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THERAPEUTIC APPLICATIONS OF CHELATING DRUGS IN IRON METABOLIC DISORDERS OF THE BRAIN AND RETINA

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Abstract

Iron is essential for normal cellular function, however excessive accumulation of iron in neural tissue has been implicated in both cortical and retinal diseases. The exact role of iron in the pathogenesis of neurodegenerative disorders remains incompletely understood, however, iron-induced damage to the brain and retina is often attributed to the redox ability of iron to generate dangerous free radicals, which exacerbates local oxidative stress and neuronal damage.

Iron chelators are compounds designed to scavenge labile iron, aiding to regulate iron bioavailability. Recently there has been growing interest in the application of chelating agents for treatment of diseases including neurodegenerative conditions, characterised by increased oxidative stress.

This article reviews both clinical and preclinical evidence relating to the effectiveness of iron-chelation therapy in conditions of iron dyshomeostasis linked to neurodegeneration in

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the brain and retina. The limitations as well as future opportunities iron chelation therapy are discussed.

Significance Statement

Neurodegenerative diseases are illnesses associated with the progressive deterioration of brain and/or retinal areas. While there is no available treatment, the incidence of these diseases has increased over the years due to increasing life expectancy. A common characteristic of many neurodegenerative diseases is progressive accumulation of iron. Iron is an essential metal for the body however excessive levels of iron are toxic. In this review we discuss the effectiveness of repurposing iron-removal medications, which are traditionally used for patients who require chronic blood transfusions, to neurodegenerative diseases.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Author Contributions

All authors take responsibility for the integrity and the accuracy of this manuscript. Conceptualization and Writing, AS; Original Draft, AS; Writing, Review & Editing, CTON, BVB, DIF; Supervision, CTON.

1. Introduction

Iron (Fe from Latin: *ferrum*) is an important micronutrient found in all living organisms; from single-celled micro-organisms (e.g. Archaea) to complex multicellular organisms (e.g. eukaryote). Iron has the significant capacity to serve as either electron donor or acceptor, which makes it an essential element involved in a vast range of metabolic pathways such as cellular energy production, proliferation and differentiation, and as an important cofactor for many enzymes (Aisen et al., 2001; Andrews, 1999; Boldt, 1999; Hentze et al., 2010; Levenson and Tassabehji, 2004). The brain and retina are two of the most highly energetically demanding tissues in the body (Country, 2017; Hare et al., 2015; Wong-Riley, 2010). Iron is important for neuronal metabolism, as it plays key roles in oxygen transport, oxidative phosphorylation, myelin production, and the synthesis and metabolism of neurotransmitters (Crichton et al., 2011; Ward et al., 2014). However, excessively high levels of iron promote the formation of reactive oxygen species (ROS), a natural by-product of Fenton and Haber-Weiss reactions, which can damage macromolecular components of cells

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(Aisen et al., 2001; Lloyd et al., 1997). This process has been illustrated in multiple neurodegenerative diseases (Rosas et al., 2012; Ward et al., 2014; You et al., 2018; Zucca et al., 2017).

It is noteworthy that under normal physiological conditions both substrates of the Fenton's reaction are normally present in cells and participate in numerous important physiological processes (Halliwell, 2012). For example, the concentration of hydrogen peroxide (H_2O_2) is between 1 to 10 nM, however at excessively higher concentrations (>100 nM) can cause oxidative stress resulting in cellular damage (Sies, 2017). This shift in the redox balance is particularly important in neurons due to their high oxygen consumption, high polyunsaturated fatty acid content and weak antioxidant defence (Rego and Oliveira, 2003).

Iron-induced damage is not limited to the products of Fenton's reaction, and there are other pathways through which errors in iron metabolism can be toxic and cause damage. Iron is involved in ferroptosis, a recently defined form of cell death which involves iron mediated lipid peroxidation pathways. Indeed, ferroptosis has been implicated in various central nervous system diseases (Dixon et al., 2012; Guiney et al., 2017; Lane et al., 2018; Masaldan et al., 2019; Moreau et al., 2018).

High levels of iron are also able to damage the tissue by affecting the expression of several classes of genes including iron-dependent oxidative metabolism and the attendant oxidative stress genes (Ingrassia et al., 2019). High intracellular iron levels regulate a number of post-transcriptional regulatory pathways, the most of which is the iron regulatory proteins (IRP)/iron-responsive element (IRE) system. This pathway allows for cellular regulation of iron uptake, sequestration, and export based on cellular iron status and involves the binding of IRPs to specific mRNA motifs known as IREs resulting in inhibition of the translation process or transcript stabilisation of the particular gene (Casey et al., 1988).

Developmentally, in the early stages when mammals consume milk from their mothers the blood brain barrier is open to the accumulation of iron (Billings et al., 2016; Dwork, 1995; Hare et al., 2015; Kaur et al., 2007). After the blood brain barrier is closed in early life, iron is then acquired into the body through the diet and absorbed by cells lining the intestine. These enterocytes located in the upper part of the intestine contain the divalent metal transporter 1 protein, which mediates iron transport (Andrews and Schmidt, 2007; Lambe et

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al., 2009; McKie et al., 2001). In the blood, iron forms a complex with other substances, notably the iron carrier protein transferrin which chaperones iron to different tissues where it is utilized for numerous iron-dependent functions (Andrews and Schmidt, 2007; Geissler and Singh, 2011).

In the human body neither the intestine nor the kidneys can actively excrete iron. The only physiologic mechanism to discard excess iron is through processes such as sloughing of mucosal cells and desquamation, menstruation and other blood loss (Andrews, 1999; Kohgo et al., 2008). Iron metabolism therefore has been referred to as a semi-closed system due to the small levels of iron excretion (Kohgo et al., 2008), and considering iron is a stable and non-biodegradable element, tissue iron accumulation occurs as humans age (Asano, 2012; Hare et al., 2017; Shu and Dunaief, 2018).

It is possible that the increased susceptibility of neural tissue to age-related degeneration maybe to do with failure of the ferroportin iron export system but requires further investigation (Ayton et al., 2013; Finkelstein et al., 2017; Lei et al., 2017; Rodrigue et al., 2011; Zecca et al., 2004). Given increasing levels of iron in the brain (Aoki et al., 1989; Bartzokis et al., 1997) with advancing age this would increase the risk of iron-induced damage and subsequent neurodegeneration.

As well as aging, disease and injury (Fleming and Ponka, 2012; Raz et al., 2011), iron dyshomeostasis conditions involving accumulation of high levels of iron (i.e. “iron loading”) although rare can occur as a result of environmental factors (e.g. high iron ingestion or blood transfusion) which is known as ‘secondary iron loading’ (Cunningham et al., 2004; Gordeuk et al., 1986), or arise due to inherited anomalies (e.g. heredity hemochromatosis) also known as ‘primary iron loading’ (Feder et al., 1996; Pietrangelo, 2003). In both primary and secondary iron loading high concentrations of circulation iron gains access to cells via nonselective pathways resulting in intracellular iron accumulation especially in the liver, heart, and endocrine glands (Adams et al., 1997; Kew and Asare, 2007).

In addition to excessive systemic iron-loading, conditions associated with abnormal iron utilization in cell can lead to aberrant iron distribution within tissues. This mechanism of iron accumulation has been postulated to occur in a number of neurodegenerative disorders such as Parkinson’s disease and Alzheimer’s disease (Ayton et al., 2013; Lei et al., 2012). While an association between iron and neurodegenerative disorders has been long established

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(Dexter et al., 1989; Lhermitte et al., 1924), it is not clear whether iron triggers the neurodegenerative process or whether iron accumulation is secondary to the neuronal damage. In either case, the complex energy demanding neural network in the brain and retina are at risk of exposure to iron-related cellular pathology.

2. Iron-chelation therapy

Iron-chelation therapy is a well-established approach for treatment of iron loading in patients with thalassaemia, sickle cell disease and myelodysplasia who require chronic blood transfusions (Brittenham, 2011; Killick, 2017). Given an increased understanding of iron accumulation and ferroptosis in neurodegenerative disease, iron chelators may have therapeutic potential beyond their current application in those requiring chronic blood transfusions.

Application of iron-chelation therapy for the treatment of CNS diseases characterised by iron-induced damage has a number of general and specific challenges. Ideally the chelator of choice should have sufficient absorbance through the digestive system and exclusively bind iron and no other biologically important divalent metals such as zinc (Zn^{2+}). Iron-chelators must also have the ability to cross efficiently through the blood-neural-barriers (i.e. blood-brain and blood-retinal barriers) (Kim et al., 2006) to provide any potential therapeutic effect in these target organs.

Currently there are three FDA-approved iron chelators; deferoxamine, deferiprone, and deferasirox (see Table 1). Among these deferiprone, a lipid-soluble iron chelator, is able to cross the blood-neural barrier (Arthur et al., 1997; Fredenburg et al., 1996) and potentially chelates mis-compartmentalised iron within the CNS. Multiple new iron chelating agents are also in the pipeline undergoing preclinical and clinical trials (Adlard et al., 2014; Crouch et al., 2011; Finkelstein et al., 2017; Lannfelt et al., 2008; Singh et al., 2019). This further highlights the importance of better understanding the role of iron in neural tissue for its application to cortical and retina neurodegeneration.

Iron removal therapy has been applied in a number of neurological disorders. The following describes the clinical evidence of the potential usefulness of iron chelation therapy in the

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CNS for rare genetic neurodegenerative syndromes as well as common sporadic disorders such as Parkinson's and Alzheimer's disease.

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Table 1. Properties of iron-chelators in clinical use

Generic name	***Deferoxamine***	***Deferasirox***		***Deferiprone***
Brand's name[1]	DESFERAL®	EXJADE®	JADENU®	FERRIPROX®
Standard dose[1]	20-60 mg/kg/day	10-40 mg/kg/ day	7-28 mg/kg/day	75-99 mg/kg/day
Administration route[1]	Subcutaneous, intramuscular or intravenous	Oral		Oral
Blood-neural-barrier penetrant	No	No		Yes
Frequency	8–12 hr/day, 5–7 days/wk	Once daily		Three times daily
Current disease indications[1]	Acute iron intoxication Chronic iron overload due to blood transfusions	Chronic iron overload due to blood transfusions, Chronic iron overload in non-transfusion dependent thalassemia syndromes		Chronic iron overload due to blood transfusions

[1] Source: www.rxlist.com

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Mechanism of action[1]	Chelates iron from ferritin and hemosiderin but not readily from transferrin, it does not combine with the iron from cytochromes and haemoglobin	Chelating agent selective for Fe^{3+}. It binds iron with high affinity in a 2:1 ratio. It has a very low affinity for zinc and copper.	Chelating agent with an affinity for ferric ion. It binds with ferric ions to form neutral 3:1 deferiprone: iron complexes. It has a lower binding affinity to zinc, copper and aluminium than iron
Side effects	Local inflammatory reaction at the infusion site, visual and auditory disturbances (Chen et al., 2005), bone dysplasia (Chan et al., 2001), allergic reaction and pulmonary symptoms with high dosage, promotion of Yersinia enterocolitica infections (Abcarian and Demas, 1991).	Gastrointestinal manifestations, skins exanthem, increase creatinine levels, potentially fatal renal and hepatic impairment or failure.	Agranulocytosis (Tricta et al., 2016), arthropathy (Berkovitch et al., 1994), increase of liver transaminases levels, gastrointestinal symptoms.[2]

3. Brain and retinal diseases: role of iron

The importance of iron for normal physiology and function of neuronal tissue including the brain and retina is garnering increasing interest (Moiseyev et al., 2006; Ward et al., 2014). Iron is the most abundant transition metal in the brain and required in many fundamental biological processes within the tissue including oxygen transport, mitochondrial respiration, DNA and myelin synthesis, and neurotransmitter metabolism (Ward et al., 2014). Some studies suggest that iron preferentially localizes in selective regions of the brain (Zecca et al., 2004).

The principal sites of iron localization in retina are the choroid, retinal pigment epithelium layer and the photoreceptor layer (Song and Dunaief, 2013; Yefimova et al., 2000). In the retina iron plays an important role in phototransduction by which photon energy is converted into an electrical signal in photoreceptor cells (Moiseyev et al., 2006). Consequently, any

[2] There is a report of deferiprone-induced hepatic fibrosis in 5 of 14 thalassemia patients (Olivieri et al., 1998), however the results were not confirmed and lack of deferiprone-induced hepatic fibrosis was further confirmed by a large study on liver biopsy before and after DFP treatment in 56 thalassemia patients (Wanless et al., 2002).

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disruption in brain and retinal iron homeostasis may have significant biological and clinical consequences.

3.1 Parkinson's disease

Abnormal iron deposition in the brains of patients with Parkinson's disease (PD) was first described almost a century ago (Lhermitte et al., 1924). Since then there has been a large body of research showing a selective and significant elevation of iron within the substantia nigra of patients with PD (An et al., 2018; Ayton and Lei, 2014; Gorell et al., 1995; Olanow, 1990). Brain iron accumulation, particularly in the substantia nigra is associated with the loss of the ability to export iron from the neuron resulting in the reduction in the number of dopaminergic neurons in this area, which is the neuropathological hallmark of PD (Dexter et al., 1987; Dexter et al., 1989). The mechanism of iron induced neuronal pathology in PD has been described extensively elsewhere (Carocci et al., 2018). In brief, repartitioning iron within the substantia nigra leads to substantiation of oxidative stress, resulting in loss of activity of mitochondrial electron transport chain complex. Mitochondrial dysfunction is associated with neuronal damage and death (Carocci et al., 2018).

One suggested mechanism through which iron is involved in PD is through oxidation of dopamine and generating quinone which is a significant driver of the oxidative stress pathways leading to degeneration of dopaminergic neurons (You et al., 2018; Zucca et al., 2017). Depletion of dopaminergic neurons causes dysregulation of the motor circuits, resulting in the classic motor-afflicting symptoms of PD such as tremor, rigidity, and bradykinesia. In fact it is shown that the ratio of iron to dopamine increases the risk of neurodegeneration (Hare et al., 2014).

The intraneuronal accumulation of protein, α-synuclein is another pathological hallmark of PD, and has been reported in the brain and retina (Bodis-Wollner et al., 2014; Martinez-Navarrete et al., 2007; Shimura et al., 2001; Veys et al., 2019). There are reports that show α-synuclein aggregation affects brain and retinal iron homeostasis (Baksi and Singh, 2017; Cahill et al., 2009; Joppe et al., 2019). Additionally, it has been suggested that iron chelators can slow the aggregation of α-synuclein in the brain (Finkelstein et al., 2017; Finkelstein et al., 2016).

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There has been a growing interest in chelation-based therapy in PD patients over the last 10 years. While the number of studies is small (Devos et al., 2014; Grolez et al., 2015; Martin-Bastida et al., 2017), they have been well designed randomised double-blind, placebo-controlled and indicate some promising results with minimum side effects.

The pathophysiological role of iron in early-stage PD was assessed by a chelation strategy using deferiprone in a randomised double-blind, placebo-controlled study of 40 patients (Devos et al., 2014). Patients were randomly assigned to receive either deferiprone (30 mg/kg/day) for 12 months (early-start group, n = 19) or placebo for 6 months followed by deferiprone for the next 6 months (delayed-start group, n = 18). The early-start group showed a significant reduction in substantia nigra iron deposits compared to the delayed-start group after 6-months. Motor assessment using the gold-standard the Unified Parkinson's Disease Rating Scale showed significantly improved motor performance in the early-start group compared to the delayed-start group at both 6 and 12-month time points. There were three adverse events; two cases of neutropenia and a single case of agranulocytosis in the first months of treatment which resolved within 2 weeks of deferiprone withdrawal (Devos et al., 2014).

Another randomized placebo controlled clinical trial also examined deferiprone-treatment in PD patients (Grolez et al., 2015). Grolez et al (2015) examined 40 PD patients who were on stable dopamine regimens. They also had a 6-month delayed-start paradigm where patients were randomly assigned to receive either oral deferiprone (30 mg/kg/day) for 18 months or placebo for 6 months and then deferiprone for 12 months. Using magnetic resonance imaging (MRI) the study reports a reduction of the abnormally high levels of iron in the substantia nigra, especially in patients that started deferiprone-treatment 6 months early. Similarly, the deferiprone-treated patients displayed clinical improvements in the Unified Parkinson's Disease Rating Scale motor score. In addition, in the early-start group of PD patients clinical improvements were associated with a significantly higher serum ceruloplasmin levels after 12 months of deferiprone-treatment (Grolez et al., 2015). Ceruloplasmin is a ferroxidase enzyme that modulates cell iron efflux. Increased ceruloplasmin activity is consistent with previous reports that patients with PD have low activity in the substantia nigra and the cerebrospinal fluid. Abnormal iron efflux may contribute to pathological iron accumulation (Ayton et al., 2013; Barbariga et al., 2015)

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Finally, another randomised double-blind, placebo-controlled trial examined 22 early onset PD patients (Martin-Bastida et al., 2017). These patients were administered 20 or 30 mg/kg/day of deferiprone for 6 months and compared to a placebo group. They found deferiprone treatment resulted a reduction in iron content in the dentate and caudate nucleus, but only 3 patients exhibited a reduction in iron content in the substantia nigra compacta. The 30 mg/kg/day deferiprone treated patients showed a trend for improvement in motor symptoms using the Unified Parkinson's Disease Rating Scale and quality of life, however this did not reach significance ($p > 0.05$). It is possible that the lack of significance in this study may reflect the smaller sample size (n = 7 - 8 per group) compared to the larger studies by Grolez et al (Grolez et al., 2015) and Devos et al. (Devos et al., 2014) which has n = 18 – 20 per group. In summary, these well-controlled the studies suggest that chelation-based therapy has promise in PD, however further investigation n larger study groups are needed.

3.2. Alzheimer's disease

Changes in iron homoeostasis also occurs during other neurodegenerative disorders such as Alzheimer's disease (AD) (Smith et al., 1997; van Rooden et al., 2015). Brain iron accumulation contributes to the formation of two major histopathological features of AD including amyloid plaques which is formed by deposition of amyloid-β, and neurofibrillary tangles caused by hyperphosphorylation of tau protein (Crews and Masliah, 2010; Iqbal and Grundke-Iqbal, 2002; Leskovjan et al., 2011; Maynard et al., 2002).

While the pathophysiological mechanisms underlying the role of iron in the development of AD are yet to be fully understood, iron accumulation has been strongly linked to the pathogenesis of AD (Ayton et al., 2015; Bush, 2013; House et al., 2007). There is strong evidence that the major proteins that play a role in AD pathology are in close interaction with iron (Bush, 2013; Lane et al., 2018). For example, iron has been implicated in regulation of amyloid precursor protein (APP); a precursor molecule that when proteolyzed generates amyloid-β. Iron not only increases the translation of APP, but also promotes the amyloidogenic processing of APP, which can promote cognitive impairment (Becerril-Ortega et al., 2014; Lane et al., 2018; Rogers et al., 2002).

The presence of hyperphosphorylated tau and neurofibrillary tangles further neural damage in AD. Hyperphosphorylation of tau protein and generation of neurofibrillary tangles has been associated with abnormal iron level (Lane et al., 2018; Yamamoto et al., 2002). In addition,

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iron-induced oxidative stress has been demonstrated to initiate several apoptotic signalling pathways (Salvador et al., 2010), increasing oxidative damage to genes, and also impeded cellular repair (Hegde et al., 2010), all of which can contribute neurodegeneration.

Iron plays an important role in expression, processing and aggregation of amyloid plaques by modulating the amyloidogenic pathway (Bush, 2003; Cho et al., 2010). Interestingly, amyloid plaques have also been detected in the retinas of AD patients (Koronyo et al., 2017).

Despite studies showing the potential role of iron in AD pathogenesis only one clinical trial has evaluated the potential utility of an iron chelator in this disease. Crapper McLachlan et al, (1991) studied 48 patients with probable AD and compared the effect of 125 mg deferoxamine administered intramuscularly twice daily, 5 days per week for 24 months to oral placebo and no treatment. Their results showed that deferoxamine reduced the rate of cognitive decline in the AD patients measured by home-behavioural assessment. In contrast, the placebo and no treatment group exhibiting similar rates of decline that approximately doubled that seen in the deferoxamine group. Of interest, deferoxamine is not a blood-brain barrier penetrant compound (Liu et al., 2010; Lynch et al., 2000), however Alzheimer's diseases been shown to increase permeability of the blood-brain-barrier (Sweeney et al., 2018; Ujiie et al., 2003). Of note, this group used deferoxamine to target a hypothesised aluminium toxicity in AD patients instead of iron (Crapper McLachlan et al., 1991) although further studies did not support this (Lidsky, 2014; Makjanic et al., 1998). While aluminium and iron share relevant chemical features and deferoxamine has the capability to chelate both metals, it has higher affinity for iron compared to aluminium (Cannata et al., 1996).

There is growing interest in using chelation therapy in AD patients. One ongoing study, the 3D study (Deferiprone to Delay Dementia 2017-2021) is a randomised, placebo-controlled, multicentre study to determine whether 52 weeks of deferiprone treatment (30 mg/kg/day) to AD patients can slow cognitive decline (Adlard and Bush, 2018) (ClinicalTrials.gov Identifier: NCT03234686).

3.3. Friedreich ataxia

Excessive iron accumulation in the brain contributes to the pathology of a number of hereditary conditions including a family of neurogenetic disorders, collectively referred to as neurodegeneration with brain iron accumulation, which is characterised by iron accumulation

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in the basal ganglia (Heidari et al., 2016; Meyer et al., 2015). Friedreich ataxia (FRDA) is the most common heritable ataxia and has an autosomal recessive inheritance and exhibits abnormal mis-compartmentalised intracellular iron distribution (Schipper, 2012). The gene associated with FRDA encodes the protein frataxin which regulates mitochondrial iron transport and is highly expressed in mitochondria-rich tissues such as brain, heart, and skeletal muscle. The mechanism and molecular details of iron regulation of frataxin are still poorly understood.

The most prevalent mutation causing this disorder is a trinucleotide repeat expansion (GAA) in the gene for this protein which leads to increasing mitochondria iron concentrations leaving the cytosol iron depleted, and resulting in compromised mitochondrial function due to oxidative stress (Babcock et al., 1997; Rotig et al., 1997). This mis-compartmentalised iron has been localised in particular to the cerebellar dentate nuclei of FRDA's patients (Babady et al., 2007; Waldvogel et al., 1999).

Clinical trials have examined the safety and efficacy of deferiprone in FRDA patients. Some studies investigate the effect of this iron chelator in isolation and some use it in combination with idebenone, which has antioxidant properties. The five studies that have evaluated the potential benefits of iron chelators on FRDA vary in their sample size from quite low to moderate sample sizes (4 to 72 patients) (Abbruzzese et al., 2011; Boddaert et al., 2007; Elincx-Benizri et al., 2016; Pandolfo et al., 2014; Velasco-Sanchez et al., 2011). All studies indicate that lower doses of deferiprone (20 - 30 mg/kg/day) had acceptable safety profiles (Abbruzzese et al., 2011; Boddaert et al., 2007; Elincx-Benizri et al., 2016; Pandolfo et al., 2014; Velasco-Sanchez et al., 2011). In contrast, higher deferiprone doses, for example 40 mg/kg, resulted in poorer Friedreich Ataxia Rating Scale and International Cooperative Ataxia Rating Scale scores compared with placebo (Pandolfo et al., 2014). Even higher doses of 60 mg/kg (Pandolfo et al., 2014) or 80 mg/kg dose (Boddaert et al., 2007) were discontinued due to increased incidence of adverse events

The lower doses used in these studies showed some treatment efficacy in FDRA. More specifically, Pandolfo et al (2014) found in 21 deferiprone treated patients compared to 11 placebo treated patients that there was not an overall effect on the standard rating scales which they partially attributed to a lack of deterioration in the placebo arm. However, when they conducted subgroup analyses on patients with less severe disease, deferiprone 20

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mg/kg/day appeared to exhibit beneficial effects on the standard rating scales including kinetic function and nine-hole peg test. This agrees with Velasco-Sanchez et al (2011) who show in 20 patients that there was a stabilising effect with idebenone (20 mg/kg/day) and deferiprone (20 mg/kg/day) for 11 months. However, this study did not have a placebo arm for comparison. Boddaert and colleagues also show in a subgroup of the youngest patients that 20 to 30 mg/kg/day deferiprone improved International Cooperative Ataxia Rating Scale scores and improved descriptive speed of performance, which we associated with reduced iron deposition as assessed with MRI. Smaller pilot studies (Abbruzzese et al., 2011; Elincx-Benizri et al., 2016; 2014) also indicated some motor or neurologic improvements in certain patients.

In summary, a handful of studies have investigated the effects of deferiprone in FDRA patients and indicate that lower doses appear to be safe and possibly effective in certain sub-populations (i.e. early stage of disease and/or young). In contrast, higher doses clearly show adverse effects. Larger, randomised, double blind, placebo-controlled studies are required to determine the role of iron chelators in FRDA.

3.4. Superficial siderosis

Superficial siderosis is a progressively deteriorating neurological condition resulting from the prolonged presence of blood in the subarachnoid space causing iron accumulation in the subpial brain matter which leads to debilitating ataxia, sensorineural hearing loss and myelopathy (Charidimou et al., 2015; Koeppen et al., 1993; Nanda et al., 2010; Wilson et al., 2017). The histochemical evaluation of a patient with superficial siderosis showed high levels of iron in macrophages, superficial astrocytes and grey matter oligodendroglia (Kellermier et al., 2009). This is an increasingly common diagnosis disorder and may be found within the general elderly population or in patient with cerebral amyloid angiopathy, a form of angiopathy in which β-amyloid deposits in the brain artery walls as the most common mechanism of the disorder (Charidimou et al., 2013; Linn et al., 2010; Nanda et al., 2010; Pichler et al., 2017). These data suggest a potential link between vascular β-amyloid deposition and vascular dysfunction which eventually leads to loss of vessel integrity and thereby haemorrhages (Charidimou et al., 2015).

Two studies have considered whether deferiprone benefits patients with superficial siderosis. Levy and Llinas (2012) conducted an open pilot study in a small population of superficial siderosis patients (n=10) who were given 30 mg/kg/day dose of deferiprone over a 3-month

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period showed no significant adverse effects on hematologic, liver, or neurological function. A subjective improvement in symptoms was observed in only four patients while two of them showed worsening symptoms. MRI evaluation exhibited a noticeable reduction in brain iron accumulation in two of the patients (Levy and Llinas, 2012).

The most recent trial was a 2-year longitudinal observational study of 38 superficial siderosis patients aged 37-86 who were administered 30 mg/kg/day deferiprone 5 days per week with 2 days off allowing for partial iron repletion by diet to mitigate the risk of iatrogenic iron deficiency anaemia. The iron susceptibility signal in the 2-year post-drug scan with the baseline MRI scan were compared in 16 patients with the same echo time and the same captured brain volume. The results showed while half of the patients experienced reduction in the total iron content of the brain (average decrease of 5%), the other half showed an average 36% increase in total iron content. The authors speculated that patients who did not respond to deferiprone either passed a certain point in the disease progression where the brain's support mechanisms could not be repaired (Kessler et al., 2018).

In addition to these small to medium sized studies some observational case studies also exist (Cummins et al., 2013; Derle, 2018; River et al., 1994). One of these reports described a 65-year-old patient diagnosed with superficial siderosis who was administered 1 g of deferiprone three times a day. After 4-6 months, some improvements in ataxia, hearing and motor weakness were noted (Cummins et al., 2013). Another case report described a 63-year-old superficial siderosis patient who went under deferiprone treatment (30 mg/kg/day). The result showed a promising improvement in motor weakness and patient was able to sit without assistance and walk with one cane after only 3 months of the treatment (Derle, 2018). An early study examined the effect of trientine dihydrochloride which is an oral copper and iron chelating agent (Roberts and Schilsky, 2008) on a 47 year old superficial siderosis patient. Following 6 month's treatment a clinical improvement was noted with a concomitant reduction of CSF iron levels. After two years, while the original pathology still existed, there were a significant reduction of iron and ferritin levels in the CSF (River et al., 1994).

At present two clinical trials and a number of case studies support a potential role for chelation therapy in a subset of superficial siderosis patients. In the future, randomized, placebo-controlled trials are needed to determine clinical benefit.

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3.5. Aceruloplasminemia

Aceruloplasminemia is an uncommon adult-onset autosomal recessive disorder caused by disruption in a gene that encodes ceruloplasmin, an enzyme that plays role in cellular iron homeostasis (Harris et al., 1995). Affected populations of aceruloplasminemia is estimated to be only one person in 2 million in non-consanguineous marriages in Japan, and less than 40 families around the world (Miyajima et al., 1999). The predominant clinical feature in aceruloplasminemia is described as a trio of diabetes, dementia and retinal degeneration along with evidence of systemic iron overload (Yamaguchi et al., 1998). The progressive neurodegeneration of the basal ganglia in the brain and retina have been suggested to be a result of iron accumulation in these tissues (Klomp and Gitlin, 1996).

As aceruloplasminemia is an extremely rare (1 in 2,000,000) there are no cohort studies available to show the therapeutic efficiency of chelation therapy. The only available reports documented two single cases of aceruloplasminemia patients treated with deferoxamine (Miyajima et al., 1997; Pan et al., 2011). While these two reports described reduction of the brain iron content, only one of them showed the signs of improved neurological symptoms. The available reports aimed to reduce systemic iron loading by administering a dose of 500 mg deferoxamine via intravenous infusion in a 5% glucose solution once a week. The first report described a 63-year old patient treated for a 10-month period resulting in reduction of brain iron stores at the striatum and thalamus and ameliorate neurological symptoms associated with neurodegeneration. The treatment was stopped due to complaints of light-headedness and photophobia (Miyajima et al., 1997). The other case study reported a long term (2006 - 2010) treatment of a 52-year-old patient with a similar dosage. There was no signs of improvement and symptoms continued to progress and the patient continued to progress to have mild ataxia and rigidity of the limbs. A study of differences in regional brain iron levels pre- and post-treatment using MRI showed a reduction in the brain iron content with the highest iron reduction at the caudate (30%) and substantia nigra (26.3%), and the lowest at the thalamus (4.3%) and dentate nucleus (3.6%) (Pan et al., 2011).

3.6. Age related macular degeneration

The retina is an extension of the brain and considered the most accessible part of the central nervous system (CNS). It is composed of a layered arrangement of 5 neuronal groups (Masland, 2001, 2012) along with their supporting glia. Iron plays a vital role in a wide range of retinal processes including the visual phototransduction cascade where light photon energy

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is converted into an electrical signal in rod and cone photoreceptor cells (Moiseyev et al., 2006).

Age related macular degeneration (AMD) is a leading cause of blindness in those over the age of 50 and excessive iron loading in the retina has been linked to this disease (Hadziahmetovic et al., 2008; Hahn et al., 2003; Song and Dunaief, 2013; Wong et al., 2007). Mechansims of iron-induced neurodegeneration in AMD have recently attracted attention, highlighting the involvement of pathways involving oxidative stress, inflammation and hypoxia (De Jong, 2006; Hadziahmetovic et al., 2008; Hahn et al., 2003; Khandhadia and Lotery, 2010; Shu and Dunaief, 2018; Song and Dunaief, 2013; Wong et al., 2007).

Interestingly, it has been suggested that polymorphism of the transferrin receptor 2 (*TFR2*), a gene responsible for cellular iron uptake, may be associated with modulation of AMD risk (Wysokinski et al., 2014). Additionally, pathologic effects of AMD are explained by another mechanism involving a role for iron in modulating the Alzheimer's disease amyloid precursor protein in the retina (Bandyopadhyay and Rogers, 2014; Becerril-Ortega et al., 2014). Amyloid precursor protein is required for normal retinal function and is expressed in inner retinal neurons (Ho et al., 2012). The by-product of APP, amyloid-β is proposed to contribute to AMD progression (Guo et al., 2014). In fact, amyloid-β and iron can both be detected in drusen, the extracellular deposits beneath the retinal pigment epithelium which is a pathologic hallmark of AMD (Dentchev et al., 2003; Isas et al., 2010; Johnson et al., 2002; Mullins et al., 2000).

A single study has investigated iron levels in post-mortem AMD and healthy control retinas from human patients (Hahn et al., 2003). In 10 AMD affected maculas, they found that AMD eyes on average (3 with drusen only, 3 with geographic atrophy, 4 with exudative AMD) had higher levels of iron assessed with Perls' staining compared with 9 age-matched controls. Interestingly, the authors showed by applying deferoxamine to the tissue samples that a portion of this excess iron was chelatable in both the retinal pigment epithelium and in Bruch's membrane. This *ex vivo* work has yet to be confirmed *in vivo*.

3.7. Retinitis pigmentosa

Retinitis pigmentosa (RP) refers to a set of hereditary retinal diseases caused by a large number of mutations that feature progressive degeneration of rod and cone photoreceptors

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(Hartong et al., 2006). Being a genetically and phenotypically heterogeneous disorder, there are multiple mechanisms that are suggested to be involved in the pathogenesis of photoreceptor cell death. In a small subset of cases, pathological effects of retinal iron accumulation has been suggested as one of the possible mechanisms of retinal degeneration (Wang et al., 2017; Yusuf et al., 2018).

It has been reported that variations in a gene encoding a heme-transporter protein, feline leukemia virus subgroup C cellular receptor 1 (FLVCR1), results in selective degeneration of a sub-population of neurons in the retina, causing retinitis pigmentosa via dysregulation of heme or iron homeostasis (Ishiura et al., 2011; Rajadhyaksha et al., 2010). In additon, mutation in the pantothenate kinase 2 gene (*PANK2*) causes the most prevalent form of neurodegeneration with brain iron accumulation disorder, called pantothenate kinase associated neurodegeneration (PKAN) (Matarin et al., 2006). PKAN has a wide clinical spectrum including parkinsonism, retinitis pigmentosa and iron accumulation in the brain.

To date, there have been no assessments of FDA-approved iron chelating agents on human nor animal models of retinitis pigmentosa. However, some novel iron-chelating compounds have been tested in mouse models of retinitis pigmentosa. Wang et al. (2017) used a common murine model of retinal degeneration 10 (rd10), which shows clear deficits in retinal function at 2-weeks of age. This retinal degeneration has been associated with altered iron homeostasis assessed by upregulated transferrin and ceruloplasmin mRNA levels as well as ferritin protein, ferritin-bound iron and total retinal iron levels in rd10 mice (Deleon et al., 2009). The effects of intraperitoneal delivery of two chelating agents, VK28[3] and VAR10303[4], were assessed and found to improve visual function assayed by electroretinography in rd10 mice in conjunction with reduced immunohistochemical markers of neuroinflammation, oxidative stress, and apoptosis (Wang et al., 2017). Another study that explored the role of chelation therapy in the rd10 mouse model employed a selection of high-affinity iron chelators in a complex (Obolensky et al., 2011). They used zinc-desferrioxamine complex to slow the progression of retinal degeneration in the rd10 model. The outcomes showed that intraperitoneal administration of the zinc-desferrioxamine three times a week from postnatal day 3-4 onward improve retinal function in week 3 old mice compared to saline-treated littermate controls (Obolensky et al., 2011). The use of iron chelating agents in retinal

[3] 5-(4-(2-hydroxyethyl) piperazin-1-yl (methyl)-8-hydroxyquinoline
[4] 5-(N-methyl-N-propargyaminomethyl)-quinoline-8-oldihydrochloride

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degeneration is still at a very early stage. Further work is needed to better understand how iron and ferroptosis are involved in the pathophysiology of retinal degeneration.

3.8 Glaucoma and diabetic retinopathy

There is some evidence that altered iron metabolism may be associated with greater risk of glaucoma and diabetic retinopathy. Glaucoma refers to a group of progressive eye disorders characterized by optic nerve connective tissue remodelling and neuronal loss, causing a concomitant pattern of visual loss (Kwon et al., 2009). This condition is associate with ageing and elevated intraocular pressure. Diabetic retinopathy is also a form of sight-threatening pathology in people with diabetes, the earliest changes of which involve the microvasculature and inner retinal neurons (Cheung and Wong, 2008). Damage to blood vessel can progress to vascular leakage and severe proliferative disease involving the aberrant proliferation of blood vessels.

The odds of developing glaucoma in individuals with high levels of iron was examined in a cross-sectional study of 17,476 participants in a South Korean demographic study. The results showed that the risk of development of glaucoma in individuals with serum ferritin level greater than 61 ng/mL were significantly higher compared to those with levels less than 31 ng/mL (Lin et al., 2014).

A similar study showed that supplementary consumption of iron (≥18 mg/per day) may increase the odds of having been diagnosed with glaucoma (Shaikh et al., 2012). Consistent with the potential for increased glaucoma risk, increased expression of iron-regulating genes including transferrin (iron-transporter), ceruloplasmin (iron efflux), and ferritin (iron storage) have been reported in an animal model of glaucoma with elevated intraocular pressure (Farkas et al., 2004).

Iron loading may be involved in the pathogenesis of diabetic retinopathy. Peterlin and colleagues (2003) found in 223 participants with type 2 diabetic that a mutation in a hemochromatosis gene was a significant independent risk factor for the development of more severe proliferative diabetic retinopathy. Increased levels of retinal iron have been reported in post-mortem retinal samples collected from diabetic patients and in animal models of diabetes (Chaudhary et al., 2018).

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While retinal iron accumulation may be a risk factor for both glaucoma and diabetic retinopathy, there are as yet no studies exploring the therapeutic strategies based on the reduction of iron in these conditions.

3.9. Systemic iron changes: retinal effects

There is growing evidence showing cortical and blood diseases that cause alterations to iron effect the retina. Misfolding of proteins in PD and AD have been found in the retina, and in some cases have been linked with increased iron loading (Baksi and Singh, 2017; Bush, 2003; Cho et al., 2010; Joppe et al., 2019; Koronyo et al., 2017; Singh et al., 2019). Rare genetic disorders characterised by alterations in iron homeostasis such as aceruloplasminemia, Friedreich ataxia, hemochromatosis exhibit retinal manifestations which range from case report findings (Song and Dunaief, 2013; Zerbib et al., 2015) to being characteristic features of the disease (Fortuna et al., 2009; Noval et al., 2012). Although the examination of iron chelators on retinal manifestations of these diseases is in its infancy, animal studies show some promise.

The low toxicity and efficacy of deferiprone on the retinal iron levels was tested using a mouse model of systemic iron loading with iron-induced retinopathy (Hadziahmetovic et al., 2011b). This mouse model has genetic disruption of two genes, ceruloplasmin (*Cp*) and hephaestin (*Heph*) which play interrelated roles in iron homeostasis. This model shows retinal degeneration in conjunction with retinal iron loading by the age of 6-months (Hahn et al., 2004). After a single day of treatment of 1 mg/mL deferiprone in drinking water, 6-month old wildtype mice exhibited increased transferrin receptor mRNA, indicating lowering of labile iron levels in the retina. After 11 days retinal transferrin receptor mRNA had increased by 2.7-fold. After 3 months of treatment there was a significant decrease in total iron in the neural retina from ~0.038 to ~0.029 μg Fe quantified by a bathophenanthroline-based spectrophotometric approach. There appeared to be no DFP-induced retinal toxicity in treated wildtype mice relative to age-matched untreated controls as determined using functional assessment (electroretinography) and confirmed by the normal retinal histology. Deferiprone was also effective at reducing total iron in the neural retina of transgenic model of systemic iron loading after 6 months of treatment relative to untreated wild type littermates.

Another genetically modified mouse model of iron dyshomeostasis with disruption of a gene that encodes an iron regulatory hormone, hepcidin (*Hepc*) was used to address the effects of

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the oral administration of deferiprone on retinal iron loading (Song et al., 2014). This mouse model has already been shown to have high levels of iron accumulation in the retinal pigment epithelium and choroid in conjunction with age-dependent retinal degeneration, most severe at 18-month of age (Hadziahmetovic et al., 2011a).

Administration of deferiprone (1 mg/mL) in drinking water from 6 to 18 month of age improved retinal function in *Hepc* mice. This was associated with significant reductions of the of oxidative stress–related genes including heme oxygenase-1 (*Hmox1*) and catalase (*C3*) in *Hepc* mice. The mRNA level of rhodopsin was significantly increased in DFP retinae consistent with increased photoreceptors. Immunolabeling showed that L-ferritin was in both the inner retina and retinal pigmented epithelium (RPE), whereas the iron transporter transferrin receptor showed increased signal in the inner retina. Given these changes, the authors suggest the oral iron chelator DFP could be a long-term preventive treatment for retinal diseases involving iron overload (Song et al., 2014).

3.10. Retinal toxicity effects of iron chelator

It is important to note that clinically, iron chelation therapy has also been shown to exhibit retinal toxicity in some cases. In patients chronically administered deferoxamine for treatment of conditions such as transfusion-related hemosiderosis the incidence of retinal changes ranged from 1.2 to 9% depending on the study and the outcome measure (Baath et al., 2008; Chen et al., 2005; Cohen et al., 1990; Di Nicola et al., 2015; Olivieri et al., 1986; Viola et al., 2012). Indeed, high doses of deferoxamine appear to be related to ocular toxicity (Dunaief, 2006; Pall et al., 1989). Signs of ocular toxicity include retinal pigment epithelium mottling on fundus examination, retinal electrophysiology deficits (reducing cone and rod responses), visual field changes which can be temporary or permanent visual deterioration. These have been reviewed in detail elsewhere (Di Nicola et al., 2015). Indeed, current FDA approved iron chelation agents have a range of safety risks (see Table 1) especially deferoxamine which has been available for nearly 50 years (Origa, 2017).

What predisposes certain patients to retinal toxicity and the mechanism by which this occurs remains poorly understood. The major site of deferoxamine ocular toxicity appears to involve the retinal pigment epithelium (Haimovici et al., 2002; Klettner et al., 2010; Rahi et al., 1986). Activation of p38 mitogen-activated protein kinases, one of the major class of mitogen-activated protein kinases (MAPKs) has been shown to play an important role in retinal pigment epithelium cell death induced by deferoxamine (Klettner et al., 2010). These

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reports accentuate the importance of regular ocular monitoring and screening patients who undergo chelation therapy. Moreover, iron chelation as a therapeutic intervention for retinal disease will require tight titration of dose and/or the use of new compounds with improved safety profiles. Indeed, new iron chelating agents are being developed for other central nervous system conditions (Finkelstein et al., 2017; Lannfelt et al., 2008; Singh et al., 2019) and thus this opens the door for repurposing these agents for eye disorders.

4. Conclusions

The current available data of clinical effects of iron removal therapy on neurodegenerative disorders shows that iron chelators are neuroprotective agents that can be applied as a disease-modifying approach in treatment of iron metabolic disorders of the brain and retina. Excessive iron loading may lead to irreversible tissue damage in the central nervous system, so early diagnosis and application of chelator agents may be a useful therapeutic approach or adjunct.

The retina is an easily accessible extension of the central nervous system which provide a unique opportunity to utilising it as a surrogate to study changes in the brain (Garcia-Martin et al., 2014; London et al., 2013; Nguyen et al., 2017). The retina can be targeted not only for understating the pathogenesis of neurodegenerative diseases but also for examination of potential efficacy of disease-modifying treatments such as iron chelation therapy. Despite the potential advantages offered by iron chelation therapy, there are no clinical trials to demonstrate safety and efficacy of this approach on the retina.

In addition, there are many unmet challenges associated with the iron chelation therapy such as heterogeneity in response to chelation therapy which could derive from the multifactorial nature of neurodegenerative disorders and/or interindividual variability in genetics, severity of disease, and additional interventional measures. This could be an opportunity to develop novel iron chelating therapeutic agents with improved safety profiles (Finkelstein et al., 2017).

The risk of worsening the condition using high doses of the chelators still exist. For example, treatment with deferiprone carries a risk of agranulocytosis which may occur at any time. Although agranulocytosis is a reversible condition, continuous monitoring blood cell counts of patients during the period of treatment is necessary for the early detection.

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Future clinical studies are required to provide a more comprehensive view of intracellular iron trafficking, particularly to mitochondria and mechanistic interpretation of the effects of iron chelators to increase our understanding of these neurodegenerative disorders and develop new therapeutic strategies. Studies into iron chelation therapies in retinal disease is a particularly understudied area and would warrant further investigation.

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