Review

Metal Toxicity Links to Alzheimer's Disease and Neuroinflammation

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Abstract

As the median age of the population increases, the number of individuals with Alzheimer's disease (AD) and the associated socio-economic burden are predicted to worsen. While aging and inherent genetic predisposition play major roles in the onset of AD, lifestyle, physical fitness, medical condition, and social environment have emerged as relevant disease modifiers. These environmental risk factors can play a key role in accelerating or decelerating disease onset and progression. Among known environmental risk factors, chronic exposure to various metals has become more common among the public as the aggressive pace of anthropogenic activities releases excess amount of metals into the environment. As a result, we are exposed not only to essential metals, such as iron, copper, zinc and manganese, but also to toxic metals including lead, aluminum, and cadmium, which perturb metal homeostasis at the cellular and organismal levels. Herein, we review how these metals affect brain physiology and immunity, as well as their roles in the accumulation of toxic AD proteinaceous species (i.e., β-amyloid and tau). We also discuss studies that validate the disruption of immune-related pathways as an important mechanism of toxicity by which metals can contribute to AD. Our goal is to increase the awareness of metals as players in the onset and progression of AD.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that leads to cognitive impairment and dementia in the elderly. Fifty million people worldwide were living with dementia in 2018, and this number is expected to more than triple to 152 million by 2050, with AD accounting for an estimated 60%–80% of these [1]. The reasons that cause individuals to be sensitive or resilient to AD are still elusive. Although mutations in the β-amyloid (Aβ)-related genes *app*, *psen1* and *psen2* are known to cause AD, these mutations account for less than 1% of total AD cases (Fig. 1). Recent genetic studies have improved our understanding of the factors that make some people prone to AD by identifying genetic variants that cause a slight to moderate increase in risk (e.g., *apoe*, *trem2*, *cd33*). These genetic studies have also revealed a broader picture of the processes and pathways involved in AD. It is now accepted that changes in lipid metabolism, endocytosis and inflammatory responses can contribute to the onset and progression of the disease. Lifestyle factors also affect an individual's risk of developing AD, many of which are potentially modifiable, including dietary habits and exposure to environmental and occupational hazards [2,3].

Neuropathologically, AD is characterized by the misfolding and aggregation of two key proteins in the brain, Aβ and tau, leading to the formation of plaques and neurofibrillary tangles (NFTs), respectively (Fig. 1).

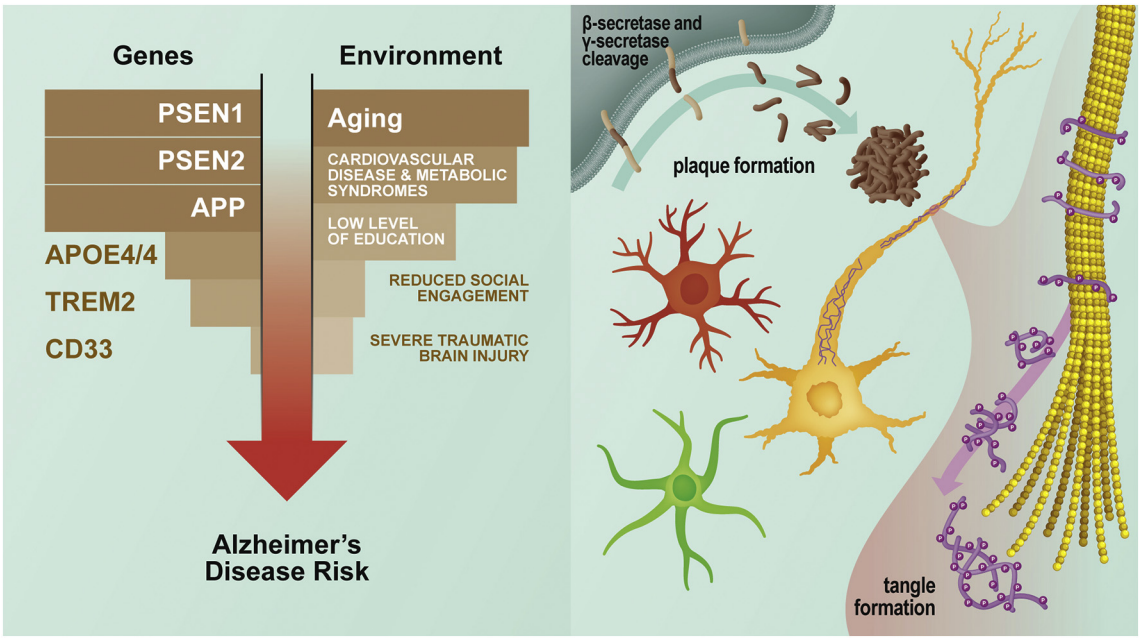

Fig. 1. AD causes and risks. (Left panel) Rare mutations in *app*, *psen1* and *psen2* alter APP processing and are known strong genetic causes of AD. Other variations in genes related to lipid metabolism, endocytosis and inflammatory responses, like *apoe*, *trem2* and *cd33*, are more common in the population but they confer moderate to low risk to AD. The environmental risks for AD include aging, cardiac and metabolic disorders (i.e., diabetes and hypertension), level of education, reduced social engagement and severe traumatic brain injury. (Right panel) Neuropathologically, AD is characterized by the formation of Aβ plaques and NFTs in the brain. The production of Aβ occurs due to aberrant processing of the APP, whereby it is cleaved by β- and γ-secretases, instead of α-secretase. The Aβ peptide is prone to misfolding and aggregation, leading to eventual oligomerization and formation of Aβ plaques, which trigger a proinflammatory response from microglia and astrocytes. Aβ also causes the hyperphosphorylation of tau, leading to its dissociation from microtubules and their eventual destabilization within neurons. Hyperphosphorylated tau is also prone to aggregation, forming NFTs, which correlates with neuronal loss and neurodegeneration.

The formation of plaques is preceded by the production of Aβ, caused by changes in amyloid precursor protein (APP) processing, with NFTs forming due to abnormal hyperphosphorylation of tau. APP is abundant in the healthy brain, where it is cleaved by α-secretase to produce the non-pathogenic protein fragment soluble APPα [4]. However, in the AD brain, APP cleavage by β- and γ-secretase leads to the production of toxic Aβ fragments. These are prone to misfolding and forming oligomers, which are considered the most toxic Aβ species. Although it has been demonstrated that Aβ production and misfolding occur prior to any of the other pathologies associated with AD, the trigger(s) for this remains to be fully identified [5]. The production of Aβ has been shown to lead to the hyperphosphorylation of the microtubule-associated tau protein, stimulated by the phosphorylation of the tau kinases glycogen synthase kinase-3β (GSK-3β), cyclin-dependent kinase 5 (CDK5) and extracellular signal-regulated kinase 1/2 [6,7]. The hyperphosphorylation of tau can cause microtubule destabilization and breakdown, perturb axonal transport, and make tau far more prone to aggregation into NFTs [8–10]. NFT load correlates with cognitive impairment and neurodegeneration, leading to the suggestion that reducing tau hyperphosphorylation and NFT formation are key to preventing AD [11,12].

The brain has mechanisms to clear toxic proteins, including degradation pathways and the immune system. Inflammation poses a key risk for AD with respect to both genetic (e.g., *apoe*, *trem2*, *cd33*) and lifestyle factors (e.g., diabetes mellitus, obesity, traumatic brain injury) [3]. With respect to the proteins involved in AD, both Aβ and tau can be altered by neuroinflammation. Accumulation of Aβ triggers a proinflammatory response from the brain's resident immune cells, microglia and astrocytes, leading to the phagocytosis of plaques as well as their proteolytic degradation. Receptors on microglia, such as triggering receptor expressed on myeloid cells 2 (TREM2) and toll-like receptors (TLRs), can recognize Aβ and trigger a phagocytic pathway [13,14]. Aβ degrading enzymes, including neprilysin and insulin degrading enzyme, can also be released to remove Aβ extracellularly, although the activity of these enzymes is reduced in AD [15,16]. Moreover, the exacerbated proinflammatory state that occurs during this period of the disease can trigger the hyperphosphorylation of tau. Several of the kinases

responsible for tau phosphorylation are activated by proinflammatory mediators and have been shown to worsen tau pathology [17,18]. Interestingly, microglial uptake of hyperphosphorylated tau is linked to the propagation of tau pathology, and the overactivation of proinflammatory microglia by Aβ may therefore lead to worsened tauopathy [19]. Microglia become senescent over the progression of AD [20,21], in part due to the excessive production of Aβ. During this phenotypic state, they continue to produce microglia-recruiting, proinflammatory mediators, including cytokines and chemokines, causing more microglia eventually becoming senescent [22]. Not only can this exacerbate Aβ and tau pathology, but microglia can become overactive in neurodegeneration, excessively pruning synapses and injuring neurons [23].

Among the chemical elements of relevance to humans, metals play a significant role in both health and disease. Metals are natural constituents of the Earth's crust and are disseminated into the biosphere through human activities [24,25]. These compounds display high stability, solubility in atmospheric precipitation, and ability to be absorbed by soil and living organisms, with human exposure soaring because of an exponential increase in their use in several industrial, agricultural, domestic and technological applications. Common sources of metals are mining, tailings, industrial waste, agricultural runoff, paints, treated timber, aging water supply infrastructure, vehicle emissions, lead-acid batteries, fertilizers and microplastics. The main routes of human exposure include ingestion, inhalation and dermal contact [25]. Physiologically, some metals are either essential nutrients (e.g., iron and zinc) or relatively harmless (e.g., ruthenium, silver, and indium), but even these can be toxic in larger amounts or certain forms (Fig. 2). This is because metals are usually essential components of larger biological molecules that can interact with or regulate the levels of relatively large numbers of other molecules [26]. This means that the optimal physiological concentration range between deficiency and toxicity of metals is relatively small and needs to be tightly controlled. Importantly, tiny amounts of non-essential metals also promote severe toxicity as they inadvertently disrupt the physiological activity of essential metals. Because of their high degree of toxicity, cadmium, lead and aluminum rank among the priority metals that are of public health significance (Fig. 2). These metallic elements are considered systemic toxicants that are known to induce multiple organ damage, even at lower levels of exposure. Notably, evidence suggests that dysregulation in the homeostasis of essential metals (Fig. 3) and exposure to non-essential metals (Fig. 4) have a significant impact on the pathogenesis of AD. In the next part of this review, we will discuss the impact that some of these trace metals exert in the brain, and how they contribute to AD and the dysregulation of the immune system.

The Essential Metals

Iron (Fe)

Besides its role in oxygen homeostasis, iron orchestrates a broad range of cellular functions, such as respiration, energy metabolism, DNA synthesis and repair, and signaling [27]. Other roles of iron in the central nervous system (CNS) include its participation in the myelination of the spinal cord and white matter, and in the synthesis, packaging, uptake and degradation of neurotransmitters. Ironically, iron's ability to undergo oxidation-reduction reactions, which is the property that makes it biologically valuable, also allows it to convert hydrogen peroxide into a highly toxic hydroxyl free radical. Through the production of these reactive oxygen species (ROS), iron can induce severe brain damage. The systemic and cellular mechanisms that control iron intake, storage, utilization and recycling are therefore strictly regulated. A recent computational study has established that the iron metabolic network consists of 151 chemical species, 107 reactions and transport steps [28]. In the brain, this network involves multiple transporter proteins that regulate the traffic of iron across different tissues and cells, including transferrin receptor 1, divalent metal transporter 1 (DMT1), lactoferrin, melanotransferrin and ferroportin [29]. Once within the cells, iron can follow different pathways depending on cellular need. Ultimately, control of the intracellular metabolism of iron occurs through iron-regulatory proteins (IRP) that bind iron-responsive elements (IREs) in regulated messenger RNAs (mRNAs) [30]. Notably, disruptions of iron brain homeostasis have been linked to several diseases. While brain iron deficiency results in unfavorable pregnancy outcomes and cognitive developmental defects in children, such as attention-deficit hyperactivity disorder [31], its excessive accumulation in adults has been linked to neurodegenerative diseases, including AD [32–34]. Changes in iron levels in AD can be detected as early as the mild cognitive impairment stage of the disease [35]. For this reason, iron-based magnetic resonance imaging contrast, which can detect iron content in the brain, has been investigated as a potential imaging biomarker due to its capacity to discriminate pathological changes related to AD [36–39]. Recent evidence has demonstrated that cerebrospinal fluid ferritin levels predict brain hypometabolism in people with underlying AD pathology [40]. Together, these studies indicate that changes in iron metabolism may facilitate disease progression in the prodromal stages, which could be used as a biomarker of AD.

Over the years, many studies have helped to mechanistically link iron metabolism and AD. For instance, APP mRNA encodes a functional IRE in its 5′-untranslated region that binds with IRP-1, and its translation is down-regulated in response to intracellular

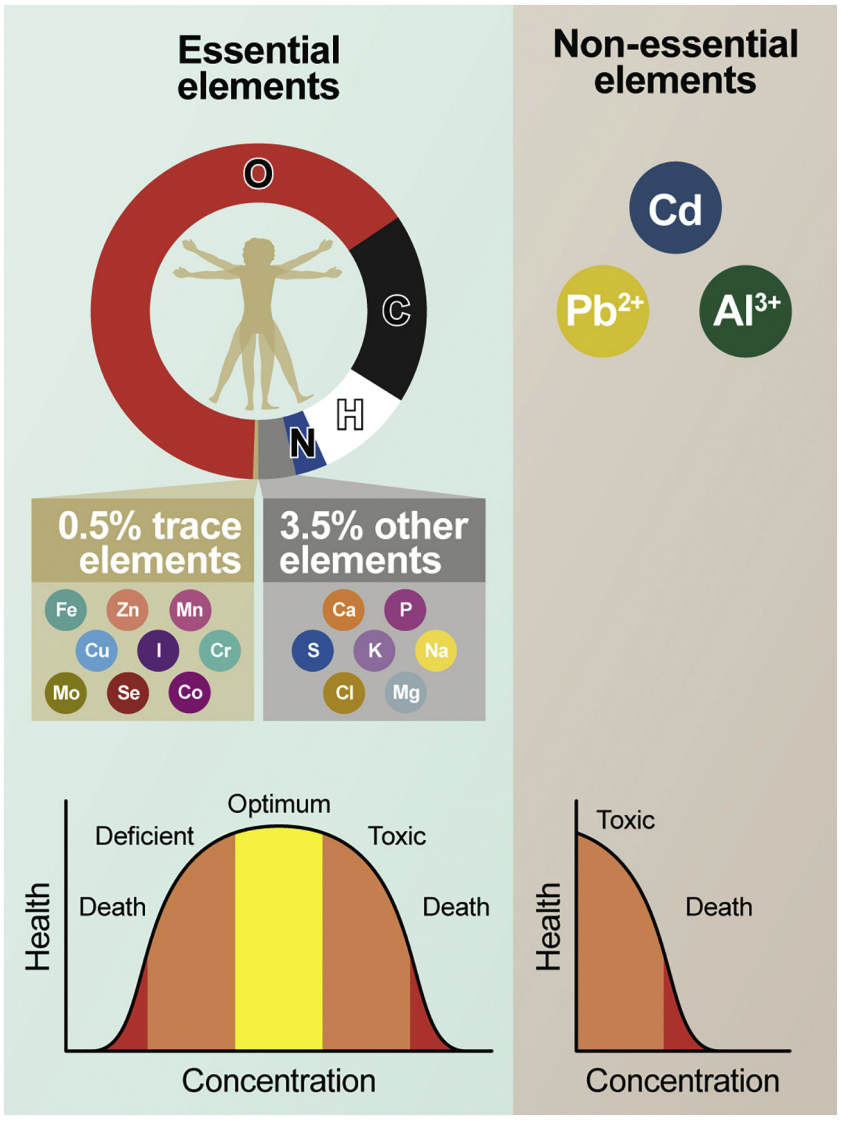

Fig. 2. The molecular composition of the body: essential and non-essential elements. In human biology, the constituents of the body are classified into four groups according to their increasing complexity: atomic, molecular, cellular and tissue system. In this system, the more complex components are built by combining the more basic ones. At the atomic level, only 4 of the 118 chemical elements currently known (i.e., oxygen, carbon, hydrogen and nitrogen) are needed to make about 96% of the mass of the human body. Further 3.5% of body is composed of seven chemical elements, namely calcium, phosphorus, sulfur, potassium, sodium, chlorine and magnesium. The remaining constituents are trace elements. Of those, iron, zinc, manganese, copper, iodine, chromium, molybdenum, selenium and cobalt are considered essential nutrient elements for humans and are listed in order of recommended dietary allowance. Each of these elements has an optimal concentration in the body—too little or too much will result in reduced functionality or even death. In contrast, there are several non-essential elements likely to induce toxicity including aluminum, lead and cadmium. Non-essential elements can cause cellular dysfunction at low concentrations, followed by death if they persist in biological systems.

iron chelation [41,42]. At the protein level, APP acts as a modulator of iron function, as it oxidizes Fe^{2+}, loads Fe^{3+} into transferrin and interacts with the iron transporter ferroportin. *In vitro* studies have shown that ablation of APP induces marked iron retention in cells, whereas APP overexpression promotes iron export. Likewise, genetic deletion of APP in mice causes iron accumulation and oxidative stress in cortical neurons, making animals vulnerable to dietary iron exposure compared to normal mice [43]. Moreover, several of the biological abnormalities seen in AD are consistent with an excessive action of oxygenic free radicals caused by impairment in iron homeostasis, and Aβ plaques and NFTs are major sites for catalytic redox reactivity [44,45]. Iron and its regulatory proteins ferritin (iron storage) and transferrin (iron mobilization) are largely found in oligodendrocytes in physiological conditions. In AD, however, substantial amounts of iron and ferritin are detected within plaques, NFTs and blood vessels [45–47]. Although iron- and ferritin-positive oligodendrocytes are present, most of the iron- and ferritin-containing cells associated with the markers of AD are microglia [48–51]. Likewise, transferrin is distributed extracellularly around plaques and in astrocytes in the AD brain rather than its normal distribution in oligodendrocytes [48]. It has been suggested that microglia and astrocytes accumulate higher iron content in AD because they are more resistant to oxidative stress than neuronal cells [52]. Despite this, the accumulation of iron in these glial cells does seem to compromise their function [53]. Other components of the iron network are also altered in AD, including lactotransferrin [54,55], melanotransferrin [56] and IRP-2 [57]. Changes in iron metabolism are therefore prominent in AD at the cellular

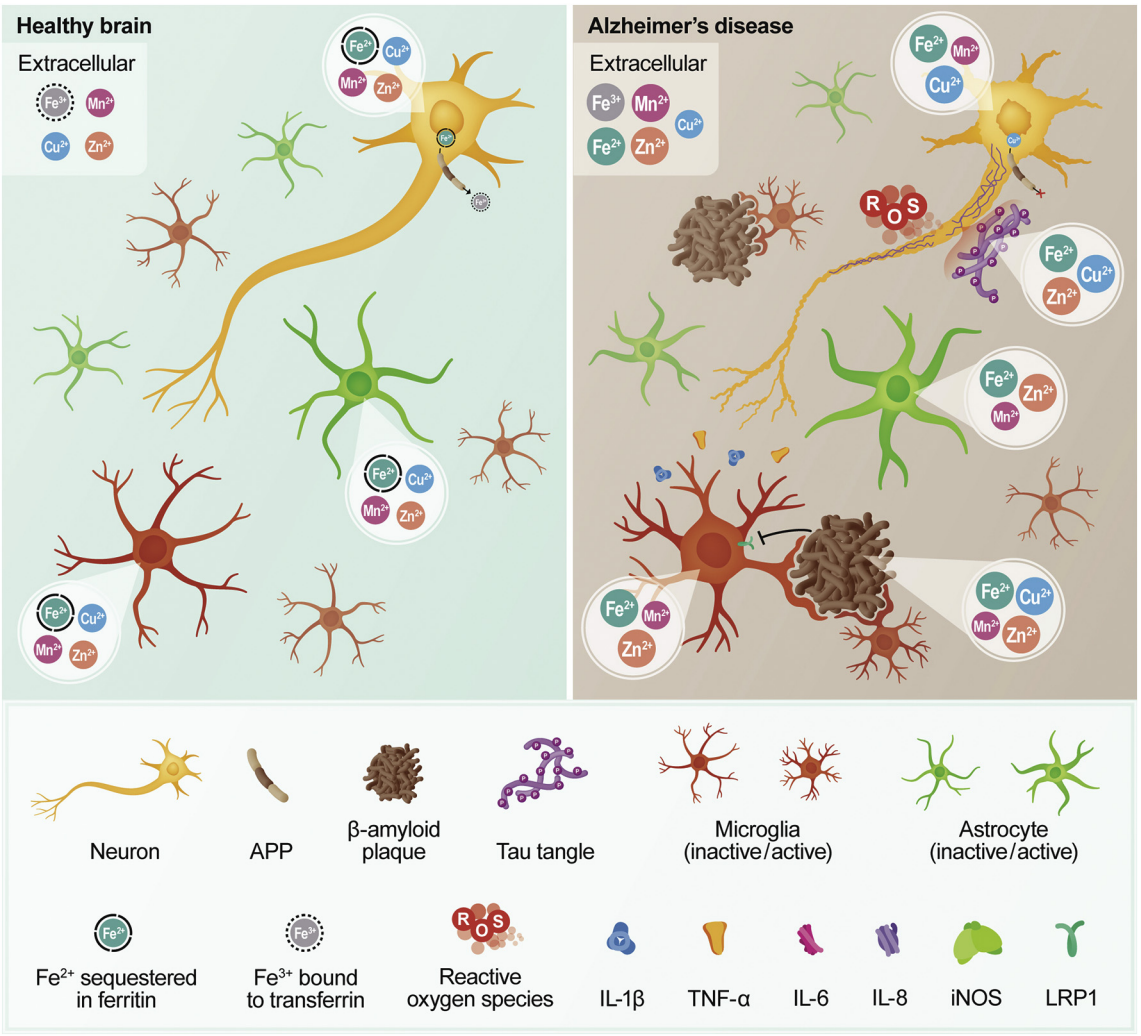

Fig. 3. The impact of essential metals in AD. (Left panel) In the healthy brain, essential metals such as iron, copper, zinc and manganese are kept at a homeostatic level to ensure optimal cellular functions. To achieve these conditions, a complex mechanism exists to tightly regulate its intracellular and extracellular concentrations. For instance, iron (Fe^{2+}) is kept within cells bound to the iron storage protein ferritin, making it available upon cellular needs. In neurons, APP can oxidize Fe^{2+} into Fe^{3+} inducing its release into the extracellular matrix. Once outside the cell, Fe^{3+} rapidly binds to the iron mobilization protein, transferrin, making iron accessible for further biological processes. APP is also involved in the conversion of Cu^{2+} into Cu^{+}, favoring its removal from the brain. Zinc and manganese are also present in trace amounts, which are finely regulated and essential to maintain brain function. (Right panel) In the AD brain, dyshomeostasis of essential metals seems to be linked with AD pathogenesis. Impairment of APP function, present in AD, can trigger an increased level of both intracellular and extracellular Fe^{2+} and Cu^{2+}, and a reduction of extracellular Cu^{+}, thus promoting its accumulation. Excessive Fe^{2+} and Cu^{2+} increases oxidative stress via production of ROS. In addition, iron, copper and zinc have higher binding affinity to Aβ and can promote its aggregation. Increased neuronal iron, copper and zinc also bind to tau protein and facilitate the formation of NFTs. Consequently, excessive amounts of heavy metals are found within plaques and NFT. Dyshomeostasis of essential metals in the extracellular space induce microglial and astrocytic activation, followed by the overproduction of proinflammatory cytokines such as, IL-1β and TNF-α.

level. However, how these changes affect the function of the distinct brain cells and their communication remains to be fully elucidated.

A large part of iron's detrimental effect in the AD is related to its cytotoxic redox properties, which are further impaired during the progression of the disease. In a mouse model, the neurological impairment induced by the infusion of Aβ peptide was exacerbated by the genetic deletion of mitochondrial ferritin, a process that was associated with an accumulation of intracellular iron and increased levels of oxidative stress [58]. *In vitro* studies have demonstrated that the affinity of Aβ for iron increases following its aggregation, and that this binding potentiates Aβ neuronal toxicity [59–62]. This

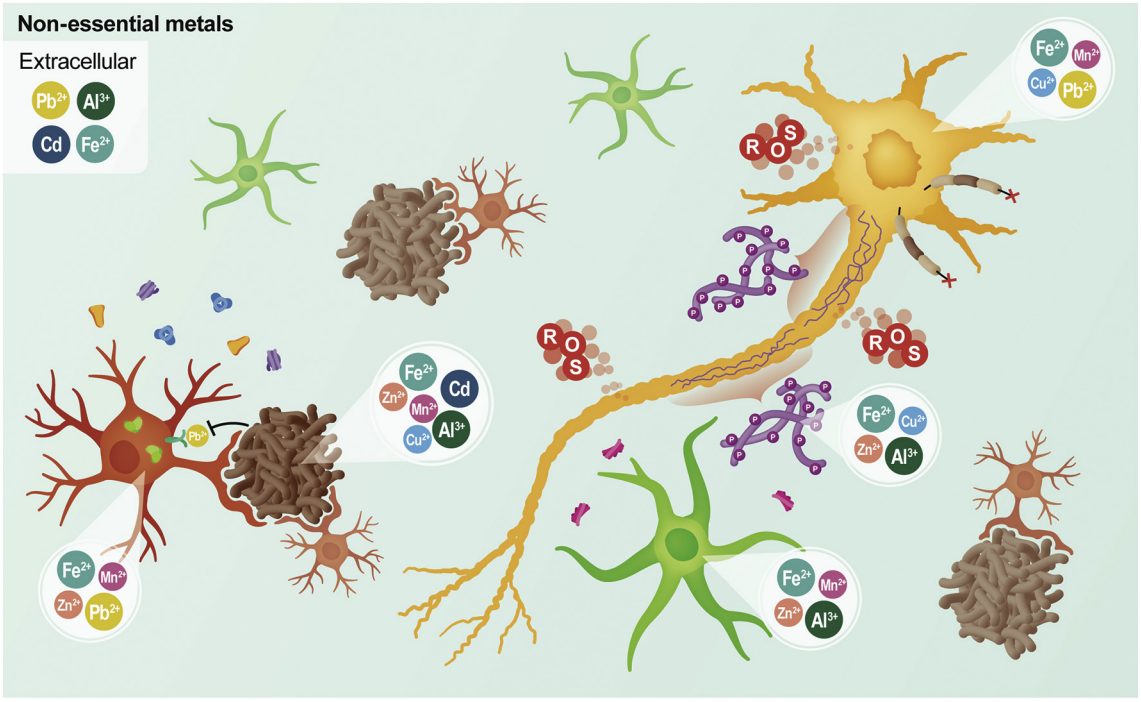

Fig. 4. The impact of non-essential metals in AD. The presence of non-essential metals such as lead, aluminum and cadmium has neurotoxic effects on the brain which are exacerbated in AD. Lead exposure increases APP and BACE1 expression and disrupts microglial functioning, together increasing Aβ production and plaque formation. Increased intracellular aluminum competes for the iron binding site in the IRE; as a result, Fe^{2+} accumulates and increases the production of ROS. Aluminum also accumulates in NFT-bearing neurons. In addition, aluminum can bind to Aβ and induce its aggregation. Cadmium also binds to Aβ and involved in the formation of plaques. Heavy metal exposure induces microglial and astrocytic activation and subsequent increase in production of proinflammatory proteins, including IL-1β, IL-8, TNF-α, IL-6 and inducible nitric oxide synthase. *Extracellular levels*: changes in metal levels in the extracellular space include the metals accumulated in plaques; note that it might not necessarily reflect the number of free ions available in the extracellular space.

occurs because the binding between iron and Aβ modulates the redox potential to a level at which iron's redox cycling occurs, resulting not only in the generation of oxidative species but also in the depletion of essential oxygen and biological reductants. By binding to iron, Aβ also competes against other essential iron-containing proteins. For example, the affinity of Aβ for iron is 8 orders of magnitude stronger than that of transferrin, and its accumulation can therefore change the iron homeostasis [63]. In agreement with this idea, it has been shown that Aβ deposition in the APP/PS1 mouse model is accompanied by changes in iron-related proteins, DMT1 and ferroportin 1, whose levels in the brain are increased and reduced, respectively [64]. Of note, DMT1 relocates to cellular and endosomal membranes, where it is a key player in non-transferrin bound iron uptake and transferrin-bound iron uptake, respectively [65]. Ferroportin 1, on the other hand, plays an essential role in the export of iron from cells to the blood [66]. Interestingly, *in vitro* studies have demonstrated that silencing of endogenous DMT1 not only reduces iron influx but also leads to reductions in APP expression and Aβ production [67–69]. Pharmacological inhibition of DMT1 also seems to reduce iron-induced tau pathology in human neuroblastoma SH-SY5Y cells, through the inhibition of the tau kinases CDK5 and GSK-3β [70]. Importantly, other studies have demonstrated the capacity of iron to interfere with markers of AD pathology, as *in vitro* and *in vivo* data show that iron overload results in higher Aβ production, neuronal toxicity and cognitive impairment [71,72]. Another relevant study in the APP/PS1 mouse model revealed that the iron chelating agent deferoxamine inhibits Aβ accumulation and improves cognitive function. It was proposed that this effect is dependent on the alternative activation of microglia, which become more prone to clear Aβ via phagocytosis [73]. This hypothesis, however, needs further validation as many agents that reduce Aβ deposition in mice can indirectly improve microglial and cognitive functions.

With regards to changes in the brain immune system, microglial dystrophy in the aged and AD brains is associated with ferritin immunoreactivity [53]. Disruption of iron homeostasis through brain hemorrhage also enhances microgliosis and astrogliosis, and results in elevated levels of the proinflammatory cytokines tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) [74]. This is particularly interesting since traumatic brain

injury is a potential risk factor for AD [3]. Excess iron has also been shown to activate microglia by inducing the nuclear factor-κB (NF-κB)-mediated transcription of proinflammatory cytokines [75,76]. Interestingly, the accumulation of inflammatory signals, such as TNF-α and IL-6, triggers the upregulation of DMT1 and downregulation of ferroportin, suggesting that the mechanism for iron accumulation into neurons and microglia during inflammation is in part due to changes in the levels of iron transporters [77]. Iron accumulation in macrophages and microglia following CNS damage has also been linked to a shift in cell activation towards a proinflammatory phenotype, which results in lower phagocytic efficiency [78]. Although these studies suggest that a positive feedback loop between iron accumulation and excessive proinflammation progressively contributes to neurotoxicity, they failed to provide a clear molecular mechanism by which iron contributes to the function of glial cells. Particularly, it would be important to determine whether iron metabolism directly regulates functions of microglia and astrocytes, like immune surveillance and synaptic pruning, during homeostasis and disease states.

Copper (Cu)

Like iron, copper is a highly desirable chemical element in cell biology due to its ability to gain and donate electrons. Once taken up and distributed in an organism, copper ions cycle between cupric Cu^{2+} (oxidized) and cuprous Cu^{+} (reduced) states, mostly bound to cuproenzymes with only a small portion available as labile copper, also known as free or unbound copper [79]. This redox property is essential for catalysis by many enzymes whose activities control a broad range of cellular biochemical and regulatory functions. The relevance of copper for human health is easily emphasized by two life-threatening disorders caused by mutations in P-type Cu^{+}-transporting ATPase pumps: Menkes and Wilson's diseases [80]. Menkes disease is an X-linked lethal disorder of intestinal copper hyperaccumulation and severe copper deficiency in peripheral and central tissues. It is caused by loss-of-function mutations in the ATP7A protein, which results in infantile-onset cerebral and cerebellar neurodegeneration due to a failure in copper transport into the CNS [81]. The neuronal damage caused by the failure in copper homeostasis is attributed to its many roles in processes essential for normal brain function, including the synthesis of catecholamines, activation of neuropeptides and hormones, antioxidant defense, connective tissue production, immune function and synaptic transmission [82–84]. Wilson's disease, on the other hand, is an autosomal recessive disease caused by mutations in the ATP7B protein, a transporter that loads Cu^{+} onto newly synthesized cuproenzymes in the trans-Golgi network and exports excess copper out of cells by trafficking from the trans-Golgi network to the plasma membrane. The disease is characterized by striking hepatic and neuronal copper overload, hepatotoxicity, and neuropsychological and other defects that require chronic therapy to enhance copper excretion or reduce its absorption [85]. Remarkably, this disease highlights the fact that copper's greatest strength is also its major weakness as excess causes it to participate in redox reactions that generate ROS, leading to catastrophic damage to lipids, proteins and DNA. Therefore, intracellular levels of copper must be tightly regulated as excessive free copper is highly toxic [79].

Considering the robust evidence for copper's essential roles in the brain, it is not surprising that many studies have proposed that an imbalance in its homeostasis is associated with neurodegenerative disorders. Besides AD, copper has been linked to amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease and prion-mediated encephalopathies [86–90]. In AD, it has been suggested that individuals suffering from the disease have higher serum levels of copper than healthy controls, with higher levels of labile copper in the serum correlating with poor cognitive performance and increased rates of conversion from mild cognitive impairment to AD [91–93]. Analyses of post-mortem human brains have revealed that the overall soluble levels of copper are reduced, whereas its presence within insoluble neuritic plaques is increased, in AD *versus* non-demented individuals [94–96]. Notably, despite a lower total copper content, AD brains possess a higher proportion of redox-active exchangeable copper, which positively correlates with increased oxidative damage and AD neuropathology [97].

Biochemical analyses have identified two binding sites for copper in full-length APP, including one within the Aβ sequence. Binding of Cu^{2+} to the N-terminal domain of APP results in its reduction to Cu^{+} [98]. Genetic studies in mouse models have demonstrated that the APP-induced conversion of Cu^{2+} to Cu^{+} favors copper removal from the brain, which could explain the fact that AD patients have lower levels of copper in their brain and higher levels in their serum [91–93,96,99,100]. Binding of copper to the N-terminus of APP may also control other aspects of this protein, including its synaptogenic function, stability and metabolism [101–105]. Interestingly, reduction in the level of brain copper increases the ratio of APP endocytosis and processing, and the production of Aβ, perhaps as a protective mechanism to reverse the excessive loss of copper [101,103]. However, newly synthesized intracellular Aβ can sequester copper, which possibly serves to initially exacerbate the imbalance in copper levels and then later enable the aggregation of Aβ into plaques. Such a process is highly relevant in the formation of neuritic plaques in AD because copper can potentiate Aβ aggregation and cell damage due to the generation of ROS [106–108]. The protein tau has also been shown to bind copper, which facilitates the formation of NFTs [109–111]. Likewise,

tau demonstrates redox activity when bound to copper, further contributing to the oxidative damage in the brain [112]. Considering the significance of tau in AD, it is surprising that only a small proportion of studies have investigated how changes in copper homeostasis affect its function. Future studies assessing whether copper regulates tau kinases and phosphatases as well as tau-mediated cognitive impairment are needed and will greatly increase our understanding of the neuropathology of AD.

In relation to neuroinflammation, copper seems to play important roles in modulating microglial activation, although there is limited evidence that it directly initiates the inflammatory process. It has been demonstrated that copper enhances the effect of Aβ on microglial activation and subsequent neurotoxicity. Copper–Aβ complexes induce microglial activation and the release of TNF-α and nitric oxide in an NF-κB-dependent manner. Interestingly, the effects produced by these complexes are not observed upon treatment with either copper or Aβ alone [113,114]. Recently, we have demonstrated that exposure to copper–Aβ reduces the phagocytic phenotype of BV2 microglia and increases TNF-α and IL-1β release, followed by significant down-regulation of lipoprotein receptor-related protein-1 (LRP-1) expression [115]. Reduced levels of LRP-1 further impair the transcytotic clearance of Aβ and exacerbate neuroinflammation [3]. It has been reported that trace copper potentiates the Aβ-induced inflammatory response in cholesterol-fed mice; however, no inflammatory effects were observed upon treatment with copper or cholesterol alone [116]. These studies highlight the role of copper as a cofactor in increasing the potency of Aβ toxicity with a subsequent contribution to microglial activation. Histological data have demonstrated that activated microglia express ATP7A specifically clustered around plaques. This ATP7A expression was found to be increased by the proinflammatory cytokine interferon-γ, but not by TNF-α or IL-1β [117]. The inflammatory response associated with AD therefore seems to cause changes in microglial copper trafficking, which may underlie the changes in copper homeostasis in the disease. Remarkably, mice fed a copper-deficient diet display signs of microglial and astrocytic activation, suggesting that copper homeostasis is required physiologically to prevent neuroinflammation [118]. It has been proposed that copper homeostasis regulates the shift between proinflammatory and anti-inflammatory phenotypes in microglia via the regulation of nitric oxide levels and disruption of *S*-nitrosothiol signaling [119,120]. Further understanding of the underlying mechanism by which copper regulates immune responses in the brain, particularly its role in the regulation of clearance of pathological forms of Aβ and tau, may provide novel therapeutic opportunities for AD.

Different strategies have been used to prevent the pathogenic effects caused by an imbalance in copper homeostasis, including administration of metal chelators that redistribute brain metal pools and reverse Aβ plaque aggregation [121–126]. Alternatively, reestablishing the proper intracellular bioavailable copper reduces secreted Aβ levels via a mechanism that is dependent on the activation of phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) and c-Jun N-terminal kinase [127]. Likewise, it has recently been shown that increased intracellular copper inhibits Aβ production by directly targeting the subunits PSEN and nicastrin in the γ-secretase complex [128]. Increasing intracellular copper bioavailability can also restore cognitive function by inhibiting the accumulation of neurotoxic Aβ and phosphorylated tau [129]. Furthermore, there is evidence of the immunomodulatory potential of systemic copper bis(thiosemicarbazones), which are stable, lipophilic neutral Cu^{2+} complexes that are capable of crossing cell membranes and the blood–brain barrier. This compound can inhibit microglial and astrocytic activation, and reducing the acute cerebrovascular inflammation caused by bacterial lipopolysaccharide [130]. Based on the evidence above, it would be expected that increasing copper levels in the body would restore its homeostasis in the brain. Unfortunately, systemic administration of copper promotes detrimental effects in AD by reducing Aβ clearance. For instance, trace levels of copper in drinking water have been associated with higher Aβ levels in the brain of distinct animal models [131,132], a process that seems to be related to the dysfunction of LRP-1-mediated Aβ clearance through the vasculature [133]. In addition to its effect on Aβ, chronic systemic copper exposure exacerbates tau pathology, promotes cognitive impairment and dysregulates the tau-related kinase CDK5 and the synaptic-related proteins complexin-1 and complexin-2, in a mouse model of AD [134,135]. Taken altogether, these studies indicate that systemic copper promotes AD and therefore controlled copper diets should be considered. Despite the challenges, mitigating dysregulation in copper homeostasis in the brain clearly has great benefits and should be further explored as a therapeutic strategy for AD.

Zinc (Zn)

The brain contains the highest zinc concentrations of any organ in the body. Seventy percent of proteins present in the brain contain zinc as a structural or catalytic component, contributing to the efficient performance of over 2000 transcription factors and more than 300 enzymes [136]. The transport of zinc into the brain parenchyma occurs via the blood–brain and blood-cerebrospinal fluid barriers [137]. Its binding with L-histidine, in both plasma and the cerebrospinal

fluid, is involved in transferring zinc to target sites, regulating its uptake across the brain barrier systems [137]. Following its uptake, zinc can be transferred freely through the cerebrospinal and the brain extracellular fluid compartments [137]. Zinc homeostasis in the brain is tightly regulated, primarily via three families of proteins: the metallothioneins, which are involved in the regulation and maintenance of intracellular zinc homeostasis [138]; the zinc- and iron-like regulatory proteins, which are responsible for zinc uptake from extracellular fluids into both neurons and glia [139]; and the zinc transporters, which are associated with cellular zinc efflux [140]. Interestingly, many of these zinc regulatory proteins also regulate other metal ions. In the brain, zinc is also present in its free ionic form (Zn^{2+}) and enriched within synaptic vesicles at glutamatergic nerve terminals from where it is synaptically released during neuronal activity [141–143]. Zinc released in the synaptic cleft affects the expression and activity of *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) glutamatergic receptors, and glycine ionotropic and γ-aminobutyric acid ($GABA_A$) receptors [144]. Therefore, zinc is intimately linked to the balance of excitation and inhibition signaling in the brain and is essential for memory function and behavior [145].

Zinc homeostasis is impacted in a wide-range of neurological diseases [146,147]. Although zinc lacks redox activity, it has been demonstrated that excess zinc in the extracellular fluid promotes neurotoxicity and affects protein aggregation [148–150]. Interest in the role of zinc in AD began with the observation that it can precipitate Aβ into plaques above a concentration of 300 nM [151]. Interestingly, the extracellular concentration of zinc during synaptic transmission rises to 300 μM, and it is therefore possible that synaptic transmission contributes to Aβ deposition in the diseased brain [152–154]. Aβ itself is a metalloprotein that contains binding sites for zinc, which is enriched in plaques and in the cerebral amyloid angiopathy surrounding diseased blood vessels [155–157]. Studies using Tg2576 transgenic mice crossed with zinc transporter 3 knockout mice, which is the transporter responsible for the accumulation of Zn^{2+} in presynaptic vesicles, have reported reduced plaque load, indicating that synaptic zinc does indeed contribute to Aβ deposition [158]. Moreover, zinc has a high affinity for Aβ, and when trapped by accumulated Aβ, it inhibits APP ferroxidase activity, thereby increasing the levels of iron and ROS [43,159].

Interestingly, induced attenuation of long-term potentiation (LTP) in dentate granule cells by Aβ and zinc treatment can be rescued *in vivo* by the administration of calcium-ethylenediaminetetraacetic acid, an extracellular zinc chelator, and by cadmium, a metal that displaces zinc from Aβ binding [160]. Accordingly, the administration of zinc chelators or zinc ionophores to AD mouse models can restore the physiological metal ions trapped within extracellular Aβ aggregates, inducing biochemical and anatomical changes which lead to improved cognition [121,161,162]. Although there is compelling evidence that zinc/copper chelators reduce Aβ accumulation, it has recently been demonstrated that this strategy can result in potentially detrimental effects in the healthy brain [121–126]. Depletion of zinc levels in the brain of young mice (2.5 months old) using the zinc/copper chelator clioquinol impaired short- and long-term memory performance. Mechanistically, treatment with clioquinol reduced levels of brain-derived neurotrophic factor, synaptic plasticity-related proteins and dendritic spine density *in vivo* [163]. These changes were regionally restricted to the hippocampus, cortex and striatum, without having any effects on the cerebellum, an area devoid of pools of cheatable zinc [163,164]. These results support the notion that zinc is an important modulator of synaptic plasticity, neurotransmission, neuronal function and cognitive processes in the brain, and highlights the potential detrimental consequences of reducing the availability of zinc in the brains of healthy individuals or in the early stages of AD. Notably, some studies that raised zinc levels via supplementation showed an increase in plaque number and size in mouse models of AD [165–167]. In Tg2576 mice, the intake of zinc acetate caused a reduction of insoluble Aβ in the brain, despite the absence of any significant changes in cognition and behavior [168]. The discrepancies related to the effect of zinc intake on plaque load might be due to its diverse roles in the regulation of Aβ, as zinc has been shown to prevent the proteolytic degradation of Aβ by matrix metalloprotease 2, and to modulate the activity of the α-, γ- and β-secretases [169,170]. Contradictory results are also present when comparing post-mortem analyses of zinc levels in AD brains, as there are studies showing increased, decreased or unchanged zinc levels [94,171–175].

Zinc not only affects Aβ aggregation, but also the level of hyperphosphorylated tau and the formation of NFTs. Like the effects of zinc on Aβ, low micromolar zinc concentrations can cause the aggregation of tau [176–178]. Zinc is also able to promote tau hyperphosphorylation indirectly via the inactivation of major tau phosphatases, such as protein phosphatase 2A (PP2A) [179,180]. Importantly, zinc chelators or blockade of synaptic zinc signaling can abolish zinc-mediated tau hyperphosphorylation [181]. Accordingly, zinc supplementation in a tau mouse model intensified the cognitive deficit, in association with an increase in tau phosphorylation, and the number of NFTs in the hippocampus, and a decrease in free zinc ion levels [182]. The influence of zinc on tau pathology was further confirmed when mice with advanced pathology were treated with a copper/zinc chaperone. This caused increased PP2A activity and was sufficient to improve memory, to decrease tau pathology and to

prevent neurodegeneration [183]. This highlights the potential value of targeting zinc in pathological conditions in which tau pathology is present. However, additional investigation regarding the impact of zinc on the activity of tau-related kinases would be welcomed to further validate the protective role of this metal on tau pathology. Oxidative stress is another factor that contributes to the progression of AD, and ROS or exogenous oxidants can promote harmful zinc release from metallothioneins [184–186]. Zinc accumulation can, in turn, induce mitochondrial dysfunction and further oxidative stress, being particularly high in AD neurons expressing mutant APP, PSEN1 and tau [187,188].

In terms of immunity, zinc seems to be essential for immune cell proliferation, antioxidant response, acquired and innate responses [189,190]. Interestingly, the molecular mechanisms by which zinc improves immune function are unknown. Studies in mice have shown that dietary zinc is an important nutritional factor for a proper immune response [191,192]. Accordingly, low zinc status is associated with increased susceptibility to infection and accumulated disease progression by affecting signaling in immune cells, such as microglia [193,194]. Some of the changes that occur in the brain during aging have been ascribed to altered zinc homeostasis, as only 40% of elderly people have a sufficient zinc intake [147,195]. Impaired zinc homeostasis promotes immune dysfunction and has been associated with enhanced chronic inflammation dependent on the pathophysiological changes that occur with aging, rather than nutritional intake [196]. Thus, zinc has been suggested as a potential candidate to reverse age-associated changes leading to healthy aging through the reduction of inflammation [197]. Although there is evidence that zinc supplementation in aging improves immune function and leads to decreased mortality from infections, zinc imbalance can result not only from insufficient dietary intake, but also from the impaired activity of zinc transport proteins and zinc-dependent regulation of metabolic pathways [198]. Thus, appropriate zinc supplementation in the aging or diseased brain may help in the prevention as well as treatment of degenerative age-related disease [199,200].

The above findings, although at times inconsistent, strongly support the hypothesis that disturbed zinc homeostasis plays an important role in the pathogenesis of AD. Giving that zinc contributes to the aggregation of Aβ into plaques as well as the formation of NFTs, inflammation and oxidative stress, research has focused on the development of compounds to neutralize its toxicity in AD. Administration of a metal–protein attenuating compound that affects copper- and zinc-mediated toxic Aβ oligomerization lowered the cerebrospinal fluid levels of Aβ and improved cognition in AD patients [201–203]. Other studies in mouse models of AD have reported comparable results. Supplementation with L-carnosine, a compound with chelating properties, in 3xTg-AD mice reduced the intraneuronal accumulation of Aβ, and completely rescued the mitochondrial dysfunction [204]. Zinc supplementation in the same mouse model delayed hippocampal-dependent memory deficits and strongly reduced both Aβ and tau pathology [205]. The results of these studies highlight the integral role of zinc in the pathogenesis of AD and support the hypothesis that restoring zinc homeostasis is a potential strategy to treat AD. However, it is also important to emphasize the need for mechanistic studies demonstrating how zinc promotes its effects, particularly at cellular and molecular levels in the brain.

Manganese (Mn)

Manganese is a naturally occurring trace element that is essential for human development and brain function. Excessive manganese is neurotoxic and has been linked to developmental disorders and neurodegenerative disorders associated with basal ganglia dysfunction, such as Parkinson's disease and Huntington's disease [206–208]. Moreover, the relevance of manganese for the regulation of brain functions has been further emphasized by the discovery of loss-of-function mutations in genes related to its transport, which lead to neurotoxicity [209]. The neurotoxicity induced by manganese overexposure includes the disruption of mitochondrial function, disruption of neurotransmitter metabolism, alteration of iron homeostasis and induction of oxidative stress [210–214]. Manganese has also been linked to the regulation of brain immunity, and it can have profound effects on microglia and astrocytes, regulating the activation of proinflammatory responses which contribute to its neurotoxic effects [215–217]. The link between manganese and AD, however, is still very limited. It has been demonstrated that the concentration of manganese does not change in response to human aging and AD [218]. In the periphery, conflicting data have been presented, although a systematic review and meta-analysis has indicated that the manganese level in the serum of AD subjects is reduced compared to that in healthy controls [219]. Although manganese can bind to Aβ, it does so with a weak binding affinity in the millimolar to micromolar range, suggesting that it does not have a large effect on plaque formation [220]. However, studies in non-human primates have shown that chronic manganese exposure produces a cellular stress response that leads to neurodegenerative changes, diffused Aβ plaques in the frontal cortex and impairments in visuospatial associative learning [221,222]. Mechanistically, manganese neurotoxicity seems to be related to excessive iron accumulation via translational repression of APP ferritin [223]. Manganese has also been shown to reduce the glial glutamate transporter-1 (GLT1), which may cause sustained glutamate neurotransmission and

excitotoxicity [224]. Likewise, manganese induces activation of inflammation and dysfunction in autophagy, resulting in hippocampal-dependent impairment of learning and memory in mice [217]. In fact, recent bioinformatics analysis has shown that manganese exposure induces the differential expression of genes related to cytokine–cytokine receptor interaction, apoptosis, oxidative phosphorylation, the TLR signaling pathway and the insulin signaling pathway in neurocytes [225]. Taken together, these studies suggest that changes in manganese homeostasis might contribute to AD via changes in inflammation and oxidative stress. However, further validation is needed, particularly regarding potential disease-modifying effects on Aβ and tau.

The Non-essential Metals

Lead (Pb)

Plumbum (Pb), also known as lead, is a chemical element categorized in the carbon group and considered a heavy metal. Although lead toxicity has been known for many centuries, it was only in 1892 that it was recognized as a serious threat to health following the report that white lead paint on the porches and rails in houses in Brisbane, Australia, was the cause of severe neurological disorders in children [226]. Environmental lead absorbed into the bloodstream has a half-life of 30 days. Lead binds to circulating erythrocytes and is distributed throughout the body, eventually accumulating in bone. The half-life of bone-deposited lead can span 20–30 years. Blood lead levels tend to increase during pregnancy, menopause, lactation and aging due to an increase bone demineralization, which causes the release of stored lead [227–229]. The presence of lead in the blood interferes with many organs and functions of the body, but the CNS is by far the most vulnerable. In the brain, the effect of lead can be classified as either morphological or pharmacological. Morphological effects alter neuronal differentiation, myelination and synaptogenesis [230–232]. Pharmacologically, lead competes with biometals, particularly calcium and to a lesser extent zinc, for their binding sites, thereby disrupting the corresponding essential biometal-dependent mechanisms [233]. Due to its ability to substitute for calcium ions, lead rapidly crosses the blood–brain barrier and causes severe damage to the brain [234]. Lead also interferes with neurotransmitter release, disrupting the function of the GABAergic, dopaminergic and cholinergic systems as well as inhibiting NMDA receptors [235,236]. Furthermore, lead is involved in the inactivation of glutathione, an important antioxidant found in cells, by binding to sulfhydryl groups [237]. It is now well known that lead exposure during childhood is associated with cognitive deficits and behavioral disturbances [238,239]. It has been reported that juvenile lead exposure inhibits NMDA and AMPA receptors, impairing LTP and promoting detrimental synaptic morphological changes in hippocampal CA1 pyramidal neurons, thereby leading to a decline in learning and memory [240]. Similarly, animals exposed to lead either prenatally or postnatally develop memory impairment and cognitive decline later in life [241,242]. Recently, it has been reported that low-level gestational lead exposure results in dendritic spine alterations in the hippocampus by down-regulating neuroligin-1 protein levels, which in turn results in learning and memory impairment [243]. Given that the effects of early life exposure to lead can persist in adulthood, it is possible that this contributes to the development of AD. In fact, a longitudinal study in former organolead manufacturing workers has shown that past lead exposure is associated with a longitudinal decline in cognitive function and persistent brain lesions [244,245].

Numerous studies have reported that either developmental or acute lead exposure contributes to the hallmarks of AD, including Aβ accumulation, tau pathology and inflammation. Early lead exposure in young rats increased the expression of APP and β-secretase 1 (BACE1) which subsequently induced AD-like pathology by inducing Aβ accumulation and plaque formation in the hippocampus and cortex [246]. Another study also reported that the expressions of APP and BACE1 were increased in the aging rat brain in response to lead exposure during the fetal stage [247]. Likewise, lead exposure during infancy increased the expression of APP, BACE1, and transcription factor-specific protein 1 (Sp1) and promoted Aβ deposition in aged monkeys [248]. Synergistic exposure to lead, arsenic and cadmium further enhanced APP and BACE1 expression, followed by maximum induction of Aβ production [249]. Developmental lead exposure has also been shown to activate the sterol regulatory element binding protein 2 (SREBP2)-BACE1 pathway, disturbing cholesterol metabolism in the young brain [246]. It is known that cholesterol dyshomeostasis in the brain is closely associated with the etiology of AD and Aβ production [250]. Moreover, acute lead exposure has been shown to increase the accumulation of Aβ in the brain tissue and cerebrospinal fluid through disruption of LRP-1-mediated clearance [251]. Notably, lead exposure also results in an increased level of total and hyperphosphorylated tau. It has been demonstrated that lead exposure increases the protein levels of tau and phosphorylated tau in SH-SY5Y neuroblastoma cells [252]. Similarly, developmental exposure to lead early in life up-regulates tau protein and mRNA, increases serine/threonine phosphatase activity, and CDK5 levels, which together contribute to the formation of NFTs late in life [241,253]. It has recently been

reported that lead also activates GSK-3β- and caspase-3-mediated tauopathy [254].

Lead poisoning is also accompanied by inflammatory events that lead to neuronal death. Individuals exposed to lead present with higher serum TNF-α and granulocyte-colony stimulating factor levels than non-exposed people [255]. Administration of lead to a rat model results in chronic glial activation, together with inflammatory and neurodegenerative features [256]. Likewise, it has been demonstrated that lead exposure results in the activation of microglia and the overproduction of proinflammatory proteins such as inducible nitric oxide synthase, IL-1β and TNF-α [257]. These factors are known to contribute to the brain neurotoxicity in AD [3]. Increased microglial activation due to lead exposure is also accompanied by impaired LTP [257]. The mechanism of lead-induced microglial activation involves activation of the transcriptional factor NF-κB and upregulation of cyclooxygenase-2. Other microglial pathways associated with lead exposure include extracellular signal-regulated kinase and protein kinase B (AKT) signaling [258]. In another study, lead exposure was reported to induce abnormal microgliosis by triggering TLR4-MyD88-NF-κB signaling, which directly impacts hippocampal neurogenesis and plasticity [259]. Activation of TLR by lead results in the increased synthesis of proinflammatory cytokines, and the production of reactive nitrogen species and ROS [260]. Collectively, these data provide unambiguous evidence that lead exposure has a long-acting effect and can increase the risk of AD. Unfortunately, no treatment is effective in preventing the effects of lead poisoning and exposure should be therefore avoided.

Aluminum (Al)

Aluminum is not essential for life but is a well-established neurotoxin. Exposure to high aluminum content in drinking water causes lifelong cerebral impairments, such as loss of concentration and short-term memory deficits [261]. Mass spectrometry studies have demonstrated that aluminum crosses the blood–brain barrier and accumulates in a semi-permanent manner [262,263]. Although no biological process is dependent on aluminum, it can influence more than 200 biologically relevant reactions and cause various adverse effects on the mammalian brain. These include essential brain processes such as axonal transport, neurotransmitter synthesis, synaptic transmission, phosphorylation or dephosphorylation of proteins, protein degradation, gene expression, and inflammatory responses [264]. Aluminum exhibits one oxidation state, Al^{3+}, which has affinity for negatively charged oxygen-donor ligands. Some of the ligands that form strong bonds with aluminum are inorganic and organic phosphates, carboxylate and deprotonated hydroxyl groups, thereby making DNA, RNA and ATP perfect targets, affecting gene expression, energy metabolism and the action of several kinases and phosphatases [265–267]. Aluminum can also cause the oligomerization of proteins, inducing conformational changes that can inhibit their degradation by proteases, and thus affect their turnover. For instance, strong binding of aluminum to phosphorylated amino acids promotes the self-aggregation and accumulation of highly phosphorylated cytoskeleton proteins, such as neurofilament and microtubule-associated proteins [268]. These properties make the presence of aluminum in the brain toxic, causing the apoptotic death of neurons and glial cells. Aluminum affects LTP, the function of enzymes, including those involved in neurotransmitter synthesis [269,270]. It also affects voltage-gated calcium channels and neurotransmitter receptors, impairing synaptic transmission [271]. The presence of aluminum therefore leads to a signaling imbalance that disturbs brain function.

More strikingly, exposure to aluminum is also suspected of being linked to neurodegeneration [272]. Several studies reported a higher incidence of AD or AD mortality in areas with high levels of aluminum in the drinking water, suggesting a strong association between aluminum and AD [273–277]. This was confirmed by later studies that demonstrated the ability of aluminum to induce neurofibrillary degeneration and promote the appearance of tangle-like structures that resembled the NFTs found in the brains of AD patients [278–281]. Moreover, aluminum accumulation was described in NFT-bearing neurons of AD brains [282–284]. When the effects of oral aluminum administration were studied using a tau mouse model showing slow progressive tau accumulation, higher tau aggregation, apoptosis and neurological dysfunction were observed in animals that already had a pathological process causing tau aggregation, but not in the controls [285], thereby suggesting an exacerbating effect of aluminum on tau pathology. Aluminum achieves these effects by enhancing the activity of the tau kinases CDK5 and GSK-3β, inhibiting the dephosphorylation of tau, and enhancing its aggregation [286–290]. Interestingly, aluminum is preferentially taken up by glial cells, which induces the production of inflammatory cytokines, including IL-6 [52,291,292]. IL-6 in turn has been reported to induce phosphorylation of tau by dysregulating the CDK5/p35 cascade [293,294]. Increased glial activation and an inflammatory response have been described upon aluminum treatment in rats [295]; however, whether glial activation due to aluminum exposure plays a role in the acceleration of an early process in the formation of AD pathology needs to be studied further.

Although the effects of aluminum on AD pathology were first attributed to its interaction with tau, it was later demonstrated that it also affects Aβ by promoting its production, aggregation and by inhibiting its degradation [296–299]. Oral administration of

aluminum to AD mice induced an increase in the amount of Aβ, both in its secreted and accumulated forms, and increased deposition in plaques [300]. In addition, Aβ coupled with aluminum is more toxic than Aβ itself as it causes membrane disruption and perturbation of neural calcium homeostasis and mitochondrial respiration [301–303]. Aluminum can also influence the expression of iron-binding proteins expression with IRE/IRP sequences in their mRNA, causing an increase in iron concentration [41,304,305]. The presence of aluminum in the brain can therefore modulate the expression, distribution and accumulation of APP and induce the dysregulation of iron-modulated signaling pathways, by interacting with IRE mRNA regions [306,307]. Consequently, aluminum stimulates iron-induced membrane lipid peroxidation and causes oxidative damage [308–310]. Despite its non-redox status, several studies have suggested that aluminum has strong oxidative activity [311,312]. The interaction of aluminum with iron generates labile iron from iron-containing enzymes and proteins, thereby increasing the intracellular pool of free iron, which in turn leads to the formation of ROS [313]. Aluminum also decreases the activity of some antioxidant enzymes such as catalase, superoxide dismutase and glutathione peroxidase, thus exacerbating the neuronal damage induced by oxidative stress in neurodegenerative disease such as AD [314,315].

Aluminum has also been reported to affect neurotransmission. Due to its ability to block Aβ-mediated formation of calcium permeable ion channel, aluminum can inhibit the increase in calcium levels induced by neurotrophic factors such as brain-derived neurotrophic factor [316–318]. The level of other neurotransmitters, such as serotonin, dopamine, glutamate and aspartate, has also been reported to decrease upon aluminum exposure [319,320]. A lower availability of glutamate induced by aluminum has been attributed to the induction of glutamine synthetase and inhibition of glutaminase activity in astrocytes [292]. Moreover, it has been reported that aluminum affects the cholinergic system, which has been shown to degenerate in AD pathogenesis [321,322]. Thus, like the therapeutic approaches used to block the neurotoxic effects of other metals, aluminum chelation has been studied as a potential therapy for AD [323]. The use of deferoxamine, a chelator of aluminum and iron, as well as silicates, which couples with aluminum and reduces its toxicity, has been shown to attenuate cognitive decline in AD patients [324,325]. Despite not being preventative, aluminum chelators could potentially minimize the neurodegenerative effects of aluminum in patients with known exposure throughout their lives.

Cadmium (Cd)

Cadmium is a carcinogenic heavy metal that is present in the environment. Unlike many heavy metals, due to its water-soluble property, cadmium can be transported from soil to plants and concentrated in the food chain [326]. Although the effect of cadmium on the plant can be detrimental, some plants, such as tobacco, show cadmium tolerance [327,328]. Therefore, consumption of tobacco products or inhalation of tobacco smoke increases the risk of cadmium-related morbidities in the general population [329]. Once taken into the body, cadmium accumulates in the kidney and liver and has an extremely long half-life of 20–40 years [330–332]. Chronic cadmium exposure is associated with hypertension, kidney dysfunction, bone demineralization and neurological diseases [333–337]. Cadmium is known to cross the blood–brain barrier and eventually accumulate in the brain, leading to neurotoxicity [338]. In the brain, cadmium induces activation of various signaling pathways involved in inflammation, oxidative stress and neuronal apoptosis [337,339,340].

Recent epidemiological studies reported that blood cadmium levels were significantly associated with AD-related mortality among older adults [341,342]. In the AD brain, there is increasing evidence that cadmium is involved in the aggregation of Aβ plaques [343–345]. In an *in vivo* study, APP/PS1 mice administered cadmium in their drinking water exhibited an increase in the number and size of plaques [343]. Cadmium ions can interact with the Aβ, subsequently promoting formation of plaques [344]. Furthermore, it has been hypothesized that cadmium treatment downregulates the expression of α-secretase (ADAM10) and neutral endopeptidase, which play essential roles in reducing Aβ levels in the brain [343,346]. Interestingly, a recent study has reported that the synergistic effects of cadmium, lead and arsenic further enhance amyloidogenic processing by increasing APP, BACE1 and PSEN1 expression, suggesting an interactive effect of cadmium with other metals in AD [249]. In addition to its effects on Aβ, cadmium is also involved in the conformation and self-aggregation of tau in the AD brain [347,348]. Cadmium has been reported to bind to the third repeat (R3) of the microtubule-binding domain of tau. As a result, the R3 domain partially loses its random coil conformation and gains an α-helix structure which promotes the self-aggregation of tau. Moreover, cadmium treatment selectively blocks muscarinic M_1 receptors, which are known to regulate GSK-3β negatively and subsequently increase both total and phosphorylated tau protein [347,349,350]. These data support the notion that cadmium is one factor that could be involved in the development of AD.

With regard to immunity, human astrocytes treated with a non-toxic concentration of cadmium have been shown to release an elevated level of IL-6 and IL-8 via activation of the mitogen-activated protein kinase and NF-κB signaling pathways, possibly leading to neuroinflammation and neuronal death [351]. Notably, it has been reported that increased IL-6 and IL-8 expression are associated with AD

pathogenesis [352]. Moreover, cadmium has been shown to induce astrocyte cytotoxicity by increasing intracellular calcium ions via the mitogen-activated protein kinase and PI3K/AKT signaling pathways [353]. These data suggest that the regulation of cadmium-induced Ca^{2+} homeostasis may be a good strategy for the prevention of related diseases in the CNS. However, there is still a lack of *in vivo* studies showing the effect of cadmium on neuroinflammation in AD mouse models.

Concluding Remarks

Altogether, evidence strongly supports that disruption in the homeostasis of essential metals and the accumulation of non-essential metals disturb the cellular metabolism, antioxidant defense, and immune responses, leading to the onset and progression of AD. Not surprisingly, greater emphasis has been given to the interaction of metals and Aβ, in which it has been shown that biometals interfere with APP function and facilitate aggregation of Aβ into plaques. The relationship between biometals and tau, however, has only recently emerged, and these studies have shown that changes in the metabolism of metals are detrimental to tau function, resulting in its loss of function and aggregation; however, the mechanism of how biometals affect tau function remains elusive. Likewise, most findings regarding to the interaction between brain immunity and biometals have been limited to evidence of the overproduction of inflammatory mediators (i.e., cytokines) in response to changes in metal metabolism, with a clear cellular and molecular mechanism still to be established. Nevertheless, studies using metal chelators have shown promising disease-modifying properties *in vitro* and in AD mouse models, emphasizing the potential therapeutic value of this approach, as well as the important role of metals in AD.

In moving forward in the understanding of the complex links among biometals, AD and immunity, studies will need to provide greater mechanistic evidence at cellular and molecular levels for how essential and non-essential metals affect the brain, with respect to the chronic accumulation of Aβ, tau and immune mediators. In this context, genetic approaches, like CRISPR gene editing, targeting specific molecular components of essential metals metabolism (e.g., point mutations in binding sites, enzymes deletion) in cell culture models are likely to provide better defined data on how biometals regulate cell function and signaling, before moving to more complex *in vivo* models. At cellular level, there is great need for research on how biometals modulate the functions and interactions of microglia and astrocytes during homeostasis and disease states, particularly regarding their roles in immune surveillance and response, and synaptic pruning. Such studies will demonstrate whether the imbalance of biometals affect the capacity of glial cells to build an immune response to properly recognize and clear pathological forms of Aβ and tau. Moreover, it is also not clear whether the potential loss of function of glial cells caused by changes in the metabolism of biometals disrupts neuronal function due to inappropriate pruning of neuritic spines and/or other mechanisms, which can have an impact in the cognitive decline in AD. Finally, considering that proteins generally display binding sites to multiple metals, it is important to determine how distinct biomentals interact during physiological and pathological conditions to modulate cellular responses in the brain.

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Abbreviations used:
Aβ, β-amyloid; AD, Alzheimer's disease; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionate; APOE, apolipoprotein E; APP, amyloid precursor protein; BACE1, β-secretase 1; CD, cluster of differentiation; CDK5, cyclin-dependent kinase 5; CNS, central nervous system; DMT1, divalent metal transporter 1; GABA, gamma-aminobutyric acid; GSK-3β, glycogen synthase kinase-3β; IL, interleukin; IRE, iron-responsive elements; IRP, iron-regulatory proteins; LRP-1, lipoprotein receptor-related protein-1; LTP, long-term potentiation; mRNA, messenger RNA; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor-κB; NFTs, neurofibrillary tangles; NMDA, *N*-methyl-D-aspartate; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; PP2A, protein phosphatase 2A; PSEN1, presenilin-1; PSEN2, presenilin-2; ROS, reactive oxygen species; SREBP2, sterol regulatory element binding protein 2; TLR, toll-like receptor; TNF-α, tumor necrosis factor-α; TREM2, triggering receptor expressed on myeloid cells 2.

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