disease Parkinson’s disease metal dyshomeostasis zinc copper iron manganese nickel aluminum

1. Introduction

The human organism is primarily made up of water, fat, proteins, and minerals [1]. Metals are present in small quantities in the body. For example, an adult male body contains 3–4 g of iron [2]. Nevertheless, metals are necessary for the preservation of physiological functions of the organism. They are involved in several biological processes such as electron transfer, oxygen transport, the maintenance of osmotic pressure, and the regulation of DNA transcription [3]. Metals such as iron, cobalt, selenium, copper, zinc, and manganese are essential for human life and are usually required in trace amounts. On the other hand, aluminum, mercury, arsenic, and others are considered non-essential metals since they possess no biological function [4][5]. The importance of metals in the human organism is so fundamental that several pathologies, among which are neurodegenerative diseases (NDs), are related to a common phenomenon known as metal dyshomeostasis [6]. The scientific literature offers a large number of papers addressing the implications of metals in NDs [7][8][9].

Metal ions have been extensively studied for their interactions with important biomolecules such as amino acids [10][11], peptides [12][13], and proteins [14][15], which are involved in structural functions, cell signaling, cell expression, and hormone synthesis, to name a few [16][17]. Proteins often need to interact with metal ions to carry out their function [18].

Several transition metal ions are known to play key roles in Alzheimer’s disease (AD) and Parkinson’s disease (PD) [8]. Altered homeostasis of biometals such as zinc, copper, iron, and manganese is associated with high

neurotoxicity and oxidative stress conditions typically observed in AD and PD cases [19][20][21][22][23][24][25].

In particular, redox-active metals such as Cu(II)/Cu(I) and Fe(III)/Fe(II) can catalyze the Fenton reaction, producing cytotoxic hydroxyl radicals from hydrogen peroxide [26][27]. In addition, copper and zinc are normally released at the glutamatergic synapse in the cortex and hippocampus and, together with iron, are able to bind amyloidogenic proteins and other hallmark molecules associated with NDs (**Figure 1**) [28][29][30][31]. Mn is a co-factor of glutamine synthetase involved in the recycling of glutamate to glutamine and thus responsible for the glutamate clearance from the synapse [32]. Mn is also essential for MnSOD activity protecting mitochondria from oxidative stress [32]. Other metal ions such as aluminum and nickel may represent risk factors for neurodegenerative diseases leading to mitochondrial dysfunction, microglial activation, and neuroinflammation [33][34]. Ni is extensively distributed in the environment. It is an essential nutrient for some animals, plants, and microorganisms, while its functional role in humans has not been recognized yet [35]. In contrast to Ni, Al is not an essential element. It is the most abundant metal on the earth's crust and is widely used in daily human and industrial activities. Both Ni and Al traces can be found in food, drinking water, and the air.

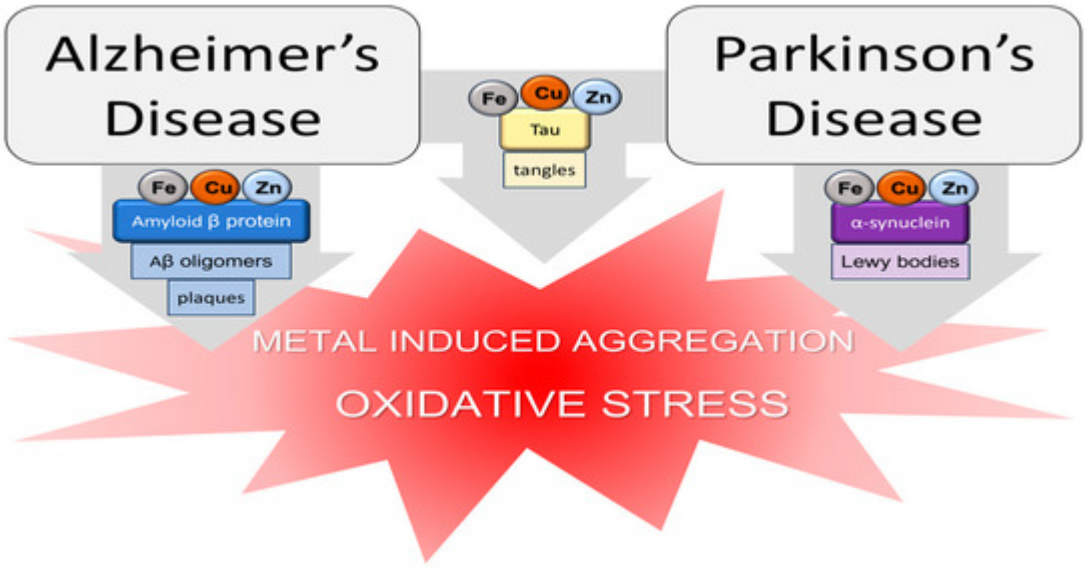

Figure 1. Schematic representation of the amyloidogenic proteins and their metal ion interactions in AD and PD.

As for vitamins, the interplay between metal ions and neurodegenerative diseases has been extensively investigated over the last thirty years. Research in this field has exponentially grown since 1990, reaching more than 3400 publications in the last ten years (Pubmed source "metal" and "neurodegeneration"). The scientific community has made great efforts to identify the role played by metal ions in the molecular associations and cellular pathways related to AD and PD. While much progress has been made in this area, several points remain to be clarified yet. In this research, the relationship between these six metal ions and the two most common NDs, PD and AD have been focused on, by briefly highlighting the metal's coordination chemistry properties and metal involvement in AD and PD states.

2. Zinc, Copper, and Iron

Zinc, copper, and iron levels in serum, hair, CSF, and the brain have been extensively measured trying to correlate their content with metal dyshomeostasis associated with AD and PD cases [36]. The most applied techniques are atomic absorption, inductively coupled plasma atomic emission spectroscopy (ICP-AES), ICP-mass spectrometry (MS), and ICP-optical emission spectrometry (OES). Serum zinc levels were generally found to be reduced in patients affected by both AD and PD [37][38][39][40][41][42][43]. Decreased Zn concentrations have also been determined in AD hair samples [44]. On the other hand, reduced and increased copper contents have been measured in both AD [39][41][43][45][46] and PD cases [40][47]. Finally, a different behavior is displayed by iron, whose levels are different according to the disease, usually lower [41][42][48] or higher [40][49] in AD and PD patients, respectively.

Altered zinc, iron, and copper concentrations have also been found in CSF and post-mortem brains [36][50][51][52][53]. In PD patients, zinc levels are higher in the substantia nigra, caudate nucleus, and lateral putamen [50]. Iron content is higher in the substantia nigra and lower in the globus pallidus [50]. In PD, copper is increased in the putamen and decreased in the substantia nigra [50], while it is decreased in AD brains [53].

The altered metal levels observed in AD also correlate with the presence of Fe and Cu, Zn, in the AD senile plaques, primarily constituted by the aggregated forms of Aβ [54][55][56][57]. Aβ is a well-known amyloidogenic protein associated with AD and it is able to bind copper, zinc, and iron by means of His imidazole, N-terminal amino, and Glu/Asp carboxylate groups [58][59][60][61][62][63][64][65]. In a similar way, the amyloidogenic proteins tau and alpha synuclein, associated with AD and PD, respectively, can steadily coordinate several transition metal ions [66][67][68][69][70] (**Figure 1**).

Metal ions such as Cu and Zn can impact the aggregation of amyloidogenic proteins by affecting the morphologies and kinetics of the aggregates. The scientific community put a lot of effort into understanding the influence of metal ions, primarily copper and zinc, in the aggregation of amyloidogenic proteins [71][72][73][74][75][76][77]. The obtained findings are quite heterogeneous primarily due to the intrinsic complexity of the systems and different experimental conditions and techniques. In general, it is evident that zinc promotes the formation of amorphous Aβ aggregates while copper favors the production of highly cytotoxic oligomers [78][79][80]. As for Aβ, metal ion binding impacts the aggregation of αSyn as well, either showing pro- or anti-aggregatory effects [81][82]. Among all the metal ions, iron and copper are able to influence αSyn aggregation by promoting the formation of multimeric species and αSyn assembly [83][84].

Zinc interaction with the third repeat unit of the microtubule-binding domain of tau (R3tau) leads to the formation of Zn(II)-R3tau aggregates [85]. Such complexes, compared to R3tau, possess higher toxicity towards Neuro-2A (N2A) cells by inducing higher ROS generation in N2A cells. Copper increases the aggregation propensity of tau through its capability to both bind tau and produce ROS [86]. Zn and Fe binding to tau-R1 and R4 was also investigated; Zn(II) and Fe(II) but not Fe(III) coordination was demonstrated by CD and ESI-MS. Both interactions induced conformational changes in R1 and R4 [87]. Copper binding to tau occurs via His residues present in R1, R2, R3, and R4 or at the N-terminal site [88][89][90]. Recent molecular dynamic studies have revealed the misfolding

of R3tau upon Cu(II) binding [91]. In addition, the ability of the copper–R3tau complex to promote the oxidation of dopamine has been recently reported [90].

The involvement of zinc, iron, and copper in AD is also supported by in vivo animal studies showing the effects of metal deficiency and/or supplementation in AD mice models [92][93][94][95][96]. For example, a zinc-deficient diet in an APP/PS1 mouse model of AD accelerated memory deficits through the induction of the NLRP3-inflammasome complex [92]. Other studies show that treatment with low levels of Cu(II) in drinking water led to an increase in Aβ production in neuroinflammation [93] and promoted Aβ accumulation, reducing mice's cognitive functions [94]. Finally, in hypercholesteremia-induced AD rabbits, the administration of Fe(III) chelator deferiprone in drinking water significantly reduced the levels of plasma iron and cholesterol and decreased tau phosphorylation, Aβ40, and Aβ42 but not ROS production in the hippocampus [95]. In contrast, the treatment of an AD mouse model with Fe(II)-containing water markedly reduced Aβ42 deposition, tau phosphorylation, and apoptotic neurons and led to an increase in Aβ40 and a reduction in the Aβ42/Aβ40 ratio [97].

3. Manganese, Nickel, and Aluminum

The relevance of Mn, Ni, and Al in both AD and PD is well documented in the literature even if to a lesser extent than the essential Zn, Cu, and Fe ions. In PD, the serum levels of Mn, Ni, and Al are generally higher compared to healthy controls [38][49][98].

Furthermore, acute exposure to Mn can result in manganism, a type of parkinsonism, considered part of the PD etiology [96]. Manganism may be caused by elevated Mn accumulation in the basal ganglia region of the brain [99].

The association between aluminum and PD was suggested by the detection of Al in the Lewy bodies of PD patients, while its value is below the limit of detection in control brains [100]. Such findings are further supported by the higher incidence of ulcer patients that make high use of Al(III)-containing antiacids in PD cases compared to controls [101]. In addition, Al(III) was found to increase monoamine oxidase B and SOD activities in a way similar to what was observed in PD patients [38][102].

As for PD, higher serum levels of Ni [98] and Al [41][103][104][105][106] have been found for AD cases. On the other hand, reduced [42][107] or increased [44][108] Mn serum levels are reported for AD and MCI subjects. Mn content was also lower in the hair and nails of AD cases compared to control subjects [108]. Nickel levels were higher in the post-mortem frontal cortex and ventricular fluid of AD subjects with respect to nondemented elderly controls [109]. At the same time, nickel supplementation in the forms of the $NiCl_2$ and $NiCl_2$-morpholine complex prevented tau aggregation and promoted its degradation with the formation of shorter aggregates [110].

Moreover, in vitro and in vivo investigations on APP/PS1 mice showed dose-dependent neurotoxicity and an increase in Aβ upon Mn(II) treatment [111].

Finally, Al(III) may be implicated in AD pathogenesis via the induction of APP overexpression and the subsequent increase in Aβ and plaque formation in the brain [112]. A laser microprobe mass analysis showed a primary accumulation of Al(III) in the neurofibrillary tangles (NFTs) of AD subjects [113]. A 15-year follow-up study revealed an association between the high consumption of aluminum from drinking water and an increased risk of AD [114]. APP/PS1 transgenic mice, treated with intracerebroventricular microinjections of $AlCl_3$, presented more extensive worsening of cognitive abilities and increases in neural apoptotic rates than APP/PS1 alone and wild-type mice exposed to Al [115].

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