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Review Article

Neurological Diseases Associated with Brain Iron Accumulation

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Abstract

Brain iron plays a very important role in maintaining normal physiological functioning and homeostasis. However, excess iron or dysregulated iron metabolism is a potent source of free radical formation and oxidative damage to neuronal and other brain cells. Abnormal high brain iron levels are associated with many neurological diseases like Alzheimer's disease, Parkinson's disease, Huntington's disease, Neurodegeneration with brain iron accumulation, Multiple sclerosis, Aceruloplasminaemia (CPM) etc. Here in this review we will focus on brain iron transport, dysregulated metabolism and the disease it causes.

Keywords: Brain Iron; Neurodegeneration; Neurodegenerative Mechanisms; Neuroinflammation; Mitochondria; Neuron; Cells; Iron Metabolism; Blood Brain Barrier; Blood CSF Barrier; Influx; Efflux

Abbreviation

DMT: Divalent Metal (Ion) Transporter; FPN: Ferroportin; CP: Ceruloplasmin; Heph: Hephaestin; SDR2: Stromal Cell-Derived Receptor; Nfts: Neurofibrillary Tangles; APP: Amyloid Precursor Protein; IRP-IRE: Iron Regulatory Protein-Iron Responsive Element; Fe: Iron; PANK: Pantothenate Kinase; FTL: Ferritin Light Chain; ROS: Reactive Oxygen Species; FRDA: Friedreich's Ataxia; FXN: Frataxin; ICH: Intracerebral Hemorrhage; GPX: Glutathione Peroxidase

Introduction

Iron is the most abundant metal in the brain [1,2]. It is responsible for many cellular activities like mitochondrial respiration, synthesis of myelin and even synthesis of neurotransmitter and its metabolism. Iron in brain plays a crucial physiological role in maintaining homeostasis [3,4]. Brain iron status is consistently maintained and tightly regulated at the level of the blood brain barrier (BBB)[5] and blood cerebrospinal fluid barrier(BCSFB) [6,7]. So it is very important for us to understand the impact of iron deficiency in development of brain and excess causing diseases which are mostly degenerative in nature [8]. May be detailed understanding the role of BBB and mechanism of transport of iron across it is vital.

The normal structure and function of the BBB is essential for brain iron homeostasis because the endothelial cells of the BBB are a regulatory site for brain iron uptake [9]. BBB endothelial cells can also regulate the two possible iron transport pathways[transferrin-bound iron (Tf-Fe) and non-transferrin-bound iron (NTBI)] by controlling receptor expression, internalization of transferrin receptor 1(TfR1) complexes, and acidification inside cell endosomes [10]. The mechanism involves two transmembrane steps: iron uptake into the microvascular endothelial cells at the luminal membrane (apical, on the blood side), followed by iron efflux into the brain interstitium at the abluminal membrane (basal, brain side) [6]. The accumulated evidence suggests that the Tf/TfR1 pathway is the major route or primary pathway for iron transport across the luminal membrane of the capillary endothelium [11] and that iron, possibly in the form of Fe2+, crosses the abluminal membrane and enters the brain parenchyma [12,13].

Apart from this two pathway there may be some other ways of transportation of iron in brain a)H-ferritin-mediated delivery of iron into the brain [14] b) transcytosis of Tf/TfR1 complexes through brain endothelial cells, leading to the release of iron from the abluminal side into the brain [15] c) lactoferrin-lactoferrin recep-

tor (Lf/LfR) [16] d) secreted melanotransferrin (p97)-glycosylphosphatidylinositol (GPI)-anchored p97(sP97/GPI-P97) [17].

Blood–Cerebrospinal Fluid Barrier (BCSFB) also separates systemic circulation from the brain parenchyma physically [6]. Tf/TfR1/DMT1 pathway may be of importance for iron transport across the BCSFB, and also that the export of iron from the choroid epithelium to the cerebrospinal fluid (CSF) is mediated by the Fpn1/CP or Fpn1/Heph pathways [7]. Once iron enters the interstitial fluid or ventricular CSF, it binds to apo-Tf, synthesized locally by the choroid plexus [11]. SDR2 is the only known ferric reductase expressed in the choroid plexus and that DMT1 is also present in the choroid plexus it is possible that iron reduction by this protein followed by DMT1-mediated absorption might be an alternative mechanism for iron transport across the BCSFB [18,19]. It is possible that the BCSFB is used more for iron removal from the brain than iron transport into the brain [20]. There is a diurnal variation of iron content in the ventral midbrain supporting the existence of mechanisms for iron export from the brain to the systemic compartment [21]. It has been suggested that the glymphatic system in the brain [22,23] may be one of the routes by which transition metals including iron are transported and cleared from the brain via convective bulk flow of interstitial fluid, possibly mediated by astrocytic end-feet-expressed aquaporin-4 (Aqp4) water channels [2]. Iron transport into the brain bypassing the brain barriers has also been suggested [24]. The circumventricular organs that receive a plethora of neuronal projections, mainly from hypothalamic nuclei, have been suggested to play a role in iron transport in the developing brain. Some motor neurons that project to peripheral organs devoid of a blood barrier express TfR1 and show retrograde axonal transport of iron into the brain [25].

Iron transport within the brain comprises of a) Tf-Fe and NTBI transport forms [11,24,26] b)uptake by neurons [27,28] c)uptake by oligodendrocytes [12] d) uptake by astrocytes [29] e) uptake by microglia [11] f) export from neurons [30], astrocytes [31], oligodendrocytes and microglia [32]. Fpn1 is the only known cellular iron expressed in neurons, astrocytes, oligodendrocytes, and microglia [32]. Transcriptional changes in Fpn1 mRNA were found to be mediated by hepcidin in differentiated neuronal-like PC12 cells subjected to iron challenge [33] and iron export through Fpn1 is modulated by the iron chaperone poly(rC)-binding protein 2 (PCBP2) [34]. CP, a critical ferroxidase, has been found in neurons and astrocytes [35], while another ferroxidase Heph is expressed in neurons [30], oligodendrocytes and microglia [32]. Iron efflux from the neuron is mediated by the Fpn1/CP and/or Fpn1/Heph pathways, from astrocytes by Fpn1/CP, and from oligodendrocytes and microglia by the Fpn1/Heph route.

Diseased caused by dysregulated iron metabolism

Alzheimer's disease (AD)

Elevated iron in AD brains was first reported in 1953 [36] and shown to be associated with senile plaques(SPs). Iron is enriched in both NFTs [37] and SPs [36]. Iron accumulation occurs in AD cortex, but not cerebellum. The iron storage protein ferritin binds most iron within the brain [38], and this protein increases with age and in AD [39]. APP-knock out mice exhibit iron accumulation in brain and peripheral tissues, and loss of APP ferroxidase activity in AD brain is coincident with iron retention in the tissue. Iron-export capability of APP requires tau [40].Tau has been implicated in axonal transport [41] and binds APP [42]. Loss of tau in mice causes age-dependent iron accumulation [40]. Genetic factors could also increase the susceptibility to iron burden in AD like Tf variant C2, Mutations in the hemochromatosis gene(H63D and C82Y).

Parkinson's disease(PD)

Several studies reported that iron deposition was increased in the substantia nigra (SN) according to the severity of the disease in PD patients [43]. In PD brain, histology studies showed that iron accumulate in neurons and glia in SN [44]. Furthermore, there are reports that a dysfunction in the IRP-IRE system that results in iron accumulation gave rise to alpha synuclein(a-Syn) induced toxicity [45,46], that led to pathogenesis in PD [47]. Similarly, in almost all PD patient brains the Lewy bodies contained aggregated a-Syn [48]. Cellular iron accumulation in PD brain may be caused by elevated influx or decreased efflux. Inflammation could contribute to iron accumulation by either increasing DMT1 uptake activity or TfR transport activity. In a mouse model, DMT1 activity was increased to mediate the iron uptake [49], and this increase may be due to direct S-nitrosylation of DMT1 [50]. In addition, the presence of LfR on neurons and the increased expression of LfR on iron-induced degenerative dopaminergic neurons in PD which may imply that an Lf/LfR-mediated pathway also may be involved iniron (Lf-Fe) uptake by neurons [51]. Ferritin can hold large amount of iron as compared to Tf and if this physiological pathway gets supersaturated with iron can lead to accumulation and nigral pathology [52,53]. The reduced expression of Fpn1 has also been connected with the activation of N-methyl-D-aspartate (NMDA) receptor (NR)-induced iron accumulation and neurodegeneration in dopamine (DA) neurons in Parkinson's disease [54].

Huntington's disease(HD)

Impairment in intracellular iron levels and energy metabolism are both features of HD pathogenesis as HTT has been reported to mediate endocytosed Fe(II) required for oxidative energy production [55,56]. Magnetic resonance imaging(MRI) studies suggest

changes in the metabolism of brain iron during early HD [57,58]. Post-mortem studies revealed increased levels of Fe(II) in the brains of HD individuals as compared to age-matched controls [59].

Neurodegeneration with brain iron accumulation (NBIA)

Neurodegeneration with brain iron accumulation comprises a number of pediatric and adult neurological diseases characterized by parkinsonism, dementia, and excessive iron accumulation in the basal ganglia [60]. Distinct genetic causes have been described within this disease spectrum yet no direct link between neurodegeneration and iron accumulation is proven. Mutations in PANK2, a gene implicated in coenzyme A biosynthesis, synthesis of lipids and citric acid cycle [61], results in panthoten kinase-associated neurodegeneration (PKAN).Though this mutation may not affect iron homeostasis directly, subsequent iron accumulation suggests that mitochondrial dysfunction may trigger iron dyshomeostasis. Although NBIA disorders are clinically characterized by the hallmark deposition of iron in the brain, for the majority of these disorders, this feature is a secondary consequence of the primary disease mechanism [62]. Detection of de novo mutations in WDR45—which encodes WD repeat domain 45, a β-propeller scaffolding protein with a presumed function in autophagy—in patients with β- propeller protein–associated neurodegeneration (BPAN) provides evidence of the association of defective autophagy with NBIA [63,64].

Multiple sclerosis (MS)

Iron content is elevated in deep grey matter structures and in the vicinity of lesions whereas it is reduced in the normal-appearing white matter (NAWM),and the extent of iron depletion correlates with disease duration. Furthermore, iron content is low in remyelinated plaques, suggesting that dynamic shuttling of iron continues throughout the MS disease process [65]. Elevated iron content has been detected using susceptibility MRI in deep grey matter structures, and is associated with increased disability and grey matter atrophy. In support of these MRI results, neuropathology of brain autopsy revealed substantial degeneration of deep grey matter structures, which corresponds with iron accumulation and oxidative damage [66]. Comparing measures from the same individual before and after death, changes indicative of iron accumulation detected by susceptibility MRI have been shown to correlate with increased iron content revealed by postmortem histopathology [67] or X-ray fluorescence [68]. In the vicinity of lesions, susceptibility MRI has revealed in vivo changes that are suggestive of iron deposition in areas that demonstrate myelin loss, focal iron deposits or both at autopsy [69,70]. Patients with MS show evidence of widespread mitochondrial damage [71,72], and the consequent increase in production of reactive oxygen species can promote iron-mediated oxidative damage that leads to progressive genomic damage and further impairment of mitochondrial function [73]. Oligodendrocyte progenitor cells (OPCs), which are implicated in remyelination in MS, have heightened susceptibility to metabolic stress compared with oligodendrocytes [74]. In MS, iron accumulates in macrophages and microglia around the rim of lesions, and these iron-laden cells show signs of dystrophy [75].

Aceruloplasminemia

Aceruloplasminemia is caused by mutations in CP, encoding ceruloplasmin [76], an enzyme that catalyzes the peroxidation of ferrous transferrin to ferric transferrin. Aceruloplasminemia presents in the third to fifth decade of life with a progressive motor disorder, dementia, diabetes mellitus, and retinal degeneration, with evidence of brain iron deposition in the basal ganglia [77]. Some of the mutant CP cell proteins that exhibit impaired copper incorporation are able to transform into a CP holoprotein in the presence of copper-glutathione, suggesting a disruption of the intracellular copper-loading process [78]. The culmination of these abnormal cellular processes is the inability to prevent internalization and degradation of ferroprotein, leading to defective iron efflux and increased intracellular iron [78-80].

Neuroferritinopathy

Neuroferritinopathy may present from adolescence to the sixth decade, commonly with a progressive extrapyramidal disorder with radiological features of iron deposition in the basal ganglia and cystic degeneration. FTL is one of the two subunits of the main intracellular iron storage protein ferritin, and mutations in the encoding gene FTL cause neuroferritinopathy [81]. Pathological analyses reveal abnormal nuclear and cytoplasmic ferritin inclusion bodies in glia and neurons of the CNS as well as in other organs in association with iron accumulation [82,83]. Furthermore, studies have found an increase in ubiquitinated proteins and redistribution of proteasome components to the site of ferritin inclusions [83]. Mouse model also showed altered gene expression profiles for proteins involved in iron homeostasis, including decreased TfR-1 (the mouse ortholog of human TFRC) and Irp1 (the mouse ortholog of human IRP1) as well as markers of oxidative stress, such as lipid peroxidation products, oxidatively modified proteins, and protein radicals [82]. Although abnormal FTL is able to coassemble with endogenous ferritin heavy and light chains, the resultant ferritin molecules exhibit reduced efficiency for iron sequestration. This

impairment in ferritin function results in an increase in the cellular labile iron pool along with enhanced ROS production, increased oxidized protein levels, and decreased proteasomal activity [84]. Defective FTL function affects normal iron metabolism, with secondary oxidative cell damage implicated as a mechanism in neurodegeneration.

Friedreich's ataxia

Iron relation was first evidenced for myocardial iron deposits in FRDA hearts [85]. Much later, iron involvement was recognized by the finding of deficiencies of aconitase and succinate dehydrogenase [86], both of which are mitochondrial iron–sulfur cluster-containing enzymes. FXN deficiency leads to mitochondrial iron overload, defective energy supply, and generation of reactive oxygen species [87].

Stroke

Growing evidence indicates that iron accumulation in neurons following ischemia increases brain susceptibility to iron-induced damage [88-90]. Red blood cell release and lysis have been considered the major factors mediating iron-induced brain damage after ICH [91]. Collagenase, which is commonly used to induce ICH, results in iron overload [92]. Moreover, iron overload may contribute to brain edema following ICH [93].

Amyotrophic lateral sclerosis (ALS)

A recent study firstly showed that the serum iron, ferritin, and transferrin saturation coefficient were significantly elevated in ALS patients, and the iron status was associated with body weight loss [94]. Serum ferritin may be a candidate biomarker for ALS aggravation [95]. Free iron level was also increased in the cerebrospinal fluid of ALS patients compared to controls [96,97]. A two fold increased level of inappropriate iron ligands in cerebrospinal fluid (CSF) was also found in patients with ALS, which may increase iron redox activity and reactive oxygen species production [98]. Autopsy study demonstrated that iron load in gray matter from the frontal cortex of ALS was increased significantly than that of controls [99]. The concentration of iron was also increased in the spinal cord of ALS patients [100-102]. Disruption in the expression of brain iron transporters such as lactotransferrin receptor, melanotransferrin, and ceruloplasmin is related to iron accumulation in ALS [103]. The deleterious effects on neuronal health and survival upon ablation of GPX4 in motor neurons might confer a role of ferroptosis to degenerative motor neuron diseases specially amyotrophic lateral sclerosis [103].

Sanfilippo syndrome

The reduced expression of Fpn1 has also been connected with the activation of N-methyl-D-aspartate (NMDA) receptor (NR)-induced iron accumulation and brain iron retention in Sanfilippo syndrome, a pediatric neurodegenerative disease [105].

Conclusions

Multifactorial cellular dysfunction is associated with iron dyshomeostasis in central nervous system resulting in iron accumulation. Mitochondrial dysfunction, protein misfolding and aggregation, autophagic-lysosomal dysfunction, neuroinflammation and ferroptosis are usually involved . Advances in MRI imaging techniques for specific detection of iron holds a great promise in future to consider iron as a biomarker for preclinical stages of neurodegeneration. Moreover, CSF levels of iron related proteins may aid in early diagnosis of sporadic neurodegenerative diseases in the future, like CSF ferritin in AD. However lot of questions has to be addressed in future regarding iron metabolism in human body right from brain sensing to different cells and pathways regulating iron content at intercellular level.

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