Journal of Neural Transmission (2020) 127:181–187
https://doi.org/10.1007/s00702-020-02149-3

NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - REVIEW ARTICLE

Parkinson's disease and iron

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Received: 29 December 2019 / Accepted: 21 January 2020 / Published online: 5 February 2020

Abstract
While the initial causes of Parkinson's disease (PD) are not clearly defined, iron deposition has long been implicated in the pathogenesis of PD. The substantia nigra of PD patients, where the selective loss of dopaminergic neurons occurs, show a fairly selective and significant elevation in iron contents. However, the question remains whether iron deposition represents the initiation cause or merely the consequence of nigral degeneration. Here, we describe existing findings regarding the interaction of iron with neuromelanin and alpha synuclein, the iron deposition in experimental animal model of PD and sporadic and familial PD patients, and the treatment option involving the use of iron chelators for targeting the aberration of iron level in brain. This review may provide us a better understanding of the role of iron in PD to address the question of cause or consequence.

Keywords Parkinson's disease · Iron · α-synuclein · MPTP · Iron chelator · PLA2G6

Introduction

Iron is an essential micronutrient in the human body, but it also poses problem of toxicity since it is redox-active and generates free radicals during its interconversion between ferrous Fe^{2+} and ferric Fe^{3+} forms (Eid et al. 2017). In the late 1900s, a number of studies have reported increased iron deposition in the substantia nigra (SN) of Parkinson's disease (PD) patients (Earle 1968; Dexter et al. 1987; Riederer et al. 1989). These reports were substantiated by the finding of a significant increase in the Fe^{3+}-binding protein, ferritin, and a shift in the Fe^{2+}/Fe^{3+} ratio in favour of Fe^{3+} which is said to induce membrane lipid peroxidation in the SN of PD patients (Riederer et al. 1989; Youdim et al. 1989). With the emergence of these studies, researchers began to query the possible connection of excess iron with the dopaminergic neurodegeneration in PD. However, whether the iron deposition represents the primary event in PD remains controversial. Here we review the recent advancement of our understanding of potential involvement of iron deposition in the context of experimental animal models and human patients.

Iron and neuromelanin

The iron distribution in brain appears to be rather heterogeneous and iron levels has been shown to be age-related. Histochemical and biochemical studies have revealed that SN and globus pallidus have the highest concentrations of iron in the normal human brains as well as rat and monkey brains (Youdim 1988; Youdim et al. 1989). A recent study which performed direct quantification of iron levels in normal human brain tissues found that the highest levels were in the putamen and globus pallidus and there was a significant positive correlation between iron levels in the basal ganglia and age (Ramos et al. 2014).

Neuromelanin (NM) is a dark coloured granular pigment present in the dopaminergic neurons of the SN and its pigmentation increases from early childhood to young adulthood, plateaus in middle age, and declines in the sixth decade (Xing et al. 2018). NM avidly chelates metals, iron in particular, but not exclusively. Iron binds to NM in the ferric Fe^{3+} form (Gerlach et al. 2003). Since NM traps large quantities of iron, it blocks hydroxyl radical production by Fenton's reaction as well as iron-mediated dopamine

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oxidation (Zecca et al. 2008). Increased tissue iron found in the parkinsonian SN may saturate iron-chelating sites on NM, and higher concentration of toxic free irons resulting from the looser association of between iron and NM may cause an increased production of free radical species, contributing to neuronal damage observed in PD. In vitro study using a nigrostriatal co-culture demonstrated induction of neurotoxic effect and lipid peroxidation by the iron–melanin complex on dopaminergic neurons (Mochizuki et al. 1993). Based on these data, the protective role of NM can be postulated until the buffering capacities toward iron become exhausted (Gerlach et al. 2003; Zecca et al. 2002).

In the SN of PD patients, neuromelanin granules with iron overload are present not only inside, but also outside neurons (Jellinger et al. 1992). Moreover, the level of redox activity detected in neuromelanin aggregates, which contributes to oxidative stress, is significantly increased and correlates with the severity of neuronal loss (Faucheux et al. 2003). While the extracellular NM released by degenerating neurons can be phagocytosed and degraded by microglia, they also unfavourably induce microglial activation, neuroinflammatory and subsequent degenerative processes, aggravating the underlying pathological condition (Langston et al. 1999; Zhang et al. 2011).

Iron and alpha synuclein

Alpha synuclein (αSyn) is the major constituent of Lewy bodies, a pathological hallmark found in sporadic and familial PD (Spillantini et al. 1997). Both pathogenic missense mutations in αSyn gene (PARK1) and multiplication of αSyn gene (duplications and triplications) (PARK4) cause familial PD (Dawson and Dawson 2003; Singleton et al. 2003). αSyn was shown to contain binding site for divalent metals including iron (Binolfi et al. 2006). In neurons exposed to excess iron, overexpression of αSyn results in increased levels of intracellular iron and iron redistribution from the cytoplasm to the perinuclear region within α-synuclein-rich inclusions (Ortega et al. 2016). Iron in both the ferrous Fe^{2+} and ferric Fe^{3+} states can bind directly to αSyn, but the ferric form has been shown to be more potent to accelerate the rate of αSyn aggregation and fibril formation (Uversky et al. 2001; Kostka et al. 2008; Levin et al. 2011). The aggregative effect of iron on αSyn can be enhanced by the presence of dopamine and hydrogen peroxide (Ostrerova-Golts et al. 2000). Phosphorylation of αSyn also augments the affinity of ferrous Fe^{2+} iron to the c-terminus of the protein (Lu et al. 2011). Interestingly, the 5′-untranslated region of αSyn messenger RNA contains a predicted iron responsive element (IRE) (Friedlich et al. 2007). Iron-responsive particles (IRPs) regulate translation and stability of IRE-containing mRNAs by binding to IREs located in the mRNAs. When iron is limited, IRPs bind with high affinity to IRE mRNAs and repress translation. When iron is abundant, IRPs bind to iron but not IREs, resulting in the translation of 5′ IRE-containing mRNAs (Anderson et al. 2012). Therefore, elevated iron levels could enhance αSyn protein translation (Lingor et al. 2017). These findings point to the important connection between αSyn and iron in the pathogenesis of PD and that the interaction of both can contribute to a vicious circle, in which increased αSyn levels result in iron accumulation and iron can hasten αSyn aggregation, although the chicken or the egg dilemma of which comes first remains perplexing (Lingor et al. 2017).

Iron deposition in experimental non-human primate models of PD

Several studies have examined changes of iron content in various animal models of PD to determine if the iron deposition in the SN is a primary or secondary event. In our previous studies, we generated a hemiparkinsonian model in cynomolgus monkeys by injecting 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) into the caudate or putamen unilaterally, and these monkeys developed a flexed posture and hypokinesia of the contralateral limbs a week after injection. We compared iron content in the SN and other basal ganglia structures by immunohistochemistry and observed a marked increase in iron staining in the ipsilateral MPTP-lesioned side, especially the SN but not in other basal ganglia structures such as pallidum, caudate and putamen. We also observed normal ferritin immunostaining on the injected side, indicating that iron accumulation is not related to altered metabolism of ferritin in this model (Mochizuki et al. 1994; Goto et al. 1996). Temlett et al. (1994) measured the total free iron concentration in a unilaterally MPTP-treated African Green monkey, which showed contralateral hemiparkinsonism. Iron, but not other trace elements, was significantly elevated in the SN of MPTP-lesioned side compared with the unlesioned side. Importantly, iron was found not only in the degenerating dopamine cells themselves, but also in the surrounding matrix and glial cells. A recent study reproduced these data by demonstrating elevated iron deposition in the MPTP-lesioned side SN of hemiparkinsonian model of cynomolgus monkeys using high resolution MRI (Li et al. 2020). Shi et al. (2019) further provided evidence that iron levels in the SN positively correlate with the pathological severity and motor deficits displayed by MPTP-injected monkeys. High iron may indicate and contribute to heightened MPTP-induced PD pathology in late or severe stages of PD, while depressed levels of iron may signal an early stage of disease. In a time-course study, He et al. (2003) investigated the changes in iron contents in

the SN and correlations of dopaminergic cell death progression with the process of iron accumulation in MPTP-induced parkinsonian monkey from day 1 to 18 months after MPTP administration. They demonstrated that apoptosis occurred in the ipsilateral SN at day 1 after MPTP injection and the number of TH-positive cells decreased significantly from 1 week onward. However, iron content was significantly increased in the ipsilateral SN from 4.5 to 18 months after MPTP injection, and the iron increase was significantly correlated to the extent of dopaminergic cell death. Taken together, these findings indicate that injury to the nigrostriatal system alone can induce iron accumulation in the SN and dopaminergic cell death precedes iron accumulation in the MPTP-lesioned monkeys, implying that iron accumulation may not be the primary event but the increased iron may contribute to the progression of nigral degeneration.

Iron deposition in PD

Over years, with advances in the magnetic resonance imaging (MRI) technology, there is accumulating evidence documenting the increased iron deposition in the SN of PD patients. Increased iron deposition was also found in other brain regions including putamen, red nucleus and globus pallidus (Kosta et al. 2006; Lewis et al. 2013; Wang et al. 2016; Takahashi et al. 2018; Langley et al. 2019). A longitudinal study further reported SN iron changes to be confined to its more ventral location in PD over three years. As pathology studies show the ventral SN to degenerate early and to the greatest extent in PD, the assessment of iron levels by quantitative susceptibility mapping in this area may potentially be used as a disease progression biomarker in PD (Bergsland et al. 2019).

Importantly, there is some evidence that iron load in the SN of PD patients correlates with motor disability. A few studies showed positive correlation of high UPDRS, rigidity and freezing of gait scores with iron accumulation in the SN of PD patients. Since the increased nigral iron accumulation in PD appears to be stratified according to disease motor severity, iron assessment may be useful for monitoring PD progression (Atasoy et al. 2004; Nadu-thota et al. 2017; Martin-Bastida et al. 2017). Increase in iron load has also been shown in the SN of Lewy body disease patients (Fernández et al. 2017). On the other hand, other works have shown lack of such changes in nigral iron contents in mild cases of PD (Riederer et al. 1989), in PD (Uitti et al. 1989; Galazka-Friedman et al. 1996) and between control and PD groups after age adjustment (Dashtipour et al. 2015). The lack of iron elevation in early-stage PD cases further supported that iron accumulation may not be an initial event, but take place along with disease progression.

Iron deposition in familial PD

A growing number of genes responsible for familial PD have been discovered. In some cases, iron accumulation in the SN has been reported. We have previously demonstrated iron staining was more intense in the SN of PARK2 patients who carry loss-of-function parkin mutations compared to that of control subjects and sporadic PD patients. Moreover, there were differences in the pattern of distribution of iron staining between PARK2 and sporadic PD (Takanashi et al. 2001). Although it is not well understood how parkin deficiency leads to iron accumulation, a role of parkin in regulating the divalent metal transporter 1 (DMT1), said to be the major transport protein responsible for iron uptake, has been implicated. Parkin, a E3 ligase, is responsible for ubiquitination of the 1B-DMT1 isoform. Overexpression of parkin results in a decrease in 1B-DMT1 isoform and a significant reduction in metal transport and toxicity. In addition, expression of the 1B-DMT1 was shown to be elevated in human lymphocytes containing a homozygous deletion of exon 4 of parkin and in the brains of parkin knockout animals (Roth et al. 2010). Therefore, parkin deficiency may increase iron entry to cell by increasing 1B-DMT1 level. Pertinently, a parkin mutation from PARK2 patients was found to render lymphocytes susceptible to iron-mediated apoptosis (Jimenez Del Rio et al. 2004).

PLA2G6, which encodes Ca^{2+}-independent phospholipase $A_2\beta$ ($iPLA_2\beta$) that selectively hydrolyses glycerophospholipids to release free fatty acid, is reported as the causative gene for PARK14-linked autosomal recessive early-onset dystonia-parkinsonism (Paisan-Ruiz et al. 2009). It is also the causative gene for infantile neuroaxonal dystrophy, neurodegeneration associated with brain iron accumulation and Karak syndrome (Khateeb et al. 2006; Morgan et al. 2006; Mubaidin et al. 2003). Patients with PLA2G6 mutations frequently exhibit brain iron accumulation. Meanwhile some do not (Yoshino et al. 2010). Beck et al. (2011) established an $iPLA_2\beta$ -knockout mouse model and discovered age-dependent iron deposition in the brains of these mice since the early clinical stages. DMT1 and iron regulatory protein 2 (IRP2) were upregulated in all examined brain regions of aged $iPLA_2\beta$-knockout mice compared to control mice. These findings suggest that the genetic ablation of $iPLA_2\beta$ increased iron uptake in the brain through the activation of IRP2 and upregulation of DMT1, a similar pathway as postulated for the case of parkin deficiency (Beck et al. 2011, 2015; Sumi-Akamaru et al. 2015). On the contrary, to investigate whether decreased $iPLA_2\beta$ activity was truly the cause of iron deposition, Guo et al. (2019) treated cells with

iPLA$_2$β antagonist and found decreased iPLA$_2$β activity led no obvious iron accumulation despite decreased iron uptake activity and increased iron storage activity. They proposed that decreased iPLA$_2$β activity may not be the main reason for iron deposition. Further studies are required to clarify the discrepancies among these studies.

Mutations in the ATP13A2 (PARK9), which encodes a lysosomal P5-type ATPase that plays important role in regulating cation homeostasis, lead to Kufor Rakeb disease, a form of autosomal recessive juvenile parkinsonism that features pyramidal signs, dementia, and supranuclear gaze palsy. Brain MRI revealed generalized cerebral atrophy and putaminal and caudate iron accumulation bilaterally in some affected individuals (Schneider et al. 2010; Santoro et al. 2011). In vitro studies have reported the relationship between ATP13A2 and iron. One study showed regulation of ATP13A2 via prolyl hydroxylase domain (PHD2)-hypoxia inducible factor 1 α (HIF1α) signalling is critical for cellular iron homeostasis. HIF1α coordinates the transcription of various cellular stress genes involved in iron metabolism and inhibition of PHD2 isoform prevents it from hydroxylating HIF1α for proteasomal degradation. This results in neuroprotective effects in various in vitro and in vivo PD models. ATP13A2 is a known HIF1α target. Therefore, PHD2 inhibition was found to result in increased expression of ATP13A2 while knockdown of ATP13A2 expression resulted in elevations in cytosolic ferrous iron levels, likely due to reduced ability to maintain lysosomal iron storage (Rajagopalan et al. 2016). On the other hand, overexpression of ATP13A2 renders cells more resistant to the iron-induced cytotoxicity. Moreover, the iron content in ATP13A2 expressing cells was lower than control cells expressing an inactive mutant of ATP13A2. ATP13A2 expression caused an enlargement of lysosomes and late endosomes and a reduced iron-induced lysosome membrane permeabilization, suggesting that ATP13A2 overexpression improves the lysosome membrane integrity and protects against the iron-induced cell damage (Rinaldi et al. 2015). These results constitute how loss-of-function mutation of ATP13A2 may underlie PD-related neuropathology. However, at this stage, it is difficult to conclude that there is a definite link between the genetic mutations in familial PD patients and brain iron accumulation due to clinical heterogeneity. Studying the alteration of iron contents in genetic models may enhance our understanding of the relationship of iron accumulation and neurodegeneration in PD.

Iron chelators for treatment of PD

Iron chelation has been introduced as a promising therapeutic concept for the treatment of neurodegenerative diseases with features of iron overload including PD. We previously reported that deferoxamine (DFO), a potent chelator of Fe^{3+}, prevented the toxic effect of iron–melanin complex on nigrostriatal co-culture (Mochizuki et al. 1993). Treatment with DFO was also found to efficiently alleviate behavioural deficits, increase the survival of dopaminergic neurons in the SN and striatum in an MPTP-induced PD mouse model, by upregulating the expression of HIF1α, TH, vascular endothelial growth factor (VEGF), and growth associated protein 43 (GAP43) and down-regulating the expression of α-synuclein, divalent metal transporter with iron-responsive element, and transferrin receptor (Guo et al. 2016). However, its poor oral bioavailability, short half time and difficulty of entry into the brain led to the discovery of another synthetic metal chelator, deferiprone (DFP), which is proved to be efficacious in MPTP-induced animal model of PD. In a pilot, double-blind, placebo-controlled randomized clinical trial, early-stage PD patients on stabilized dopamine regimens were enrolled in a 12-month single-center study with DFP. Early-start patients responded significantly earlier and sustainably to treatment in both substantia nigra iron deposits and UPDRS scores compared to delayed-start patients with safety maintained throughout the trial (Devos et al. 2014).

Several 8-hydroxyquinoline analogs also demonstrated considerable potential for the treatment of neurodegeneration in PD. Clioquinol, a lipophilic iron chelator, can reverse iron accumulation in the SN of MPTP-induced PD animal model (Kaur et al. 2003). Furthermore, treatment of transgenic mice overexpressing A53T αSyn with clioquinol prevents an iron–αSyn interaction, the formation of αSyn aggregates, αSyn-related cell loss in the SN, reduction in dendritic spine density of hippocampal and caudate putamen medium spiny neurons, and the decline in motor and cognitive function (Finkelstein et al. 2016). VK-28, another potent brain-permeable iron chelator, was able to protect neuronal cells against 6-OHDA-induced toxicity in rats (Ben-Shachar et al. 2004). Increase in nigral iron and monoamine oxidase B (MAO-B) activity are characteristic features of PD and hence the targets for treatment (Youdim et al. 2005). Rasagiline, with the propargylamine moiety, shows potent MAO-B inhibitory and neuroprotective activity (Youdim et al. 2001). The neuroprotective activity of propargylamines led to the development of several bifunctional iron chelators possessing propargylamine moiety (HLA-20 and M30) from the prototype iron chelator, VK-28. These compounds showed iron chelating potency comparable to DFO as well as MAO-A and B selective inhibitory and neuroprotective actions (Youdim et al. 2005; Zheng et al. 2005; Gal et al. 2005, 2010). These neuroprotective compounds with dual iron chelating and MAO-B inhibitory activity may be potential drug candidates for treatment of PD.

Conclusion

Studies in animal models of PD and patients suggest that iron deposition may not be an initiation process and yet increased iron is a major event that contribute to the progression of nigral degeneration. Although we cannot answer definitively what comes first in the pathogenic cascades of PD, the use of iron chelators has been proven efficacious in the rescue of neurodegeneration in different animal models, highlighting a pivotal role of iron as a mediator of neuronal death in PD. Recent advances in MRI techniques have the potential to usher the assessment of iron levels to be used as a biomarker for monitoring disease progression in PD.

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