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The relationship between iron dyshomeostasis and amyloidogenesis in Alzheimer's disease: Two sides of the same coin

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ABSTRACT

The dysregulation of iron metabolism in Alzheimer's disease is not accounted for in the current framework of the amyloid cascade hypothesis. Accumulating evidence suggests that impaired iron homeostasis is an early event in Alzheimer's disease progression. Iron dyshomeostasis leads to a loss of function in several enzymes requiring iron as a cofactor, the formation of toxic oxidative species, and the elevated production of beta-amyloid proteins. Several common genetic polymorphisms that cause increased iron levels and dyshomeostasis have been associated with Alzheimer's disease but the pathoetiology is not well understood. A full picture is necessary to explain how heterogeneous circumstances lead to iron loading and amyloid deposition. There is evidence to support a causative interplay between the concerted loss of iron homeostasis and amyloid plaque formation. We hypothesize that iron misregulation and beta-amyloid plaque pathology are synergistic in the process of neurodegeneration and ultimately cause a downward cascade of events that spiral into the manifestation of Alzheimer's disease. In this review, we amalgamate recent findings of brain iron metabolism in healthy versus Alzheimer's disease brains and consider unique mechanisms of iron transport in different brain cells as well as how disturbances in iron regulation lead to disease etiology and propagate Alzheimer's pathology.

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1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia affecting six million people in the United States and forty million people worldwide. The literature base supports that there are two distinct

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clinical manifestations of Alzheimer's disease; familial and sporadic. Both are characterized by molecular lesions attributed to the aggregation of misfolded proteins, inflammation and metabolic failure leading to neurological dysfunction. Familial Alzheimer's disease (FAD), also characterized as Early Onset Alzheimer's disease (EOAD), has been linked to genetic mutations, affects people under 60 years old, and makes up less than 5% of all Alzheimer's cases. Sporadic Alzheimer's, also referred to as Late Onset (LOAD), is the most common form affecting people over 60 and has no direct pattern of inheritance. Although AD is not a certain outcome of the aging process, age is the primary risk factor as the incidence for Late Onset AD doubles every five years after 65 (Den Dunnen et al., 2008; Hirtz et al., 2007). The prevalence of AD is expected to triple by 2050 as the average lifespan increases in the future (Hebert et al., 2003).

The recognition that iron dyshomeostasis is critical in Alzheimer's disease pathology is based on observations that patients have elevated iron levels in cortical, subcortical, and white matter areas affected by the disease (Raven et al., 2013; Connor et al., 1992a). MRI analysis reveals that increased iron levels in the hippocampus, an important structure perturbed early in Alzheimer's disease, negatively correlates with memory test performance (Ding et al., 2009). Increased iron loading in the brain is also associated with beta-amyloid (Aβ) plaque formation, where it is focally incorporated into the core and halo regions, and hyperphosphorylated tau (pTau) tangles in the brain (Meadowcroft et al., 2009; Smith et al., 1997; Connor et al., 1992b). Increasing the concentration of iron *in vitro* accelerates Aβ plaque and pTau tangle aggregation and increases their toxicity (Rottkamp et al., 2001). Iron dyshomeostasis may lead to toxic pathological features, but the same imbalance can disrupt innate biological systems that depend on iron.

Iron is one of the most abundant elements on Earth and was utilized by early organisms before our current oxygen rich atmosphere was established (Coby et al., 2011). As a transition metal, iron is uniquely involved in reductive and oxidative (redox) cycling reactions and as a cofactor in iron–sulfur clusters within numerous enzymes (Sheftel et al., 2012). The majority of the body's iron (70%) is bound to hemoglobin within red blood cells to aid in tissue oxygen transport. The balance of non-hemoglobin bound iron is found within proteins (~6%) facilitating the metabolic energy needs of the body through cellular respiration (ATP synthesis through the TCA cycle, ferredoxin, cytochromes, and aconitase) and those involved in ribosome function, DNA repair, and synthesis (Shi et al., 2012; Rovira and Carloni, 1999; Kennedy et al., 1983). The remainder is stored within globular ferritin protein complexes (~24%) for controlled iron sequestration, detoxification, and release (Ford et al., 1984). Proper iron maintenance is critical for the body and in the brain; thus, there are specialized cells, regions, and organs for storing and releasing iron.

The brain has a large amount of iron, unevenly distributed to the neurons of the basal ganglia, brain capillary endothelial cells (BCECs), and glia. The basal ganglia require iron for neurotransmitter synthesis, BCECs confer an iron shuttle between the blood and brain, and astrocytes and microglia help to distribute and sequester iron in the perenchyma (Rouault, 2013; Moos et al., 2007; Hohnholt and Dringen, 2013). The relative distribution of non-heme iron in the vertebrate body is 55% liver, 20% kidney, 15% heart, and 10% brain (Chen et al., 2013). During vertebrate brain development the brain is highly permeable to iron to facilitate neural growth and intercellular connection (Dallman, 1977). After development, the brain tightly controls circulating non-heme iron entering and exiting the brain. The brain normally acquires approximately 10% of its iron from the diet where it crosses the gut and enters the bloodstream, relatively less iron than any other organ: three-fold less than the liver (Chen et al., 2013). Thus, the brain needs more reserve non-heme iron than any other organ to carry out its function. The reason behind this is not well understood, but there are several possibilities. Firstly; the brain is one of the most metabolically active organs in the body, consuming a significant amount of the body's oxygen (Sasaki et al., 1999). This requires the brain to have an iron reserve to assure that its energy requirements are met during a potential lull in iron status. Secondly; iron influx into and efflux out of the brain is tightly controlled by the blood–brain barrier (BBB), brain–cerebrospinal fluid interface (BCSFI), and the blood–CSF barrier (BCSFB) (Moos et al., 2007; Moos and Morgan, 2000; Connor and Benkovic, 1992). This regulation resides outside the control of the brain making it difficult for the brain to finely adjust the influx and efflux of iron. Thirdly; while neuronal growth and division in the brain during adulthood is minimal, limiting the necessity for new exogenous iron to create new synaptic connections, iron rich oligodendrocytes continually require large amounts of the element (Bartzokis, 2002).

Brain iron is most prevalent in oligodendrocytes where it is required in the myelination of neuronal axons to form the white matter in the brain facilitating saltatory conduction over longer distances with increased speed (Connor and Menzies, 1996). Humans have proportionally more white to gray matter than any other animal, and we are the only species to have heterochronologic development with brain regions myelinating at different timepoints (Rakic et al., 1986; Bartzokis, 2004). This difference may help to explain our advanced cognitive processes and IQ as well as human brain atrophy later in life (Schoenemann et al., 2005; Sherwood et al., 2011). Iron deficiency during infancy causes delayed neurocognitive development, impaired learning and memory, and in some cases, psychiatric disorders; all in part due to the impairment of myelination (Radlowski and Johnson, 2013). Oligodendrocyte precursor cells (OPCs) propagate throughout life to form new oligodendrocytes to myelinate additional structures and to replenish damaged myelin during remyelination. As the brain ages, remyelination is outpaced by myelin breakdown leading to a loss of white matter volume (Bartzokis, 2004). The rate and loss of white matter due to normal aging increases free iron, which is toxic to the brain. *In vivo* magnetic resonance imaging (MRI) analysis illustrates that white matter damage precedes gray matter damage in AD compared to age-matched controls (Agosta et al., 2011). Exacerbated white matter loss late in life can contribute to increased neuronal loss associated with AD. This damage can be due to increased toxic radical production and impaired molecular systems necessary to ameliorate them.

Alterations in iron load and the proteins responsible for iron metabolism can exacerbate the excess formation and harmful effects of reactive oxygen (ROS) and nitrogen species (RNS), leading to cell death (Jomova et al., 2010). The increased expression of amyloid precursor protein (APP) at the site of axonal damage may underlie the need for amyloid proteins to repair tissue and manage cellular debris (Sherriff et al., 1994). The response of amyloid and tau to free radicals and hypoxia induced ischemia, as is witnessed in brain trauma, is hypothesized to ameliorate their effects. However, over time APP and cleaved amyloid fragments harbor ferric iron (Fe^{3+}) that cannot be stored or transported adequately (Corrigan et al., 2012; Ayton et al., 2014). Aβ bound Fe^{3+} is easily reduced to ferrous iron (Fe^{2+}), escalating the production of ROS species (Khan et al., 2006). This milieu favors the increased pathogenic production of toxic Aβ oligomers and plaques that propagate from monomeric $A\beta_{42}$ through β-secretase cleavage (Zhang et al., 2007; Cohen et al., 2013). Once formed, tau tangles and aberrant amyloid structures induce synaptic loss and apoptosis independent of ROS (Ittner et al., 2010; Lacor et al., 2004).

Dietary ingredients that chelate iron and remove oxidative species are hypothesized to reduce the onset time of Alzheimer's disease (Jiao et al., 2006; Vaquero et al., 2004; Scarmeas et al., 2006). Deferoxamine (DFO), a ferric iron chelator used to treat iron overload, has been shown to decrease tau phosphorylation, slow down amyloidogenesis, and improve behavioral impairment in an Alzheimer's mouse and rabbit models (Guo et al., 2013a,b; Prasanthi et al., 2012; Savory et al., 1998). DFO also improves behavioral performance in AD patients after a 24 month administration period (McLachlan et al., 1993). However, the longitudinal follow-up of these studies has not been adequately

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