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ORIGINAL PAPER

Iron: The Redox-active Center of Oxidative Stress in Alzheimer Disease

Rudy J. Castellani · Paula I. Moreira · Gang Liu · Jon Dobson · George Perry · Mark A. Smith · Xiongwei Zhu

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Abstract Although iron is essential in maintaining the function of the central nervous system, it is a potent source of reactive oxygen species. Excessive iron accumulation occurs in many neurodegenerative diseases including Alzheimer disease (AD), Parkinson's disease, and Creutzfeldt-Jakob disease, raising the possibility that oxidative stress is intimately involved in the neurodegenerative process. AD in particular is associated with accumulation of numerous markers of oxidative stress; moreover, oxidative stress has been shown to precede hallmark neuropathological lesions early in the disease process, and such lesions, once present, further accumulate iron, among other markers of oxidative stress. In this review, we discuss the role of iron in the progression of AD.

Keywords Alzheimer disease · Chelation · Neurodegeneration · Oxidative stress · Redox active iron

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R. J. Castellani
Department of Pathology, University of Maryland, Baltimore, MD, USA

P. I. Moreira
Center for Neuroscience and Cell Biology of Coimbra, University of Coimbra, Coimbra, Portugal

G. Liu
Department of Radiology, University of Utah, Salt Lake City, UT, USA

J. Dobson
Institute of Science and Technology in Medicine, Keele University, Staffordshire, UK

G. Perry
College of Sciences, University of Texas at San Antonio, San Antonio, TX, USA

G. Perry · M. A. Smith (✉) · X. Zhu
Department of Pathology, Case Western Reserve University, 2103 Cornell Road, Cleveland, OH 44106, USA
e-mail: mark.smith@case.edu

Introduction

As the incidence of Alzheimer disease (AD) continues to grow exponentially, progress in treating this disease continues to stagnate. Indeed, the leading effective therapy available today targets cholinergic deficits, i.e., the result of the disease process rather than the cause [1]. It is therefore not surprising that therapy provides some symptomatic relief only, and fails to alter the progression of the disease or outcome. This overall paucity of treatment options has provided impetus for potential treatment based on more fundamental pathogenic concepts (e.g., amyloid cascade hypothesis). Such approaches can be considered ''lesion-centered'' as they have as their foundation a specific hallmark lesion of AD (e.g., the senile plaque). The problem with the lesion-centered approach is that the hallmark lesions of AD also occur in ''normal aging,'' and from the standpoint of the neuropathology of AD, such lesions are more likely a consequence of the disease process rather than a cause [2]. Therefore, not surprisingly, progress in AD treatment based on lesion-centered hypotheses continues in a Brownian-like motion. A fundamental reorganization of the concepts related to etiology, pathogenesis, and treatment of AD seems warranted (e.g., [3]). In this review, we discuss the role of iron in AD pathogenesis as a potential therapeutic target. The relevance of iron in AD pathogenesis is suggested by data showing that: (1)

iron is associated with oxidative stress and neurotoxicity; (2) iron accumulation and oxidative stress precede AD-associated lesions; and (3) iron is more readily treatable. We will outline the role of iron in cellular metabolism and neurodegenerative disease, and hopefully provide a stimulus to generate new ideas and new approaches for treating this devastating condition.

Iron uptake, transport, and interaction with oxidative products

Much like oxygen, iron is both an essential element for cellular metabolism, and a source of cytotoxicity when metabolism is dysfunctional. Indeed, excessive iron deposition is observed in the central nervous system (CNS) in a number of neurodegenerative diseases [4–6]. Iron uptake in the brain is tightly controlled by transferrin receptor in the endothelial cells and choroid plexus cells [7], or lactoferrin receptor on neurons [8, 9]. For the export of iron from neurons or non-neuronal cells, a brain-specific ceruloplasmin is suggested to play a role [10, 11]. The importance of ceruloplasmin in brain iron metabolism is highlighted by the extreme accumulations of iron in patients with hereditary aceruloplasminemia (R. J. Castellani, G. Perry, and M. A. Smith, unpublished observations).

The CNS uses its own transferrin whose expression is regulated by a CNS specific promoter [12, 13]. Regarding iron storage, ferritin binds and stores intracellular iron in most CNS cells, keeping it in a redox-inactive state [14]. In the pars compacta region of the substantia nigra, neuromelanin is known to play a part in iron storage [15]. To maintain iron homeostasis, iron regulatory protein-1 and -2 (IRP1 and IRP2) regulate the expression of ferritin and transferrin receptor post-transcriptionally through iron response element (IRE) [16]. Iron is involved in various cellular metabolisms, in particular, mitochondrial iron is incorporated into heme and cytochromes [17]. For the regulation of heme metabolism, heme oxygenase plays an important role in the CNS [18, 19].

During the reduction of molecular oxygen, mitochondria produce superoxide ($O_2^{\cdot-}$). Enzymatic dismutation by superoxide dismutase (SOD) in turn yields hydrogen peroxide (H_2O_2). Although $O_2^{\cdot-}$ and H_2O_2 by themselves are relatively non-toxic, H_2O_2, which is freely permeable in tissues, may lead to the production of the highly toxic hydroxyl radical ($^{\cdot}OH$) through a metal ion-catalyzed Fenton reaction. This reaction is referred to as the superoxide-driven Fenton reaction or iron-catalyzed Haber-Weiss reaction. Superoxide may also produce H_2O_2 non-enzymatically. In its normal metabolic state, superoxide favors the oxidation of Fe^{2+} to Fe^{3+}. However, if the intracellular concentration of superoxide is elevated, the reaction favors the reduction of Fe^{3+} to Fe^{2+} and elaboration of hydroxyl radicals.

In light of the high levels of oxygen consumption in the CNS, the generation of a high level of reactive oxygen species (ROS) is expected, as well as anti-oxidant defenses commensurate with the free radical production. Under normal situations, oxidative balance is maintained and free radicals are detoxified. In disease, various modifications of macromolecules such as sugars, lipids, proteins, and nucleic acids, come into play, and it is now well established that neurodegenerative diseases are associated with oxidative imbalance and its sequelae. In the case of AD, many lines of evidence now indicate that ROS induced by redox-active metals including iron play a pivotal role in pathogenesis [20–29]. In the following sections, we will discuss the suggested mechanisms of iron in the neuropathology of AD.

Iron deposition and senile plaques

Iron accumulation in AD has been shown to be particularly abundant in brain regions vulnerable to AD, including the hippocampal formation and association cerebral cortices [25]. At the microscopic level, it has been demonstrated to accumulate in senile plaques in AD [30]. Further, increases in iron accumulation and oxidative stress in AD brains are related with changes in the concentration of soluble and deposited amyloid-β protein. Experimentally, such metabolic stresses including hypoglycemia, ischemia, and traumatic brain injury all augment amyloid-β protein precursor formation and/or its mRNA [31–36]. Likewise, suppression of mitochondrial energy metabolism alters the processing of amyloid-β protein precursor to produce amyloidogenic derivatives [37, 38] such that several studies have shown that oxidative stress increases the production of amyloid-β [39–41], and that H_2O_2 affects increased intracellular [39, 42] and secreted amyloid-β in neuronal cell lines [40]. On the other hand, amyloid-β itself has been suggested to have an ability to generate ROS, driving a potential positive feedback loop whereby increased generation of ROS generates increased amyloid-β, and vice versa.

The three histidine residues of amyloid-β at position 6, 13, and 14 and one tyrosine residue at position 10, all located in the hydrophilic N-terminal part of the peptide [43, 44], behave as iron binding sites. The iron bound to these sites has been shown to generate H_2O_2 by the Fenton reaction [45–47]. Not only production of ROS but also binding of iron to these residues induces amyloid-β aggregation. Substitution of the histidine residue significantly decreases the aggregation by Fe^{3+} [44]. Whether or not the aggregation of amyloid-β and formation of senile plaques is important in neurotoxicity [23, 26, 48–50], it appears likely that extracellular iron is a major source of

free radicals in the oxidatively damaged brain and that any deleterious effects of amyloid-β are mediated by adventitiously bound iron [51]. Notably, the redox potential of iron is significantly attenuated by amyloid-β suggesting a neuroprotective chelating role for amyloid-β in disease pathogenesis [51, 52].

Besides the suggested direct involvement of iron, plaque formation also induces an activation of microglia or reactive astrocytes [53]. Activation of microglia and macrophages synthesize and secrete various cytokines such as interleukin (IL)-1, IL-6, and IL-8. Chronic production of these cytokines consequently causes activation of macrophages that produce large amounts of ROS [54]. Activated microglia also release iron from ferritin in a superoxide dependent fashion and result in lipid oxidation in vivo [55]. In fact, elevated levels of IL-1 and IL-6 in AD brain have been reported [56]. Whether such microglial activation, like amyloid-β activation [51], is mediated by iron is unclear.

Iron in neurofibrillary tangles

Neurofibrillary tangles (NFT) are another hallmark lesion of AD and, interestingly, are another site of iron accumulation. The presence of redox metals in NFT has been shown to induce oxidative stress via H_2O_2 [57]. Although NFT possibly act as a redox center, we previously demonstrated that neurons, which lack NFT also contain oxidative modifications [21], suggesting that oxidative stress precedes the formation of NFT.

Among the macromolecules modified by ROS, RNA is suggested as an early target of oxidative damage in AD brain [26]. Using 8-hydroxyguanosine (8OHG) as a marker of nucleic acid oxidation, oxidative damage can be found within the neuronal perikaryal cytoplasm. Moreover, 8OHG essentially disappears after treatment with RNase. Since 8OHG is formed by an attack of the hydroxyl radical, and cannot permeate through the plasma membrane, 8OHG must be produced within the cytoplasm in the vicinity of RNA. It is possible, therefore, that transition metals such as iron play a pivotal role in oxidation of RNA. In fact, studies show RNA oxidization is increased in AD brain [58] and subsequent protein translation is impaired [59].

Among the unanswered questions pertaining to the role of iron in neurodegenerative disease is the precise source of redox-active iron. Although mitochondria possess various iron containing functional molecules, such as heme, cytochrome, and aconitase, little 8OHG is accumulated. On the other hand in situ hybridization and ultrastructural observations reveal that mitochondrial abnormalities exist in AD brain and many abnormal mitochondria are targeted to lysosomes [60]. Since lysosomes also accumulate iron, mitochondrial turnover and lysosomal activity are a potential metabolic source of iron within damaged cells.

Iron-containing compounds related to Alzheimer disease

In spite of the importance of dysregulation of iron homeostasis in AD and other neurodegenerative diseases, relatively little is known about the resulting forms of iron, which accumulate in the brain. Recently, studies have begun to address this issue by using techniques such as synchrotron X-ray absorption spectroscopy (XAS), electron tomographic imaging, and superconducting quantum interference device (SQUID) magnetometry to characterize, locate and quantify specific iron compounds related to AD, PD, and other neurodegenerative diseases.

The development of XAS as a technique for analyzing and mapping iron and other metals related to tissue structures in avian brain tissue was first reported in 2005 [61]. Later that same year, Collingwood et al. [62, 63] demonstrated the application of this technique to AD tissue sections. This work provided the first map of iron distribution in AD tissue in which specific iron anomalies (areas of high iron concentration) were not only located but characterized with 5 μm spatial resolution. It was clear from this work that the ''normal'' biological iron oxides, such as ferrihydrite and goethite-like hemosiderin, were not the only iron compounds responsible for these anomalies. Biogenic magnetite (a ferrimagnetic iron oxide—Fe_3O_4—which contains both Fe^{2+} and Fe^{3+}) was the primary component of many of the regions of high iron concentration.

Biogenic magnetite has been reported in human brain tissue from studies dating back to 1992 and is present as an iron biomineral in many species [64–66]. However, in a recent SQUID magnetometry study, Hautot et al. [67] reported elevated levels of biogenic magnetite in female AD subjects compared to both male and female controls. The significance of these findings is that magnetite provides a potential source of ferrous iron, which is available for oxidation and participation in Fenton chemistry (the oxidation product of magnetite, maghemite—γFe_2O_3, has also been found in AD tissue) and may potentiate free radical formation in AD tissue via triplet state stabilization [68–71].

These studies are beginning to highlight the importance of understanding the specific biochemical pathways associated with neurodegenerative diseases and the resulting iron compounds, which are formed. This is particularly important for the potential development of metal chelators as therapeutic agents [72, 73] and this information may also be exploited for non-invasive early detection of MRI

based on the effects of magnetic iron compounds on proton relaxation rates as suggested several years ago [68, 74, 75].

Treatment potential

To date, treatment of AD with chelating agents such as desferroxamine and clioquinol, a Cu^{2+} chelator, has been met with limited success [76, 77]. The reasons for this may be multifactorial. First, brain penetrant chelators are essential [78]. Second, as oxidative injury begins at a relatively early stage in disease, removal of iron by chelation therapy years later may simply be a case of too little too late. Early intervention is critical since the effects of oxidative stress are both cumulative and on-going. Moreover, iron is not the only source of free radicals within the brain. Other heavy metals (e.g., Cu, Hg, and Pb), reactive nitrogen species, soluble mediators of inflammation, among other sources, may also play a role. In this respect, a multifaceted approach to treatment that targets early events, prior to the onset of neuropathology, makes more mechanistic sense. Targeting end-stage lesions likewise appears all the more naïve as understanding of AD and its relationship with the aging process continues to improve [48, 50, 79, 80].

Conclusion

There is no doubt that oxidative stress plays a pivotal role in pathophysiology of AD and in regards to ROS generation, iron would be a key molecule responsible for the formation of highly reactive hydroxyl radical. Both extracellular and intracellular events related to ROS generation have a great impact on the fate of neurons. Suggested by the successful reports of metal chelation therapy for improving neuronal function and cell viability, redox-active iron is an attractive target for treatment of neurodegenerative disease [81, 82]. Further investigation of iron will more clearly define the role of this redox-active element in the pathophysiology of AD.

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