

## Review Article

# Metal Ions in Alzheimer's Disease Brain

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## Abstract

There is substantial evidence supporting a critical role for metal ions in the pathogenesis of Alzheimer's disease (AD). This originated with the observation that certain metal ions (principally copper, iron and zinc) are enriched in the neuritic plaques of AD brains, leading to an overall reduction in their bioavailability, such as in the synaptic cleft. Imbalances of metal ions associated with aging and AD may affect the disease progression, leading to metals being reduced or increased from their physiological steady state. Because metal ions are essential cofactors for many proteins and they can compete with each other for binding to proteins, it is essential to maintain metal homeostasis in order to preserve neuronal function. Some heavy metals may aggravate the progression of the disease due to their high neurotoxicity and their ability to induce epigenetic changes. On the other hand, alterations in the levels of certain metal ions in other compartments in the brain could affect A $\beta$  enzymatic degradation, increase A $\beta$  and tau aggregation as well as the processing of the amyloid precursor protein (APP) and other intracellular processes. Metal ions are also instrumental in enhancing the production of reactive oxygen species in the brain, which could have consequences for neuronal viability and function. Here we review the studies reporting the concentrations in brain, CSF and plasma in AD patients and how alterations in their transport and storage mechanisms can lead to their redistribution in the brain, contributing to AD neuropathology.

## Keywords

- Alzheimer
- Amyloid
- Copper
- Iron
- Metal
- Tau
- Zinc
- Transporter

## ABBREVIATIONS

AD: Alzheimer's Disease; APP: Amyloid Precursor Protein; ATOX1: Antioxidant 1 Copper Chaperone; ATP7A And ATP7B: Atpases-7A And 7B; BACE1: Beta-APP Cleaving Enzyme; BBB: Blood-Brain Barrier; CSF: Cerebrospinal Fluid; CTR1: Copper Transporter-1; DMT-1: Divalent Metal Transporter-1; IDE: Insulin-Degrading Enzyme; MMP2 and MMPP3: Metalloproteases 2 and 3; MT: Metallothioneins; NFT: Neurofibrillary Tangles; PS1: Presenilin-1; Tf: Transferrin.

## INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia and the main pathological feature is massive neuronal loss in areas of the brain responsible for memory and learning. In the brain, the major neuropathological hallmarks associated with this disease are the presence of amyloid- $\beta$  (A $\beta$ ) plaques and neurofibrillary tangles (NFTs) of hyperphosphorylated microtubule-associated tau, as well as synaptic loss [1,2].

Epidemiological studies have shown an association between heavy metals such as lead (Pb), cadmium (Cd), and mercury (Hg) and AD, because of their involvement in cell toxicity and epigenetic mechanisms [3]. One of the major effects of the heavy

metals at both poisoning levels and long term exposure to low levels is insufficient supply of oxygen to the brain and results in anoxia/hypoxia in the brain (no oxygen or little oxygen), leading to serious brain injuries [4].

On the other hand, changes in the levels of biologically important metal ions, regarded as essential for human health in trace amounts including iron (Fe), zinc (Zn), copper (Cu), manganese (Mn), chromium (Cr), and molybdenum (Mo) because they form an integral part of one or more enzymes, could affect their normal function and consequently, the metabolic or biochemical processes in which they are involved. In particular, metals such as iron, zinc, and copper appear to be dysregulated in AD [5] and perturbances in their levels have been linked to cognitive loss and neurodegeneration. It is worth noting that enzymes such as monoaminoxidase B, which is important for the degradation of certain neurotransmitters, is modulated by metals like aluminium [6]. This is the basis for the "Metals Hypothesis of AD", which states that maintenance of metal homeostasis is crucial for neuronal function [7].

There is evidence to support that alteration of metal ion homeostasis leads to neuronal death. Redox metal ions are instrumental in enhancing the production of reactive oxygen

species (ROS) [8], affecting cellular redox homeostasis (e.g., the depletion of glutathione), and/or the disruption of mitochondrial function (e.g., dissipation of mitochondrial inner membrane potential). Ion metal dysregulation can also induce intracellular free calcium ( $[Ca^{2+}]_i$ ), which is part of a signalling pathway leading to cell death [9].

Metal ions may also contribute to AD by accelerating protein aggregation [10]. Copper, zinc and iron are found in high micromolar concentrations in amyloid plaques [11] because A $\beta$  is able to bind these metals with different affinities [12,13], which may vary depending on the aggregated state and length of A $\beta$ , and pH. Interestingly, the rat and mouse A $\beta$  sequences have structural changes in some amino acids that mitigate metal ion coordination and lower the aggregation propensity. This could be the reason why these animals do not form cerebral A $\beta$  deposits unless genetically modified to carry the humanised A $\beta$  sequences [14]. The interaction of metals with soluble A $\beta$  may also contribute to its precipitation within the synaptic cleft, leaving the brain tissue and cells deficient in these metals [14,15]. Therefore, sequestration of metals by binding to A $\beta$  may contribute to synaptic dysfunction and cognitive impairment [16].

Metals can also affect A $\beta$  synthesis, degradation and clearance. The exposure to some heavy metals such as Pb during brain development predetermined the expression, regulation, processing of APP later in life, and potentially influences the course of amyloidogenesis and oxidative damage [17]. In addition, APP levels have been shown to be translationally increased by cytosolic free iron levels and decrease upon addition of an iron chelator in neuroblastoma cells [18]. Iron regulation of APP may be conferred by a non-canonical 'type-II' IRE structure within the 5' UTR of the APP transcript [19]. Copper has also been reported to regulate APP expression [20]. There is evidence that other metals such as arsenic also increase APP levels [21]. Additionally, APP trafficking is directly influenced by Cu, since Cu treatment of neuronal cells revealed an increase of APP at the cell surface [22]. Recently it was been reported that Cu binding is required for APP dimerization [23] and APP synaptic function, although additional studies are necessary to decipher the exact mechanism by which Cu exerts this effect.

Furthermore, alterations in the distribution, activity and levels of enzymes involved in the amyloid precursor protein (APP) processing, such as BACE1 [24,25],  $\alpha$ -secretase [26,27] and presenilins have been observed upon metal exposure [28, 29], contributing to increases in the generation of A $\beta$ .

The role of metal ions in the degradation of A $\beta$  has been associated with the regulation of the enzymatic activities of proteins such as metalloproteases, including matrix metalloproteases 2 and 3 (MMP2 and MMP3) [30], neprilysin [31] and the Insulin-degrading enzyme (IDE) [32].

**Metals have also been involved in Tau aggregation:** *In vitro* studies have shown that tau can bind to copper and iron in a similar fashion to their binding to A $\beta$  and contribute to neuronal oxidative stress [33]. The results on the effect of copper on tau *in vivo* are conflicting, showing increases in tau phosphorylation in triple transgenic 3XTg mice treated with copper [34] but

decreases in tau phosphorylation and A $\beta$  aggregation in APP/PS1 mice when animals are treated with a compound that increases copper availability [30]. In addition, it has been shown that synthetic copper ligands can increase copper concentrations and inhibit GSK3 *in vitro*, reducing tau phosphorylation [35]. Zn<sup>2+</sup> also promotes tau aggregation [36] and NFT contain high levels of Zn<sup>2+</sup>. Low levels of Zn facilitate tau fibrillization, however higher levels have the opposite effect [36].

## LEVELS OF METALS IN AD BRAIN

The comparisons of the levels of transition metals in the brain, blood and CSF among AD patients and healthy controls described in the literature are heterogeneous [37]. This has been associated to fluctuations based on diet [38] and other factors such as blood-brain barrier (BBB) leakage. In addition, there have been issues related to artefacts in metal quantification caused by tissue handling (e.g. formalin fixation) or whether the metal concentrations have been determined using either dried or wet tissue weights or variability due to differences in the number of samples included in different reports [39]. Other important contributors to this diversity are differences between free, chelatable metals such as Zn<sup>2+</sup> versus protein-bound Zn<sup>2+</sup> pools, and redistributions within the brain as a function of disease progression and age [40].

### Levels of ion metals in the brain

The levels and distribution of metals in the brain have been visualized using different methodologies, including distinct immunohistochemical staining (directly of the metal or the metal storage protein), MRI and ICP-MS, providing different outcomes depending upon the technique used.

Most of the articles in the field have focused the attention on Cu, Fe and Zn, because they are the most abundant transition metals in eukaryotes. As commented above, studies in brain have suggested that Cu, Fe and Zn are enriched within amyloid plaques, because of their binding to A $\beta$  [11], however their levels in the affected regions of the AD brain are decreased [39,41], suggesting an imbalance of these metals in AD [42] and leading to a decrease in their bioavailability.

There is a consensus in the literature regarding increased iron levels in the brain of AD patients compared to controls, although the magnitude of change may depend on each particular brain region [37,43,44]. The elevated iron levels registered in the neocortex could be related to the accumulation of iron with ageing described in that region [37], while in other areas like hippocampus and amygdala iron concentration does not correlate with age [39] or are even reduced with aging [44]. Fe localization is relevant because it correlates with the production of reactive oxygen species in those areas of the brain that are prone to neurodegeneration [45]. Iron distribution also varies among different cell types, because of the different expression of transporters and metalloproteins [46]. Fe is found in all cell types in the brain, including neurons, astrocytes, oligodendrocytes and microglia [18]. However, microglia were found to be the most efficient in accumulating iron, followed by astrocytes, and then neurons [47]. There is evidence that excess iron within activated microglia is able to enhance the release of pro-inflammatory cytokines and free radical (Rathnasamy et al., 2013), which has

been to be associated with neurodegeneration. Furthermore, changes in the concentration of Fe have been shown to have adverse effects on the activity of certain enzymes, such as furin, which is involved in the cleavage and activation of the  $\alpha$ -secretase [49].

Conversely, the average concentrations of Cu in the AD hippocampus and amygdala have been found reduced compared with controls in several studies [39,44], perhaps reflecting brain mass loss. Recent findings indicate that Cu levels gradually decline with aging [44]. Transgenic APP mice, such as Tg2576 and the APP23, also show reduced brain Cu levels compared to wild-type mice in brain [50], whereas in APP- and APLP2-knockout mice, Cu levels were found increased in cerebral cortex and liver [51,52].

The levels of free trace elements such as Zn seem to be unchanged in AD brains [39, 44]. Although it has been found a significant change in zinc concentration in the parietal lobe, the other lobes did not appear to be affected [37].

### **Metal transporters and proteins involved in metal storage in AD brain**

The regulation of the influx of metals into the brain which takes place at the BBB is critical to modulate the levels of metals. Therefore, abnormal flux of metal ions across the BBB and the choroid plexus, from blood and CSF, respectively, can lead to their accumulation in brain [53]. It is worth noting that abnormalities in vascular structure and function that have been reported in the AD brains could lead to abnormal metal accumulation in the brain [29].

Metals transporters are key elements to control the uptake of metals. Interestingly, metals sharing the same transporter can compete with each other, as is the case of transferrin (Tf). Tf presents the ability to bind several metals, such as Fe, Mn, Zn, Cr, Co, Cd, vanadium (V) and Al, acting as a potential transporter agent via the transferrin receptor [54]. Tf is found in senile plaques at increased concentrations, perhaps due to its binding to Fe and Zn [55].

On the other hand, low molecular mass metallic species can enter into the brain through nonspecific transporters, such as the divalent metal transporter-1 (DMT-1), which is implicated in the uptake of divalent ions such as Fe and Mn, and to a lesser extent Zn, Cu, Co, Cd, and Nickel (Ni) [53].

An important transporter for Fe is ferroportin; without it Fe cannot be released into the brain. Ferroportin is localized in the brain in most cell types including neuronal perikarya, axons, dendrites and synaptic vesicles and its levels have been found decreased in hippocampus from AD cases [29]. However, ferroportin has not been confirmed on the abluminal side of the BBB. Its role is crucial, because Duce and colleagues have reported that APP may bind to ferroportin to facilitate neuronal iron export and that disturbances in these processes may be implicated in AD brain pathology [56]. Nevertheless, the potential ferroxidase activity of APP has been proven controversial in the last years.

Brain zinc uptake is facilitated by L- and D-histidine at the BBB. The levels of Zn transporters, such as ZnT-1, ZnT-4, ZnT-6

and Zn-10 have been found altered in AD brain as well [57,58], thereby contributing to Zn dyshomeostasis.

In the case of copper, it is likely taken up by transporters CTR1 (copper transporter-1), ATPases ATP7A, and ATP7B and the chaperone ATOX1 (antioxidant 1 copper chaperone), which are expressed differentially in different tissues [59]. Recently, it has been shown a genetic association between ATP7B variants and AD risk [60]. In the brain it appears to be found as free copper or bound to proteins such as ceruloplasmin, SOD and some metallothioneins [59]. Ceruloplasmin has been found increased in brain tissue and cerebrospinal fluid in AD [61], although neuronal levels of ceruloplasmin remain unaltered [62].

In addition, studies in postmortem brains of AD patients have shown differences in the levels of proteins involved in the storage of metal ions, such as ferritin. This intracellular Fe-storage protein is increased in microglia and senile plaques [63]. On the other hand, in the neurons of the substantia nigra, the major iron storage protein is neuromelanin in normal individuals [64], which will have implications for PD patients. Other proteins involved in the storage of metals are the Metallothioneins (MT), which bind  $\text{Cd}^{2+}$ ,  $\text{Cu}^+$  and  $\text{Zn}^{2+}$ , and are responsible for transport, storage and regulation of zinc and copper and the detoxification of heavy metals [40]. MT might play a role in AD due to their abnormal expression in AD brains [65], thereby contributing to abnormal metal homeostasis.

### **Levels of metals in CSF and plasma**

Some publications regarding copper levels in the CSF and plasma of AD patients compared to healthy controls have shown a tendency towards an increase with aging, especially in the capillaries [14,66] and in AD patients [67-69], while others have shown the opposite results [70]. The controversy also applies to Zn ions, which levels have been found decreased in serum and blood of AD patients [71] but increased or unchanged in the CSF [72, 73]. Publications regarding Fe levels in plasma, serum and CSF are more heterogeneous and meta-analyses have shown no significant difference in iron in AD subjects compared to controls [74].

Other metal ions of interest in AD such as cobalt have been implicated as an important component of vitamin B12, the deficiency of which is associated with an increased risk of AD due to its effect on homocysteine and folate levels [75]. Subjects with AD show significantly lower plasma levels of cobalt when compared with controls, although no changes in Co concentrations have been observed in the CSF [76].

Chromium and manganese levels are inversely correlated with A $\beta$ 42 levels in CSF of AD patients [77], while the results regarding the levels of other metals in AD brain that have been linked to the disease because of their high toxicity, such as arsenic, lead, mercury and aluminium, are conflicting [14, 78].

## **DISCUSSION AND CONCLUSIONS**

While there is documented evidence for a link between the levels of certain metals in the brain with AD pathogenesis, epidemiologic association is inconclusive, probably due to the complexity of the pathways involved. To date, most of the research work has been focused on the interaction between

A $\beta$  and metal ions, although there are many more additional mechanisms in which metals are affecting neurodegeneration. Several critical enzymatic processes associated fundamentally with AD pathology are influenced substantially by metals, however the molecular basis of this regulation are not yet understood. It seems that mis-localization of metal ions in the AD brain is more likely to play a significant role in AD pathogenesis than excess or deficiency of biological metals. This will be crucial in order to design future strategies to treat AD by restoring metal homeostasis.

The understanding of this complex disease require more comprehensive and long term bio-monitoring and this can bridge metal to specific gene risk factors and reveal genetic and epigenetic connections with the disease.

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