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Iron homeostasis and toxicity in retinal degeneration

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Abstract

Iron is essential for many metabolic processes but can also cause damage. As a potent generator of hydroxyl radical, the most reactive of the free radicals, iron can cause considerable oxidative stress. Since iron is absorbed through diet but not excreted except through menstruation, total body iron levels buildup with age. Macular iron levels increase with age, in both men and women. This iron has the potential to contribute to retinal degeneration.

Here we present an overview of the evidence suggesting that iron may contribute to retinal degenerations. Intraocular iron foreign bodies cause retinal degeneration. Retinal iron buildup resulting from hereditary iron homeostasis disorders aceruloplasminemia, Friedreich's ataxia, and panthothenate kinase-associated neurodegeneration cause retinal degeneration. Mice with targeted mutation of the iron exporter ceruloplasmin have age-dependent retinal iron overload and a resulting retinal degeneration with features of age-related macular degeneration (AMD). *Post mortem* retinas from patients with AMD have more iron and the iron carrier transferrin than age-matched controls.

Over the past 10 years much has been learned about the intricate network of proteins involved in iron handling. Many of these, including transferrin, transferrin receptor, divalent metal transporter-1, ferritin, ferroportin, ceruloplasmin, hephaestin, iron-regulatory protein, and histocompatibility leukocyte antigen class I-like protein involved in iron homeostasis (HFE) have been found in the retina. Some of these proteins have been found in the cornea and lens as well. Levels of the iron carrier transferrin are high in the aqueous and vitreous humors. The functions of these proteins in other tissues, combined with studies on cultured ocular tissues, genetically engineered mice, and eye exams on patients with hereditary iron diseases provide clues regarding their ocular functions.

Iron may play a role in a broad range of ocular diseases, including glaucoma, cataract, AMD, and conditions causing intraocular hemorrhage. While iron deficiency must be prevented, the therapeutic potential of limiting iron-induced ocular oxidative damage is high. Systemic, local, or topical iron chelation with an expanding repertoire of drugs has clinical potential.

Keywords: Iron; Retina; Age-related macular degeneration; Oxidative stress; Ferritin; Ferroportin; Chelator; Ceruloplasmin; Hephaestin.

Contents

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1. Introduction

Iron is essential for life, but can produce toxic reactive oxygen species. Enzymes from the citric acid cycle, succinate dehydrogenase and aconitase, are iron-dependent. Iron is also a critical component of cytochromes *a*, *b*, and *c*, cytochrome oxidase, and the iron–sulfur complexes of the electron transport chain, making iron essential for the production of adenosine triphosphate (ATP) (Wigglesworth and Baum, 1988; Poss and Tonegawa, 1997). Iron is also required for activity of ribonucleoside reductase, the rate-limiting enzyme of the first metabolic reaction committed to DNA synthesis (Wigglesworth and Baum, 1988). In the CNS, additional demands on iron arise from myelogenesis and myelin maintenance by oligodendrocytes, which have higher iron relative to other CNS cells (LeVine and Macklin, 1990; Morris et al., 1992). Iron deficiency in children results in auditory defects from disruption of myelin (Roncagliolo et al., 1998), and demylinating diseases such as multiple sclerosis are associated with defects in cellular iron homeostasis (Drayer et al., 1987). Iron is also a necessary cofactor for the synthesis of neurotransmitters, dopamine, norepinephrine, and serotonin, and disruption of iron homeostasis may be involved in Parkinson's disease and/or mood disorders (Youdim, 1990).

In the retina, iron is particularly important for the visual phototransduction cascade. Photoreceptor cells are constantly shedding and synthesizing their outer segments containing disc membranes. Photoreceptors thus depend highly on iron-containing enzymes including fatty acid desaturase for synthesis of lipids used in generating new disc membranes (Schichi, 1969). Additionally, iron is an essential cofactor for the enzyme guanylate cyclase, which synthesizes cGMP, the second messenger in the phototransduction cascade (Yau and Baylor, 1989). RPE65 (RPE—retinal pigment epithelium), the isomerohydrolase found in the microsomal membrane of the RPE responsible for catalyzing the conversion of all-*trans*-retinyl ester to 11-*cis*-retinol in the visual cycle, is an iron-containing protein that is also dependent on iron for its isomerohydrolase activity (Moiseyev et al., 2005).

While iron is necessary for retinal function, excess iron can be harmful. Free Fe^{2+} participates in the Fenton reaction by catalyzing the conversion of hydrogen peroxide to the hydroxyl radical, the most reactive of reactive oxygen species. Hydroxyl radicals can cause lipid peroxiation, DNA strand breaks, and degradation of biomolecules (Halliwell and Gutteridge, 1984), and have been implicated in the pathogenesis of Alzheimer's and other CNS diseases (Smith et al., 1997). Particularly in the photoreceptors, where there is a high oxygen tension and high concentration of easily oxidized polyunsaturated fatty acids, iron must be carefully regulated to provide necessary iron levels without causing oxidative damage.

1.1. General iron homeostasis

In general, iron is taken up by most tissues through transferrin-mediated uptake following binding to the transferrin receptor. Most non-heme iron in the circulation is bound to transferrin, an 80 kDa protein capable of binding two molecules of ferric (3+) iron with high affinity (Baker and Morgan, 1994). Adults normally have approximately 3 mg of circulating non-heme iron, with transferrin binding sites only approximately 30% saturated. As transferrin cannot diffuse across the blood–brain barrier (BBB), cells that comprise this barrier must import the iron and transfer it to neural tissue. At a cell surface, iron-laden transferrin binds to transferrin receptor, and this complex