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Potential of Application of Iron Chelating Agents in Ophthalmic Diseases

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Abstract

The investigations discussed in this review indicate that iron may exacerbate different eye diseases. Therefore, it is plausible that reducing cellular or body iron stores could influence disease pathogenesis, so it is logical to consider the iron chelators' potential protective role in the various ophthalmic diseases in the form of topical eye drops or slow releasing injectable compounds as an adjuvant treatment.

Keywords

Iron chelating agents; ocular infection; lens damage; age-related macular degeneration (AMD); nitrogen mustard gas eye injury

INTRODUCTION

Iron is a critical element in the basic biochemical cycles in human physiology. Numerous proteins that have important parts in cell physiology need iron to work. A significant number of these proteins are profoundly rationed across prokaryotes and eukaryotes, and the unique situation of iron in cell digestion is kept up in practically all types of life. It is also necessary for fundamental metabolic processes, including DNA synthesis and repair, transcription, and energy production in the mitochondria.¹ Insufficient intracellular iron levels impair the activity of iron-containing proteins, ultimately compromising cell function and viability. Iron's basic role is its capability to change between oxidation states, principally between divalent ferrous (Fe²⁺) and trivalent ferric (Fe³⁺) iron.² Iron catalyzes the production of reactive oxygen species (ROS).³ Exposure to these highly reactive radicals damages lipids, nucleic acids, and proteins, causing cell and thus tissue damage. Although iron metabolism is subject to relatively rigid physiological control, many disorders have recently been related to deregulated iron homeostasis. Because of its involvement in these diseases' pathogenesis, iron metabolism constitutes a promising and mostly unexploited therapeutic target for developing new pharmacological treatments.

IRON AND OCULAR INFECTIONS

Understanding how iron metabolism and infectious agents interact might suggest new methods to control the disease. Investigations indicate that iron loading can exacerbate viral disease. Therefore, it is plausible that reducing cellular or body iron stores could influence disease pathogenesis, as seems to be the case for viral infection.⁴ Iron withdrawal is part of the natural innate immune response in infection. During inflammation and infection, a “hypoferremic response” is observed (anemia of inflammation).⁵ Replication of HIV-1, Herpes simplex, CMV, HBV, HCV, Epstein-Barr virus, Parvovirus B-19, Coxsackie-B, and Herpes Zoster can be influenced by iron.^{6,7} Hence, decreasing the availability of iron may inhibit viral replication. Almost a third of all viral proteins are metalloproteins, with some responsible for a wide variety of essential viral functions.^{4,8}

The chelating agents may have an effect against virus-associated RNA polymerase, which would be an effective chemoprophylactic agent against RNA viruses, or had a wider range of inhibitory activity for cellular RNA or DNA polymerase enzymes.⁵ Further, there are reports on the use of isatin 3-thiosemicarbazone and its derivatives as antiviral agents,⁶ and these compounds act as chelators of metal ions, particularly zinc and copper.⁷

In spite of the fact that viruses do not need to iron themselves, infected cells need iron for replication and viral particles assembling. Previous studies have indicated a decrease in intracellular iron load affecting Human Immunodeficiency Virus⁸ and Hepatitis C Virus replication.⁹ In vitro studies have shown that iron reduces HCV replication through its effect on several host genes, like eukaryotic translation initiation factor 3, which is involved in translation.¹⁰

The unavailability of iron limits microbial growth and impairs host resistance,¹¹ including impaired lymphocyte mitogenic response¹² and abnormalities in granulocyte function such as impaired phagocytosis, abnormal bactericidal activity, respiratory burst, and myeloperoxidase activity.¹³⁻¹⁵ The antibacterial effect of cytokines is mediated by intracellular iron depletion. In response to several cytokines such as interferon (INF)- γ , IL-1, and tumor necrosis factor (TNF), the cell depletes its intracellular metabolically active iron pool by enhancing ferritin synthesis. This may result in a shift of cellular iron into the relatively inert ferritin storage compartment.^{16,17} It causes down-regulation of transferrin receptor production, decreasing cellular iron uptake and limiting iron availability for intracellular pathogens.^{18,19} Activation of nitric oxide synthesis and formation of iron-sulfur-nitric oxide complexes inactivates iron-sulfur centers of vital cellular enzymes.²⁰ It has been demonstrated that the antibacterial effect of cytokines may be reversed by iron therapy and potentiated by deferoxamine treatment.²⁰

Iron overload is known to exacerbate many infectious diseases.²¹ Infectious complications are considered the second leading cause of morbidity and mortality in iron-loaded patients, such as hereditary hemochromatosis, causing a higher susceptibility to various infectious diseases.²¹ Iron withholding or removal is an important defense strategy for mammalian hosts, primarily accomplished by the iron chelating proteins transferrin and lactoferrin. Chelating agents could inhibit microbial growth and assume a fundamental role in the

antimicrobial therapeutic effect. Specific mechanisms and interactions apply in the exchange or retaining of iron between the chelating drugs with microbial microorganisms such as bacteria, fungi, and protozoa.²² One major host defense strategy is to limit iron availability for pathogens via intracellular sequestration.²³ Inflammatory cytokines (e.g., IL6) induce the expression of the iron-regulated hormone hepcidin that degrades the iron exporter located in macrophages and duodenal enterocytes, thereby reducing iron export to the circulation.²⁴

During bacterial infection, induced hypoferremia may limit the growth of extracellular bacteria. However, cellular iron sequestration increases intracellular bacteria growth, such as *Chlamydia psittaci*, *C. trachomatis*, and *Legionella pneumophila*.²⁵ Iron also serves as a co-factor for several genes essential for replication. Iron may be functioning to accelerate mycobacterial growth either as a necessary nutrient for the bacteria or by inducing serum lipids' oxidation.^{26,27} Iron chelators could enhance or decrease the uptake of iron by cells, and their ability to catalyze the oxidation of lipids and other biomolecules.^{28,29}

Siderophores are essential biomolecules for the growth and proliferation of both pathogenic and non-pathogenic microbes, and their synthesis is a target for the production of new antimicrobial pharmaceuticals. The major classes of siderophores are the hydroxamate siderophores (e.g. Desferrioxamine), which are found in fungi, and the catechol siderophores (e.g. enterobactin), which are found in bacteria.³⁰ The iron chelating proteins transferrin and lactoferrin have been involved in the uptake and transfer of iron in mammalian cells via specific pathways, preventing microbial pathogens from accessing iron. As a result, they prevent or inhibit the growth and proliferation of pathogenic organisms in mammals.³¹ Many chelators, especially chelating drugs, were designed based on siderophore prototypes. All the iron chelating drugs, dietary molecules and other drugs with chelating properties, such as the tetracyclines, anthracyclines, salicylates, hydroxyurea, etc., can affect iron uptake by microbial pathogens and can accordingly inhibit or promote microbial growth and proliferation.^{32,33} This interaction is particularly important for iron-loaded patients who are using chelating medicines and other similar drugs almost daily for their entire lives.²²

Iron withholding using chelating drugs could also be an important defense strategy for mammalian hosts in many non-iron loaded conditions, especially in situations with failed antimicrobial therapies.³³ These include patients not responding to established antimicrobial treatments, immunocompromised patients, and patients who have developed resistance to existing antimicrobial drugs.²² The study revealed the desferrioxamine-gallium ability to kill *P. aeruginosa* under conditions where this bacterium can tolerate high antibiotic levels. In an experimental rabbit model for *P. aeruginosa* corneal ulcer, topical application of desferrioxamine-gallium with gentamicin diminished both infiltration and final scar size by about half, contrasted with the use of gentamicin alone.^{34,35}

Antifungal effects of iron chelators were tested alone or in combination with antifungal drugs against *Aspergillus fumigatus* conidia. Antifungal synergy against conidia was observed for combinations of ketoconazole with ciclopirox or deferiprone, lactoferrin with amphotericin B, and fluconazole with deferiprone. Iron chelation alone or combined with antifungal drugs may be useful for the prevention and treatment of mycosis.³⁴

IRON CHELATION AND CHEMICAL EYE INJURY

It was demonstrated that topical application of low concentrations of desferrioxamine-zinc or desferrioxamine-gallium after corneal exposure to nitrogen mustard markedly reduced conjunctival, corneal, iris, and anterior chamber injury. In the cornea, faster healing of epithelial erosions, reduced long-term opacification, and lower levels of neovascularization were observed. In the anterior chamber, decreased inflammation and better maintenance of IOP was achieved. Iris pigmentation and atrophy were not as severe, with less posterior adhesion of the iris to the lens. Cataractous changes were also notably milder.³⁵ It is assumed that nitrogen mustard gas injury, at least in part, is mediated by the formation of reactive oxygen species (ROS), in addition to its action as an alkylating agent. After ocular exposure to mustard, oxidative stress has also been observed in other clinical studies and animal models.³⁶ It has been demonstrated that topical application of zinc desferrioxamine may be an adjunctive treatment in protecting the cornea against induced alkali injury.³⁷

IRON CHELATION AND LENS DAMAGE

Oxygen may play a key role in senile cataract formation. This view is supported by observations demonstrating the rapid development of cataract under conditions of high oxygen load in humans treated by hyperbaric oxygen.³⁸ Oxygen is also believed to be one of the potential causative agents for developing nuclear cataract following vitrectomy.³⁹ Under normal clinical circumstances, the effects of oxygen load accumulate over many years of exposure to relatively low oxygen loads. The observations regarding the acute changes in the lens under this high load exposure may have clinical implications regarding changes taking place under chronic low load exposure during many years of human life.⁴⁰ The addition of desferrioxamine-zinc resulted in the prevention of irreversible optical damage to the lens, probably through enhancement of lens inherent defense mechanisms as evident by the better function of lens catalase and Na, K-ATPase in the oxidative environment.⁴¹ The observed antioxidant protective effects of desferrioxamine-zinc can result from intra-lenticular action, extra-lenticular action, or both. More studies are needed to determine clinical applications for the possible use of desferrioxamine-zinc for cataract prevention or reversal of cataract.⁴¹

IRON AND AGE-RELATED MACULAR DEGENERATION (AMD)

Age-related macular degeneration is a common cause of irreversible vision loss worldwide.⁴² The Age-Related Eye Disease Study (AREDS) reported in 2001 that antioxidant vitamins plus zinc were effective in reducing the risk of AMD progression.⁴³ Iron is likely to be an important cause of oxidative stress in AMD.⁴⁴ Elevated iron levels have also been found in the photoreceptor layer of the postmortem macula of a patient with GA.⁴⁴ When iron levels in aqueous humor were measured in patients with cataract surgery, they were increased by more than two-fold in patients with nonexudative AMD.⁴⁵ Although iron accumulation was discovered in AMD retinas, its role in the pathogenesis remains unproven, but some evidence suggests a causal link. Retinal iron levels increase with age.⁴⁶ Aceruloplasminemia had drusen-like deposits in the retina at an uncharacteristically young age.⁴⁷ Double knockout mice with iron accumulation in the neural retina and RPE

have retinal degeneration sharing features of AMD.⁴⁸ The extracellular iron-binding protein transferrin is up regulated in AMD retinas.⁴⁹

The mechanisms of iron accumulation in AMD retinas are an area of active investigation. Intravenous iron not only elevated mouse serum and RPE iron levels, but also led to AMD-like histological lesions, including Bruch's membrane thickening showing complement C3 deposition, as well as hypertrophy and vacuolization of the RPE.⁵⁰ A 43-year-old patient with iron deficiency anemia (IDA) who received intravenous iron therapy developed numerous retinal drusen within 11 months of receiving the iron, suggesting that intravenous iron therapy may have caused retinal iron accumulation that promoted early AMD.⁵⁰

SIDEROSIS

Following a metallic foreign body ocular penetration, ocular siderosis results from intraocular iron deposition. In this condition, ferrous iron makes radicals and causes oxidative stress.⁵¹ The clinical features include corneal iron deposition, iris heterochromia, pupillary mydriasis, accommodation failure, anterior subcapsular cataract, lens discoloration, retinal arteriolar narrowing, retinal detachment, retinal pigment epithelium clumping, and RPE atrophy.^{51,52} Glaucoma may occur if the trabecular meshwork and Schlemm's canal are involved.⁵¹⁻⁵³ Electroretinography (ERG) results vary in different stages of the disease.⁵⁴ ERG a- and b-wave amplitudes may increase initially, and gradually decrease as the siderosis progresses and photoreceptors degenerate.⁵⁵ Since iron overload-induced oxidative damage may be involved in AMD's pathogenesis and other retinal diseases, iron chelators may help reduce the occurrence and progression of AMD.⁵⁵ Several reports suggested that iron chelators could help treat neurological diseases, such as Alzheimer's, Parkinson's, and Huntington's diseases.^{56,57} Iron chelators may also be beneficial in treating retinal diseases associated with iron overload. The iron chelators that have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with systemic iron overload include deferoxamine, deferasirox, and deferiprone. Another iron chelator, salicylaldehyde isonicotinoyl hydrazine, is effective in cell culture but has not yet been tested extensively in vivo.⁵⁵

THERAPEUTICS TARGETING IRON AVAILABILITY

The use of iron chelating agents is a straightforward approach for limiting and redistributing iron availability. Therefore, it is frequently used in the clinical management of primary or secondary iron overload. The currently available chelators are deferoxamine, deferiprone, and deferasirox. More than 50 years ago, deferoxamine was the first chelator that showed clinical promise.⁵⁸ Iron chelation therapy was then rapidly demonstrated to be an effective strategy for mobilizing and removing iron via fecal and urinary excretion, illustrated by a marked decrease in mortality and iron-related complications in patients with thalassemia major.⁵⁹ Despite its success, deferoxamine has poor bioavailability and requires parenteral administration that is often painful. It should be executed slowly (up to 10 h infusion) and regularly (5–7 times a week), making patient compliance a significant limitation. In the following decades, the oral iron chelators deferiprone⁶⁰ and deferasirox⁶¹ were developed and approved to treat iron overload, improving iron chelation therapy patient satisfaction

as compared to treatment with deferoxamine.⁶² Both deferoxamine and deferasirox are currently recommended as first-line chelation therapy in iron overload, but the toxicity profile of these compounds includes hypersensitivity reactions, liver dysfunction, renal dysfunction, and neuronal hearing loss,⁶³ warranting further developments in iron chelation therapies.⁶⁴

The investigations discussed in this review indicate that iron may exacerbate different eye diseases. Therefore, it is plausible that reducing cellular or body iron stores could influence disease pathogenesis, so it is logical to consider the iron chelators' potential protective role in the various ophthalmic diseases in the form of topical eye drops or slow releasing injectable compounds as an adjuvant treatment.

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