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Role of iron in neurodegenerative diseases

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Abstract Currently, we still lack effective measures to modify disease progression in neurodegenerative diseases. Iron-containing proteins play an essential role in many fundamental biological processes in the central nervous system. In addition, iron is a redox-active ion and can induce oxidative stress in the cell. Although the causes and pathology hallmarks of different neurodegenerative diseases vary, iron dyshomeostasis, oxidative stress and mitochondrial injury constitute a common pathway to cell death in several neurodegenerative diseases. MRI is capable of depicting iron content in the brain, and serves as a potential biomarker for early and differential diagnosis, tracking disease progression and evaluating the effectiveness of neuroprotective therapy. Iron chelators have shown their efficacy against neurodegeneration in a series of animal models, and been applied in several clinical trials. In this review, we summarize recent developments on iron dyshomeostasis in Parkinson's disease, Alzheimer's disease, Friedreich ataxia, and Huntington's disease.

Keywords Iron · Neurodegeneration · Parkinson's disease · Oxidative stress

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Introduction

As the population is aging worldwide, neurodegenerative diseases, especially Parkinson's disease (PD) and Alzheimer's disease (AD) are becoming a main challenge to health care professionals (Brookmeyer et al. 2007; Dorsey et al. 2007). Unfortunately, so far we have no cure or effective intervention to slow down the progression of these neurodegenerative diseases. Although PD and AD have different symptoms and pathological changes, several processes are common in their pathogenesis and cell death: iron accumulation, excess oxidative stress, and mitochondrial dysfunction (Ward et al. 2014; Crichton et al. 2011; Parker et al. 1994; Deibel et al. 1996; Connor et al. 1992; Dexter et al. 1989; Riederer et al. 1989; Devi et al. 2008; Jenner et al. 1992). Moreover, iron overload has direct interplays with the key components of pathological hallmarks, α-synuclein in PD, β-amyloid and tau protein in AD (Ostrerova-Golts et al. 2000; Golts et al. 2002; Ortega et al. 2015; Becerril-Ortega et al. 2014; Bodovitz et al. 1995; Everett et al. 2014; Yamamoto et al. 2002). Besides, in several hereditary neurodegenerative diseases such as Huntington's disease, and Friedreich ataxia, iron dyshomeostasis also plays a critical role, and these diseases share a common core mechanism of neurodegeneration with PD and AD (Babcock et al. 1997; Rotig et al. 1997; Hilditch-Maguire et al. 2000; Bulteau et al. 2004; Bartzokis et al. 2007; Mena et al. 2015). Neuroimaging examination, especially MRI, is a good measure to detect iron accumulation early in the disease process, monitor iron overload along disease progression, and evaluate the effect of treatment (Ward et al. 2014; Apple et al. 2014; He et al. 2015; Wieler et al. 2015; Devos et al. 2014). Iron chelation is demonstrated effective in several animal models of the above diseases, and promising in clinical trials of PD and

Friedreich's ataxia (Pandolfo et al. 2014; Dexter et al. 2011, 2014; Grolez et al. 2015; Devos et al. 2014; Kaur et al. 2003). In this review, we mainly discuss iron dyshomeostasis and its role in the pathogenesis of PD, the application of imaging tools for iron detection in research and clinical practice, and the prospect of iron chelation therapy in PD. Additionally, we will give a brief overview of iron dysregulation in AD, Friedreich ataxia, and Huntington's disease.

Regulation of cellular iron in the brain

Regulations of cellular iron in different cell types of the brain varied. In microglia, oligodendrocytes, and most neurons, the majority of the iron is stored in ferritin as a non-reactive but bio-available form (Connor et al. 1994; Hansen et al. 1999). However, in dopaminergic neurons of the substantia nigra (SN), neuromelanin serves as the main non-reactive iron storage. In the study by Zecca et al. (2001), iron, ferritin, and neuromelanin in the SN of normal subjects all increase with age. Since the second decade, neuromelanin is the predominant molecule reserving iron, and its proportion in total iron content increases with age. In subjects aged 80–90 years, the concentration of total iron, ferritin and neuromelanin are 109–199, 300–400, and 3500 ng/mg, respectively (Zecca et al. 2001). We need to note that the authors did not discriminate the iron, ferritin and neuromelanin distributions between different cell types, but we can infer the mainstay of neuromelanin in storing iron in dopaminergic neurons because of the significant predominance of neuromelanin in SN. Studies on Macaca arctoides and rat brains reported that astrocytes lack ferritin (Connor et al. 1994; Hansen et al. 1999). However, researches using cultured rat astrocytes showed that stimulations with iron together with TNF-α, iron oxide nanoparticles, or ferric ammonium citrate induced a significant increase of ferritin in astrocytes (Hoepken et al. 2004; Rathore et al. 2012; Geppert et al. 2012). These studies suggest that astrocytes can store iron into ferritin to reduce oxidative stress under the above stimulations. In addition to iron stored in ferritin or neuromelanin as non-reactive forms, a small proportion (less than 5 %) of iron in the cell is in the labile cell pool, where the iron is redox-active, chelatable and exchangeable. Labile cell iron is maintained within a range of 0.5–1.5 μM physiologically (Cabantchik 2014). Iron-sulfur clusters and heme are two crucial iron-containing prosthetic groups, which are essential elements of the mitochondrial electron transport chain (Gille and Reichmann 2011; Zhang et al. 1998; Beinert et al. 1997; Lin et al. 1982).

Normally, iron homeostasis is strictly controlled by a series of regulators. In the plasma, iron is transported by transferrin (Tf). To enter the central nervous system, iron must cross the blood–brain barrier and the blood–cerebrospinal fluid barrier, and there are transferrin receptors (TfR) on the luminal surface of the capillary endothelial cells. Firstly, transferrin with Fe^{3+} and TfR form a Tf–TfR complex on the luminal surface of the endothelial cells, and then this complex is taken up into the endothelia by endocytosis (Visser et al. 2004). How iron is expelled out of the abluminal surface of the endothelia and into the brain interstitial fluid is still controversial. Some studies showed that iron was segregated from Tf in the endothelia and then released to the brain interstitial fluid (Moos et al. 2006). Afterwards, iron is mainly incorporated with Tf in the interstitial fluid. Neurons can import iron by endocytosis of Tf–TfR complex (Leitner and Connor 2012; Moos et al. 1998), then divalent metal ion transporter 1 (DMT1) helps iron transport from the endosomes to the cell cytoplasm (Moos and Morgan 2004), where some of the iron is sent to ferritin with the help of the chaperone poly-r(C)-binding protein 1 (PCBP) family (Leidgens et al. 2013), some imported into mitochondria for heme and iron-sulfur cluster (ISC) synthesis, and few of the iron stays in the labile iron pool (Lane et al. 2015). How iron is transported into mitochondria is still not fully elucidated, and mitoferrin is a putative mitochondrial iron importer in neuronal cells (Carroll et al. 2011; Lane et al. 2015). Mastroberardino et al. (2009) demonstrated a Tf–TfR2 pathway importing iron into mitochondria in the neurons in SN. As neuromelanin is the main protein storing iron in dopaminergic cells in SN, it is synthesized in the process of dopamine oxidation (Zucca et al. 2015). Excess iron is transported by ferroportin out of the neurons, with the help of ferroxidases such as ceruloplasmin (CP) (De Domenico et al. 2007). The homeostasis of cellular iron is kept by two iron regulatory proteins (IRP1 and IRP2), which regulate the translations of the mRNAs of proteins involved in iron storage, influx, and efflux (Rouault 2006; Klausner et al. 1993).

The iron transport related to the glia is less clear than that in the neurons. Virtually no DMT1 or transferrin receptor can be detected in quiescent astrocytes, microglia, and oligodendrocytes (Moos and Morgan 2004; Pelizzoni et al. 2013; Skjorringe et al. 2015; Moos 1996). Ferroportin was not detected in astrocytes and resting microglia (Moos and Rosengren Nielsen 2006). Microglia iron uptake is performed via phagocytosis of ferritin (Leitner and Connor 2012), and oligodendrocytes also obtain iron from ferritin (Todorich et al. 2008). Astrocytes acquire iron through the resident transient receptor potential (TRP) channels in the quiescent state, and the de novo expressed DMT1 in activated state (Pelizzoni et al. 2013).

Interplay between mitochondrial injury, iron dyshomeostasis, and oxidative stress

Mitochondria provide energy for the cell via oxidative phosphorylation. This makes mitochondria a source of hydrogen peroxide and superoxide, which can react with iron. In addition, heme and ISC are synthesized in mitochondria, so iron is actively transported into and within mitochondria (Lill et al. 2006; Heinemann et al. 2008; Nilsson et al. 2009). Through Fenton and Haber–Weiss reactions, the most reactive oxygen species (ROS) hydroxyl radicals are produced (Wardman and Candeias 1996; Kehrer 2000). Therefore, iron overload can lead to increased oxidative stress, which can induce lipid peroxidation, damage DNA, and oxidize proteins (especially protein carbonylation) (Catala 2009; Stadtman 2006; Keyer and Imlay 1996). In particular, mitochondrial DNA is vulnerable to oxidative damage because of the absence of protection from histones (Shokolenko et al. 2009). Mitochondrial injury leads to reduced synthesis of ISCs and heme, then decreased ISCs causes IRPs activation and further exacerbates iron accumulation and related oxidative stress. Thus mitochondrial injury, iron accumulation, and oxidative stress form a vicious cycle that can lead to cell death (Mena et al. 2015). Moreover, this process discussed above can trigger inflammation response by activating microglia, adding oxidative stress in the vicious circle (Urrutia et al. 2014).

Iron and PD

Iron overload in the substantia nigra in PD

The Lewy body is the pathological hallmark of PD, and SN is an especially vulnerable area. Neurons in the SN progressively decreased in PD, which is responsible for the disabling motor symptoms. Total iron in SN is demonstrated to be increased by multiple post-mortem examinations (such as inductively coupled plasma spectroscopy, atomic absorption spectroscopy), MRI, and transcranial sonography in PD (Dexter et al. 1989; Riederer et al. 1989; Zecca et al. 2005; Michaeli et al. 2007; Rossi et al. 2013; Martin et al. 2008). Furthermore, ferritin and neuromelanin are reported to be decreased in the SN of PD patients (Dexter et al. 1990; Connor et al. 1995; Zecca et al. 2002). Considering the increase of total iron, and the decrease of iron-binding proteins, the labile iron pool of the cells in SN of PD patients is probably enlarged. Riederer et al. reported that Fe(III) was significantly increased in SN in PD, while Fe(II) remained unchanged (Riederer et al. 1989). Iron dyshomeostasis is caused by increased expression of the iron import transporter DMT1, decreased expression of the iron export protein ferroportin and CP activity (Salazar et al. 2008; Song et al. 2010; Ayton et al. 2013). Moreover, IRP is up-regulated in PD, rather than down-regulated to keep iron homeostasis (Wong and Duce 2014; Faucheux et al. 2002; Jiang et al. 2010). The shift of IRP may be partially caused by increased oxidative stress. So far, it is unclear what is the primary drive for the above mechanism of iron excess in SN of patients with PD, but it is suggested that α-synuclein aggregation, oxidative stress, and mitochondrial dysfunction might be involved. In addition, these factors and iron accumulation compose a vicious circle leading to neuroinflammation and neurodegeneration (Mena et al. 2015; Urrutia et al. 2014).

Iron involvement in the pathogenesis of PD

The vicious circle of mitochondrial injury, oxidative stress, iron dyshomeostasis and neuroinflammation has close interactions with several factors in PD. Firstly, dopamine metabolism creates highly reactive species in SN, and co-localization of iron and dopamine in SN raises the risk of oxidative stress (Hare et al. 2014). Secondly, as oxidative stress can induce protein carbonylation, Münch and colleagues suggested that the products of protein carbonylation could induce α-synuclein crosslinking and Lewy body formation (Munch et al. 2000). Thirdly, ferric iron may directly catalyze the formation of α-synuclein oligomers, and α-synuclein overexpression can exacerbate iron accumulation (Ostrerova-Golts et al. 2000; Golts et al. 2002; Ortega et al. 2015). In turn, aggregated α-synuclein can impair mitochondria, enhance oxidative stress and iron dyshomeostasis, thus intimately participate into the positive feedback loop (Davies et al. 2011; Devi et al. 2008; Funke et al. 2013). Moreover, neuromelanin released by dying dopaminergic neurons contains large amounts or iron, which can lead to the activation of adjacent microglia. The activated microglia induces inflammation and aggravates the vicious circle of oxidative stress, mitochondrial injury and cell death. Then more neuromelanin can be released from the demised neurons, and form a positive feedback of neuroinflammation and neurodegeneration (Zucca et al. 2014).

Imaging modalities for brain iron detection in PD

MRI can display the morphological changes of SN and evaluate the iron content in SN. MR imaging of SN is based on its iron components. Generally, SN has a high level of iron, so it appears as low intensity in T2WI, T2*,

and susceptibility weighted imaging (SWI) (Lehericy et al. 2014; Jin et al. 2011). The iron level can be quantitatively assessed by R2*, SWI phase values, quantitative susceptibility mapping (QSM) and similar techniques (Rossi et al. 2013; Jin et al. 2011; He et al. 2015). Recently, it was recognized that neuromelanin had a T1 shortening effect, and could be well demonstrated by neuromelanin MR imaging (Lehericy et al. 2014; Blazejewska et al. 2013). Studies using 1.5 Tesla and 3.0 Tesla MRI have shown that the volume of SN is decreased, while iron load of SN is increased in PD. Furthermore, iron elevation of SN is correlated with disease severity and disease duration (He et al. 2015; Rossi et al. 2013). Due to the better spatial resolution and contrast, 7 Tesla MRI can reliably differentiate SN pars reticulata (SNr) and SN pars compacta (SNc), and in particular recognize the nigrosome-1 with high confidence. That is because SNr has abundant iron while SNc is rich in neuromelanin (Lehericy et al. 2014; Kwon et al. 2012; Blazejewska et al. 2013). Research using 7 Tesla MRI suggests that the main abnormalities in SN in PD are: loss of nigrosome-1 hyperintensity, abnormal SN contours, and volume changes (Lehericy et al. 2014; Kwon et al. 2012; Blazejewska et al. 2013). MRI can also be used for early diagnosis (even presymptomatic), differential diagnosis, monitoring disease progression and assessing the effect of iron chelation treatment, as well as exploring the pathophysiology of iron toxicity (Jin et al. 2011; Ward et al. 2014; Pyatigorskaya et al. 2015; Boelmans et al. 2012; Devos et al. 2014).

SN hyperechogenicity in transcranial sonography is detected in approximately 90 % of the patients with PD (Berg et al. 2001; Berg 2011). The source of SN hyperechogenicity may be increased iron content and microglia activation (Berg 2011; Zecca et al. 2005). About 10 % of the healthy people also have SN hyperechogenicity, and longitudinal studies showed that those healthy people with SN hyperechogenicity had a significantly higher risk to develop PD (Becker et al. 1995; Behnke et al. 2007; Berg 2011). On one hand, SN hyperechogenicity can present early in the disease course, even before motor symptoms occur (Haehner et al. 2007; Miyamoto and Miyamoto 2013). On the other hand, it does not change during disease progression, and is poorly correlated with striatal FP-CIT uptake (Li et al. 2015). Therefore, it may be an appropriate tool for early diagnosis. Although in patients with hyposmia or rapid eye movement sleep behavior disorder, the sensitivity and specificity of SN hyperechogenicity for predicting future PD is not satisfactory, combining other biomarkers may improve the ability of future PD prediction (Miyamoto and Miyamoto 2013; Haehner et al. 2007). In addition, transcranial sonography can provide help in differentiating PD from other Parkinsonian disorders (Berg 2011; Tsai et al. 2007).

Iron chelation therapy in PD

Iron chelation therapy in PD is still an expanding field of research. Genetic (overexpression of ferritin) and medical iron chelation treatments showed neuroprotective affects in various PD animal models, including 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA), mouse/rat models of PD (Dexter et al. 2011; Kaur et al. 2003; Shachar et al. 2004; Devos et al. 2014). Devos et al. (2014) had demonstrated that deferiprone reduced iron overload in SN, decreased neuronal labile iron, increased levels of glutathione, diminished oxidation products of lipid and DNA, reduced dopamine depletion and improve motor symptoms in the MPTP mouse model. It showed that deferiprone could stop the vicious cycle of iron accumulation, mitochondrial injury and oxidative stress, then decrease neuronal destruction (Devos et al. 2014). Moreover, the authors showed deferiprone can slow down the motor symptom progression and decrease iron accumulation in SN in PD patients (Devos et al. 2014). Additionally, Grolez et al. (2015) showed CP activity might play a role in the therapeutic mechanism of deferiprone, and PD patients with lower CP responded better to iron chelation therapy. The authors pointed out insights for the prospect of future pharmacological modulation of CP activity in PD (Grolez et al. 2015). In recent years, Youdim and colleagues have developed a series of multifunctional iron chelators, such as M30, HLA20, and VAR. These drugs can both chelate iron and inhibit monoamine oxidase (MAO) activity. In a recent study by Bar-Am et al. (2015), VAR not only chelated iron, and alleviated oxidative stress induced lipid peroxidation, but also inhibited MAO-A and MAO-B, and increased dopamine and 5-Hydroxytryptophan (5-HT) levels. In 6-OHDA and MPTP rat models, VAR could increase dopamine and 5-HT, as well as improve motor function (Bar-Am et al. 2015). Since PD patients often have accompanying depression which is related to 5-HT (Goetz 2010), VAR is a promising drug that can slow disease progression, improve motor symptoms, and alleviate depression in PD. Another novel chelator M30, has the ability of chelating iron, up-regulating hypoxia-inducible factor (HIF)-1α and its downstream proteins such as vascular endothelial growth factor, erythropoietin, enolase-1, inducing the expression of a series of neurotrophic factors like brain-derived neurotrophic factor, glial cell-derived neurotrophic factor and antioxidant enzymes including catalase, superoxide dismutase, and glutathione

peroxidase in the brain, and regulating several factors involved in pro-survival signaling pathways such as phosphorylated protein kinase C, ERK1/2, -Akt and GSK-3β, in the CNS. Therefore, M30 has an extensive effect of neuroprotection (Kupershmidt et al. 2011).

Iron and other neurodegenerative diseases

Iron and AD

Excessive iron is deposited in multiple regions of the brain in AD, especially in the hippocampus. Iron also accumulates in senile plaques and neurofibrillary tangles, which are pathologic hallmarks of AD (Connor et al. 1992; Deibel et al. 1996; Good et al. 1992). The changes of iron regulating proteins drive iron overload, iron importer DMT1 is increased, while ferroportin 1 and CP that are responsible for iron exportation are decreased (Zheng et al. 2009; Crespo et al. 2014; Raha et al. 2013; Connor et al. 1993; Guerreiro et al. 2015; Wan et al. 2011). Similar as in other neurodegenerative diseases, iron also induces oxidative stress and mitochondrial dysfunction in AD (Wan et al. 2011; Mena et al. 2015). Moreover, amyloid β (Aβ), its precursor amyloid precursor protein (APP) and hyperphosphorylated tau have close interactions with excess iron in AD (Mena et al. 2015; Crichton et al. 2011; Everett et al. 2014; Yamamoto et al. 2002; Bodovitz et al. 1995). Normally, APP is cleaved by α- and γ-secretase. This process produces neuroprotective extracellular soluble sAβPPsα fragments and avoids Aβ formation. On the contrary, in AD, APP is cleaved by β- and γ-secretase, and this pathway leads to Aβ production and aggregation. Whether APP is firstly cleaved by α- or β- secretase is regulated by iron via furin. Iron overload can decrease furin expression, and as a result promote Aβ accumulation (Crichton et al. 2011; Bodovitz et al. 1995; Silvestri and Camaschella 2008; Silvestri et al. 2008). Besides, APP expression is modulated by IRP. Thus excessive iron can enhance APP production, and this will further increase Aβ formation (Rogers et al. 2002). In turn, Aβ can impair mitochondrial function, reduce ferric iron into a redox-active ferrous state, induce oxidative stress, and then exacerbate iron overload, thus aggravating the common pathway of neurodegenerative diseases (Mena et al. 2015; Everett et al. 2014; Wang et al. 2008; Smith et al. 1998). Iron can also interplay with hyperphosphorylated tau and induce the formation of neurofibrillary tangles (Castellani et al. 2012; Sayre et al. 2000; Yamamoto et al. 2002).

MRI is capable of evaluating iron accumulation in AD, and is promising for assisting diagnosis, as well as monitoring the efficacy of iron chelation and disease progression (Ward et al. 2014; van Rooden et al. 2015). In addition, a recent post-mortem study using 7 Tesla MRI demonstrated activated iron-containing microglia in the hippocampus of patients with AD (Zeineh et al. 2015). The advent of 7 Tesla MRI may provide more information on the role of iron in AD.

In recent years, clinical trials in AD targeting Aβ have failed one after another (Mangialasche et al. 2010; Salloway et al. 2014; Doody et al. 2014). Part of the reasons is that the pathophysiology of AD is complex, and contains a self-propagating vicious circle of iron accumulation, oxidative stress, and mitochondrial injury. Only cutting off the upstream factors such as Aβ cannot stop this vicious circle. On the other hand, iron chelation therapy may provide some hope. Iron chelation treatments using deferoxamine, clioquinol, and PBT2 can improve cognition, reduce Aβ accumulation and tau phosphorylation in animal models (Guo et al. 2013a, b; Grossi et al. 2009; Adlard et al. 2008). A clinical trial by Crapper McLachlan showed desferrioxamine significantly slowed down the decline of daily living skills in AD (Crapper McLachlan et al. 1991). More recently, the multi-target iron chelators M30 and HLA20 improved cognition of sporadic AD rat models. Additionally, chronic M30 therapy completely restored streptozotocin induced tau hyperphosphorylation in the hippocampus of those rats (Salkovic-Petrisic et al. 2015). Incorporating iron chelation in AD treatments is a promising approach in the future.

Iron and Friedreich ataxia

Friedreich ataxia is the most prevalent hereditary ataxia, and most of the patients with Friedreich ataxia are caused by an expanded GAA trinucleotide repeat in Frataxin (FXN) gene. This mutation decreases the level of FXN protein. FXN is an iron chaperone in iron–sulfur cluster and heme synthesis, and plays a critical role in keeping iron homeostasis and reducing oxidative stress (Gille and Reichmann 2011; Bulteau et al. 2004). Therefore, reduced expression of FXN leads to mitochondrial dysfunction, oxidative stress, and mitochondrial iron dyshomeostasis (Gille and Reichmann 2011; Babcock et al. 1997; Rotig et al. 1997). Whether overall iron is increased in the dorsal root ganglia and cerebellum is still controversial, and recent research showed iron was relocated from degenerated neurons to peripheral glial cells (Martelli and Puccio 2014; Koeppen et al. 2009, 2012, 2013). A quite recent phase 2, multicenter clinical trial on the safety and efficacy of iron chelator deferiprone did not find a significant improvement in clinical outcomes. However, subgroup analysis implied that deferiprone might be effective in less severe patients (Pandolfo et al. 2014). The effectiveness of iron chelation therapy in Friedreich ataxia warrant further investigation.

Iron and Huntington's disease

Huntington's disease is caused by a CAG trinucleotide repeat expansion in the huntingtin gene. Then the mutant huntingtin protein leads to multiple detrimental outcomes such as mitochondrial dysfunction, oxidative stress, abnormal transcription of multiple genes, calcium dyshomeostasis, activation of proteolytic enzymes, and microglia activation (Muller and Leavitt 2014). As a redox-active metal, iron is closely involved in the mutant huntingtin-induced pathological cascade (Firdaus et al. 2006; Muller and Leavitt 2014). In addition, iron homeostasis is influenced in this process, and iron accumulation in multiple brain regions has been demonstrated by MRI and post-mortem examinations (Bartzokis et al. 1999, 2007). MRI examination incorporating iron-sensitive techniques (such as T2*, SWI, R2*, SWI phase values, and QSM) is promising to assist presymptomatic diagnosis and monitor disease progression (Bartzokis et al. 2007; Apple et al. 2014; Macerollo et al. 2014; Dominguez et al. 2015; Sanchez-Castaneda et al. 2015). So far, there is scarce evidence on iron chelation treatments in Huntington's disease. Recently, Chen and colleagues demonstrated the neuroprotective efficacy of deferoxamine in a mouse model (Chen et al. 2013). The effectiveness of iron chelation therapy in Huntington's disease animal models warrants further exploration.

Conclusions

Although the above neurodegenerative diseases have distinct causes and pathology features, iron dyshomeostasis, oxidative stress and mitochondrial dysfunction form a vicious circle and play a crucial role in their pathogenesis. The mechanisms of abnormal iron metabolism in those neurodegenerative diseases are to be further elucidated. MRI is a helpful tool in revealing iron accumulation in the brain, and is increasingly used in early and differential diagnosis, tracking disease progression, and evaluating the efficacy of chelation therapy. Iron chelation is promising and has already exhibited its effectiveness in several clinical studies.

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