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Role of Metal Dyshomeostasis in Alzheimer Disease†

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Abstract

Despite serving a crucial purpose in neurobiological function, transition metals play a sinister part in the aging brain, where the abnormal accumulation and distribution of reactive iron, copper, and zinc elicit oxidative stress and macromolecular damage that impedes cellular function. Alzheimer disease (AD), an age-related neurodegenerative condition, presents marked accumulations of oxidative stress-induced damage, and increasing evidence points to aberrant transition metal homeostasis as a critical factor in its pathogenesis. Amyloid-β oligomerization and fibrillation, considered by many to be the precipitating factor underlying AD onset and development, is also induced by abnormal transition metal activity. We here elaborate on the roles of iron, copper, and zinc in AD and describe the therapeutic implications they present.

A Introduction

Alzheimer disease (AD) is a progressive and fatal neurodegenerative condition that affects 35 million people worldwide.[1] Though early-onset, familial AD may be attributed to mutations in several known chromosomal regions, the much more prevalent late-onset, sporadic AD is far less well characterized. Sporadic AD accounts for approximately 95% of all AD cases and results from a complex array of biomolecular cascades that aggregate to produce cognitive decline, severe memory impairment, and ultimately death.[1] These cascades initially occur within a defined region of the brain, namely the mediotemporal lobe, before spreading cortically outward to the neocortex. The peculiar consistency and predictability with which such anatomic dysfunction progress is at present a mystery. Importantly, the pathophysiological end-products of familial and sporadic AD are quite similar despite their differing causations and ages of onset (40–60 years old for the former, 65 and older for the latter).[1]

AD is pathologically characterized by widespread oxidative stress, neuroinflammation, calcium dysregulation, mitochondrial malformation and altered distribution, neurofibrillary tangle (NFT) formation, amyloid-β (Aβ) oligomerization, synaptic toxicity, and metal dyshomeostasis.[1] Despite an extensive understanding of each of these phenomena individually as they occur within the cell, an adequate explanation for their origins, interactions, and evolution as they pertain to AD is lacking. Oxidative stress undoubtedly plays a critical role, as evidence for its molecular impact exists very early in disease

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progression.[2, 3] Similarly, Aβ, perhaps the most studied facet of AD pathology, confers striking neurotoxicity to neurons and is certainly an important aspect of the disease. Notably, both phenomena (i.e., oxidative stress and Aβ accumulation) share a common instigating factor reactive transition metal aberration.

Transition metals, though crucial to many biochemical neuronal processes, are abnormally aggregated and distributed in AD.[4, 5] Imbalances in aluminum, silicon, lead, mercury, zinc, iron, and copper have been reported in AD, and the latter three are known to be elevated in AD neuropil.[6] Furthermore, in situ iron detection has revealed a marked association between redox-active iron and both NFTs and Aβ-rich senile plaques.[4] Iron, copper, and zinc are also known to accumulate in high concentrations within the core and peripheral areas of senile plaques such that tissue exposure to metal-selective chelators prevents lesion detection.[7] The extensive role of metals in AD-type neurodegeneration is quite compelling and provides a potential window for therapeutic intervention in AD.

B Metals and Oxidative Stress Production

Oxidative stress occurs when cellular antioxidant defense mechanisms become overwhelmed by reactive oxidative species (ROS) production such that macromolecular damage results. Stochastic modifications in DNA, RNA, membrane proteins, and phospholipids by free radicals impose deleterious consequences to cellular functioning and can potentially initiate cascades of molecular aberration within the cell. Notably, ROS are inevitable byproducts of oxidative phosphorylation,[8] and oxidative stress plays a large role in normal aging as well as in neurodegenerative disease.[9] AD is marked by elevations in oxidatively damaged RNA, DNA, proteins, and phospholipids,[10] and these damages temporally precede the appearance of hallmark AD pathologies, such as NFT deposition and Aβ aggregation.[3, 11]

Transition metals, such as iron and copper, can facilitate the generation of free radicals *in vivo*.[12] The Fenton reaction between reduced transition metals (typically iron (II) or copper (II)) and hydrogen peroxide is particularly harmful, as it yields the hydroxyl radical: a highly reactive oxidative species with a limited diffusion distance.[7] RNA-bound iron poses a significant threat to neuronal viability in vulnerable neurons in AD. Its oxidation via the Fenton reaction produces abnormalities in RNA, and in AD, ribosomal RNA is particularly affected, yielding a great reduction in protein synthesis.[13]

Copper exerts similar oxidative disturbances in neuronal tissue. Its interactions with the regulatory protein ceruloplasmin, which converts redox-active iron (II) to a less reactive iron (III), suggests a role in oxidative damage in AD, as copper is increased in AD brains.[13] Copper also interacts with amyloid-β protein precursor (AβPP) in an electron transfer reaction that reduces copper (II) to copper (I), enhancing the production of a hydroxyl radical intermediate.[13] Manganese, zinc, and aluminum have also been implicated in free radical generation in AD,[14] and their altered concentrations and distributions in AD brains[15] suggests their importance in disease pathogenesis.

C Metals and Aβ

Aβ peptides are the product of the constitutive proteolytic cleavage of AβPP by β- and γ-secretases and may be 38, 40, or 42 amino acids in length ($Aβ_{38}$, $Aβ_{40}$, $Aβ_{42}$, respectively). The biological functions of these cleavage products are unknown, however their deposition and aggregation in AD is extensively documented. Interestingly, AβPP has been found to contain an iron responsive element (IRE) on the 5′ untranslated region of its mRNA with sequence homology to the IRE of the iron-storage ferritin protein.[16, 17] Studies on primary neuron cultures indicate a ferroxidase activity of AβPP, noting its upregulation in response

to increased iron stores.[17] AβPP seems to facilitate iron export from cells, likely in an attempt to minimize potential ROS generation by the presence of reactive iron. AβPP has also been reported to prevent the release of iron (II) from heme,[18] thereby further reducing the toxic accumulation of redox-active iron, and exogenous iron load reportedly promotes the α-secretase cleavage of AβPP, which generates a soluble, potentially neuroprotective Aβ peptide.

Transition metal ions, however, also accelerate $A\beta_{40}$ and $A\beta_{42}$ aggregation *in vitro* and contribute to their toxicity. [19] Specifically, aluminum, iron, and zinc, but not cobalt, manganese, copper, magnesium, calcium, sodium, or potassium, elicit increased Aβ aggregation. A mildly acidic environment with increased copper (II) and zinc (II) common features of inflammation and head trauma also induce aggregation of $A\beta_{40}$.[20] As stated above, iron, copper, and zinc are associated with Aβ plaques *in vitro*, and reports on Aβ-copper binding have revealed a corresponding generation of hydrogen peroxide: a significant contributor to oxidative damage in the brain.[21] Similarly, studies have shown that the coordination of oxidized copper (Cu(II)) or iron (Fe(III)) to Aβ result in the reduction of these ions and thus their ability to engage in ROS-generating chemistry.[22] Zinc (II), along with inducing Aβ aggregation, seems to simultaneously inhibit the ferroxidase activity of AβPP mentioned above,[17] thus further contributing to aberrant iron accumulation and ROS-generation. Taken together, the role of transition metal accumulation and Aβ deposition invites scrutiny for therapeutic intervention.[23] Several agents have indeed been identified, and testing is underway.

D Therapeutic Considerations: Metal Chelation Therapy

The ubiquitous role of transition metals in AD-type neurodegeneration has received a great deal of attention in the field and has prompted the discovery of agents that prevent their toxic actions *in vivo*. Metal-chelating compounds that selectively bind to and remove, or redox-silence, transition metals are particularly attractive, and several candidates have reached clinical trials. Desferrioxamine (DFO), for instance, an FDA-approved drug for iron overload disease, has impeded the progression of AD in clinical trials, purportedly due to its chelation and clearance of iron (III) from the brain.[24] DFO also moderately binds aluminum, zinc, and copper,[25, 26] which may contribute to the AD-attenuating effects of the drug. The large molecular weight and hydrophilicity of DFO, however, impedes its ability to cross the blood-brain barrier (BBB), and thus the positive clinical results are due to long, subcutaneous administration of the compound.[26, 27] Likewise, Deferiprone, or L1, is an iron and aluminum chelator that is approved for therapeutic use in Europe, but not in the United States.[28] It has moderate chelating effects, but its small size and lipophilicity, in contrast to DFO, renders it somewhat toxic when administered orally. Specifically, the ease with which L1 penetrates the BBB enables it to quickly remove iron from intracellular pools, thereby eliminating the supply of iron needed for human ribonucleotide reductase, which is required for DNA synthesis and cell proliferation.[29] Even more, L1 and other small lipophilic metal chelators, are thought to directly penetrate the ribonucleotide reductase enzyme and physically remove the iron from within, thus directly inhibiting enzyme functioning and DNA synthesis.[30] These hindering factors have ultimately led to the development of nanaoparticle delivery systems of metal chelators that enable a safe and effective administration of chelating compounds for AD.

Nanoparticle delivery involves the binding of polymeric particles (ranging in size from 10–1000 nm) to drug compounds such that the latter may be delivered to physiological regions typically prohibitive of their entry.[24] DFO, for instance, a large, hydrophilic molecule incapable of crossing the BBB, may be bound to a nanoparticle that is able to breach the lipid barrier and may thus enter the brain regions that necessitate metal chelation.

Nanoparticle delivery offers several benefits to chelation therapy that could otherwise not be achieved: 1) the chelator needs not be lipophilic to cross the BBB and enter the brain if it is bound to a nanoparticle, thereby eliminating the use of small chelators with toxic side effects; 2) the nanoparticle system enables large, lipophobic molecules like DFO to enter the BBB without prolonged, invasive means of administration; and 3) the mobility of the nanoparticle through the BBB facilitates its removal from the brain following chelation. This latter phenomenon is crucial to the effectiveness of any chelation system, as a redox-silenced transition metal must be removed from its site of action before it becomes reactivated.[24] Interestingly, even the small, lipophilic chelators do not possess the ability to exit the BBB once they have complexed with a metal substrate due to their altered lipophilicity following transition metal binding.[24, 31]

The method of BBB penetration of nanoparticle conjugates is not fully understood. Several scenarios have been identified, all of which likely act in combination to yield the desired effect. These include: 1) increased retention of nanoparticles in blood-brain capillaries combined with absorption into capillary walls, creating a higher concentration gradient and enhancing their transport across endothelial cell layers into the brain; 2) enhanced drug permeability due to a surfactant effect; 3) tight junction opening between endothelial cells; 4) transcytosis of nanoparticle compound through the endothelial cell layer; 5) an inhibition of the efflux system; and 6) endocytosis of the nanoparticle-chelator conjugate.[32] Notably, evidence for the endocytosis of the conjugate is the most compelling. When coated with polysorbate-80, nanoparticles absorb the trafficking protein apolipoprotein E (ApoE) onto their surface in a manner that coincides with the BBB penetration of the conjugate.[33] ApoE absorption facilitates the endocytosis of low-density lipoprotein (LDL) across the BBB via LDL receptor-mediated endocytosis,[32] and thus polysorbate-80-coated nanoparticles may mimic LDL via ApoE absorption and utilize LDL receptor-mediated endocytosis to penetrate the BBB. This ApoE mimetic system may also be responsible for the ability of the nanoparticle-chelatormetal conjugate to exit the brain as needed. In any case, the nanoparticle delivery system seems to offer a safe and effective method of transition metal chelation.

In vitro studies on nanoparticle delivery of metal chelators has demonstrated an effective prevention of Aβ aggregation and toxicity.[34] Cells cultured with Aβ plus nanoparticle chelator conjugates were salvaged from Aβ-induced cell death, and cells cultured with only nanoparticle compounds did not suffer any toxic side effects. Although more research is necessary before any conclusions are made, it seems that nanoparticle delivery of metal chelators is a viable candidate for AD therapy.

Conclusions

A delicate balance of transition metal activity is necessary for prolonged neuronal functioning. As with any physical system, errors inevitably occur, and within the brain, transition metals gradually become disproportionately positioned such that impaired cellular functioning results. AD presents a strong correlation with age and is certainly the result of such aberration in metal homeostasis, at least partly. Transition metal chelation therefore provides a method of therapeutic intervention that targets early-occurring disturbances in transition metal activity. Such sequestration would ultimately help prevent the generation and accumulation of ROS that incur oxidative damage to neuronal tissue and would simultaneously prevent the aggregation and deposition of Aβ peptide. Furthermore, the nanoparticle delivery system provides a method of chelator administration that ensures an effective bioactivity with little or no adverse consequences. There is substantial need for an efficient and early preventative measure for AD in the rapidly aging population, and

targeting transition metals in the brain, particularly with nanoparticle conjugates, is an increasingly attractive means of doing so.

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