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Molecular targets and therapeutic interventions for iron induced neurodegeneration

Siddhi Bagwe-Parab, Ginpreet Kaur*

Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, SVKM's NMIMS, Mumbai-400056, Maharashtra, India

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ABSTRACT

Iron overload due to repeated blood transfusions in β-thalassemia patients or in predisposed diseases like hemochromatosis may prove lethal. Regulation and deposition of iron is a significant process, which is been explored extensively in the past decade. Iron deposition in the body can cause cellular dysregulation, including neuronal damage. Significant research has been conducted in understanding how iron accumulation in the brain leads to neurodegeneration. Iron chelators have been tested pre-clinically and are in clinical trials for determining their potential role in the treatment of neurodegenerative diseases like Alzheimerös (AD) and Parkinsonös (PD). It has been reported that iron chelators show promising effects pre-clinically in the amelioration of neurodegenerative disorders. In the clinical setup, the main challenge for any drug is to penetrate the blood brain barrier (BBB) and to show therapeutic action. Smaller anti-oxidant molecules that cross BBB, can be expended for the treatment of neurodegenerative disorders. This review exclusively presents an assessment of original research articles published from year 2017–2019. It also addresses the mechanism of brain iron accumulation focusing more on AD and PD, their genetic predispositions, the detrimental effects of iron overload leading to neurodegeneration, iron-induced neuronal apoptosis and treatment strategies for the same.

1. Introduction

Atypical iron accumulation in the brain has been detected in various neurodegenerative disorders. The mechanism of neurodegeneration caused by iron overload remains partially unclear. The diseases which are caused by genes responsible for iron overload are cumulatively termed as "neurodegeneration with brain iron accumulation' (NBIA) diseases" (Rouault, 2016). However, some reports claim that, diseases like AD and PD also have iron accumulation as one of the causative factors for pathogenesis (Nikseresht et al., 2019; Qu et al., 2019). Recent studies have displayed the postmortem MRI reports of patients with early or late-onset AD to demonstrate the presence of iron in the amyloid plaques and cortical region of the brain (Bulk et al., 2018; Chen et al., 2018; Gong et al., 2019). Also, a study on parkinsonian patients suggests the severity of the disease associating it with high iron content in the motor-related subcortical nuclei and nigral iron content with dopaminergic neurodegeneration (Martin-Bastida et al., 2017).

Abbreviations: AD, Alzheimer disease; ADP, Adenosine diphosphate; AKT/PKB, Protein kinase B; APAF1, Apoptotic protease activating factor 1; APP, Amyloid precursor protein; ATP, Adenosine triphosphate; Aβ, Amyloid beta; BAX, BCL2 Associated X, Apoptosis Regulator; BBB, Blood Brain Barrier; C19orf12, Chromosome 19 Open Reading Frame 12; CBD, Cannabidiol; COASY, Coenzyme A Synthase protein gene; CP, Ceruloplasmin gene; CUL4, Cullin 4 gene; DCAF17, DDB1 and CUL4 Associated Factor 17 gene; DDB1, Damage Specific DNA Binding Protein 1; Dex, Dexmedetomidine; DFO, Desferrioxamine; DNA, Deoxyribonucleic acid; DNA, deoxyribose nucleic acid; EDTA, Ethylenediaminetetraacetic acid; FA2H, Fatty Acid 2-Hydroxylase protein gene; Fe, S– Iron sulfur clusters; Fpn, Feroportin; Ft, Ferritin; FTL1, Ferritin Light chain 1 gene; FXN, Frataxin gene; GLRX5, Glutaredoxin-related protein 5 gene; GSK3β, Glycogen synthase kinase 3 beta; GTPB2, GTP-binding proteins 2 gene; HSPA9, Heat Shock Protein Family A (Hsp70) Member 9 gene; IL, Interleukin; IRE, Iron response element; IRP, Iron response proteins; ISCU, Iron-sulfur cluster assembly enzyme gene; LYRM4, LYR motif containing 4 protein gene; MAPK, Mitogen-activated protein kinase; MFRN2, Mitoferrin-2; MRI, Magnetic resonance imaging; mTOR, Mammalian target of rapamycin; NBIA, Neurodegeneration with brain iron accumulation; NFS1, Cysteine desulfurase enzyme gene; NFT, Neurofibrillary tangles; P13K, Phosphoinositide 3-kinase; PANK2, Pantothenate kinase 2 protein gene; PARP, Poly (ADP-ribose) polymerase; PLA2G6, Phospholipase A2, Group VI protein gene; RNA, Ribonucleic acid; ROS, Reactive Oxygen species; SCP2, Sterol Carrier protein 2 gene; TNF, Tumor necrosis factor; TPP, Triphenylphosphonium; UTR, Untranslated region; WDR45, WD repeat-containing protein 45 gene

* Corresponding author at: Department of Pharmacology, SPP School of Pharmacy & Technology Management, Narsee Monjee Institute of Management Studies, V.L. Mehta road, Vile Parle (W), Mumbai, 400056, India.
E-mail address: Ginpreet.Kaur@nmims.edu (G. Kaur).

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1.1. Manifestations of Iron overload

As the metabolic rate in the brain is high, it has abundant non-heme iron. Iron in the brain is majorly concentrated in the basal ganglia and substantia nigra. The iron content in these areas, is almost equal to the level of iron in the liver (Haacke et al., 2005). If there is a systemic iron imbalance, the BBB protects the brain from the same. Therefore, the brain is least affected if there is systemic iron imbalance. As the BBB is made up of tight junctions, the transfer of iron to the brain is mediated by Transferrin, Divalent metal transporter 1 and Ferroportin (Fpn) receptor pathways. Fe^{2+} which is released by Fpn at the endothelial tight junction of BBB, is oxidized by Cerruloplasmin. This is then taken up by transferrin which circulates in the brain. The iron in the brain is circulated and transported via molecules like ATP, ascorbate and citrate (Ke and Qian, 2007).

The pathologies that are known for AD are mitochondrial dysfunction, Brain metal overload, compromised glial cell function, neuroinflammation, and oxidative stress (Von Bernhardi and Eugenin, 2012). These mechanisms likely have intersecting pathways. Interestingly, iron is found to be playing a role in all the pathways responsible for the pathogenesis of AD. The levels of iron in the brain increase with the increasing age. This proves the increased levels of iron in the brain of AD patients. The accumulated iron contributes to the formation of Aβ plaques or is bound to ferritin which is located in the glial cells (Smith et al., 2007). Also, iron accumulation leads to the formation of Neurofibrillary tangles in turn causing lipid peroxidation and oxidation of proteins and DNA. The increased oxidative stress damage the neurons, as they are highly vulnerable to oxidative stress. (Smith et al., 1997). Aβ has a high affinity to iron. Also, due to accumulated iron, the ferroxidase activity of APP is impaired leading to the formation of Aβ peptides. Therefore, this is a vicious cycle which leads to the formation of Aβ in outsized amount (Huang et al., 2004; Duce et al., 2010). Many studies suggest that Aβ is synthesized under normal physiological process. The Aβ toxicity occurs due to iron which binds to histidine residue N-terminal domain at 6, 13, and 14. Also, there is a reduction reaction of iron by methionine located at residue 35, which leads to an increase in oxidative stress. (Butterfield and Kanski, 2001)

Iron plays a critical role in various brain functions, as it can gain and lose electrons easily. At the cellular level, iron significantly assists in cell growth. However, its accumulation in the cells can induce oxidative stress and can cause dysfunction of the cellular physiology (Fillebeen et al., 1999). Blood brain barrier (BBB) limits the entry of extra iron in the brain via highly regulated transport systems. In the case of iron overload, the BBB can disrupt to facilitate the excess entry of iron in the brain (Hentze et al., 2004). Increased iron levels in the brain can cause severe neurodegeneration. The ability of Iron to donate electrons to oxygen can lead to increased levels of hydroxyl anions and free radicals. Peroxyl/alkoxyl radicals are also generated due to Fe^{2+}-mediated lipid peroxidation. The generation of these reactive oxygen species (ROS) can impair the cellular organelles and macromolecules such as DNA, proteins and lipid matrix. In the normal conditions, these ROS are eliminated by several antioxidant defense mechanisms to avoid the impairment.

However, when the levels of iron increase beyond the antioxidant defense systems, the oxidative stress is induced. This, in turn, exacerbates the positive feedback mechanism which releases more iron bound to ferritin (Ft), iron-sulfur (Fe-S) clusters and heme proteins (Gammella et al., 2017; Li et al., 2018). This causes iron overload and thus accelerating the neurodegeneration. In neurological diseases like AD, PD and Huntington's disease; iron accumulates in various parts of the brain such as the hippocampus, cortex, basal ganglia, substantia nigra etc. Also, iron accumulation has been reported in the neurons and neuronal organelles (Stankiewicz and Brass, 2009).

Numerous researchers are experimenting to bring down the iron deposits in the brain. The pathological hallmarks of AD include amyloid β peptide (Aβ) plaques, neurofibrillary tangles of tau (NFT)/ tau phosphorylation, and brain iron overload (Sohre and Moosmann, 2018). It has been reported that the Aβ aggregation in the brain is triggered by excessive exposure to metals such as iron, zinc and copper (Kim et al., 2018). Several preclinical studies have implied the role of these metals in the activation of CDK5/p25 complex and GSK-3β kinase, thus leading to phosphorylation of tau (Kitazawa et al., 2009; Sun et al., 2012; Guo et al., 2013). As iron is responsible for the formation of Aβ plaques and Aβ plaques are responsible for the propagation of AD, it can be postulated that iron is one of the responsible factors for stimulating AD (Atwood et al., 1999). Some preclinical studies have demonstrated the role of iron in the formation of Aβ plaques (Meadowcroft et al., 2009). Also, oxidative stress caused by iron overload exaggerates the formation of senile plaques and NFT, thus increasing the cognitive decline. A study has also demonstrated that iron not only promotes the formation of Aβ plaques but also regulates its production from amyloid precursor protein (APP) (Quintana et al., 2006). Aβ peptides are formed when APP is cleaved by β- and γ-secretases in the amyloid genesis. These Aβ peptides aggregate and form Aβ plaques in the vicinity of iron. The translation of APP for the formation of Aβ plaques is also regulated by intracellular iron via IRE RNA stem loop present in the 5′-UTR of the APP transcript. This APP IRE binds with IRP2 in the neurons to increase the expression of APP, in turn increasing the Aβ plaques (Liu et al., 2018; Uranga and Salvador, 2018). A recent study has reported the role of mitochondrial ferritin in the depletion of the labile iron pool. In Aβ25-35 exposed neurons, overexpression of mitochondrial ferritin decreased oxidative stress and averted cytochrome c release from mitochondria by activation of mitogen-activated protein kinase (MAPK) pathway. The reduction in oxidative stress and cytochrome c expression aided in inhibition of neuronal apoptosis (Yang et al., 2015).

The current drugs therapies which are available for the treatment of AD and PD do not modify the disease but only give symptomatic relief. Also, there are other hindrances like; Lesser drug reaching the brain due to the presence of Blood Brain Barrier (BBB), reduced bioavailability of the drug due to first-pass metabolism, extensive side-effects due to site non-specificity, toxicity of drugs etc. (Tonda-Turo et al., 2018). There is an unmet need for discovering potential drug candidates to ameliorate neurodegeneration. The current drugs for AD are developed on the basis of conventional pathology of neurodegeneration, therefore this review investigates manifestations of iron overload leading to neurodegeneration and proposes therapeutic interventions based on same mechanism.

2. Oxidative stress due to iron overload in the brain

All the metabolic processes in the body lead to the generation of ROS. However, various repair/detoxifying mechanisms attenuate the generation of ROS and undertake a repair mechanism for the normalization of the damage caused by the same. If the threshold of the ROS formation is breached, then it becomes difficult to mitigate the damage caused due to oxidative stress and further impair the intracellular molecules like DNA, nucleic acids, proteins, lipids etc. (Fig. 1) (Gutteridge and Halliwell, 2018). Oxidative stress is reported to play an important role in the damage caused in the brain leading to the pathogenesis of neurodegeneration. Diseases like AD and PD are reported to be caused due to increase in oxidative stress (Thawkar and Kaur, 2019). The typical hallmarks in these diseases like neurofibrillary tangles, Aβ plaques have zinc, copper and iron as metal components. These are responsible for the generation of ROS and thus induce damage (Cheignon et al., 2018). Iron is the main component in the formation of Aβ plaques. A recent study performed using 2D NMR obtained for the conjugation of iron with Aβ has suggested that the carboxylate group and the terminal amine of Asp1, Asp1-Ala2, His6-Asp7 (carbonyl bonds), His6 (imidazole ring), His13 and His14 are involved in the conjugation (Bousejra-Elgarah et al., 2011).

The colloidal form of iron, which is obtained from ferritin is present

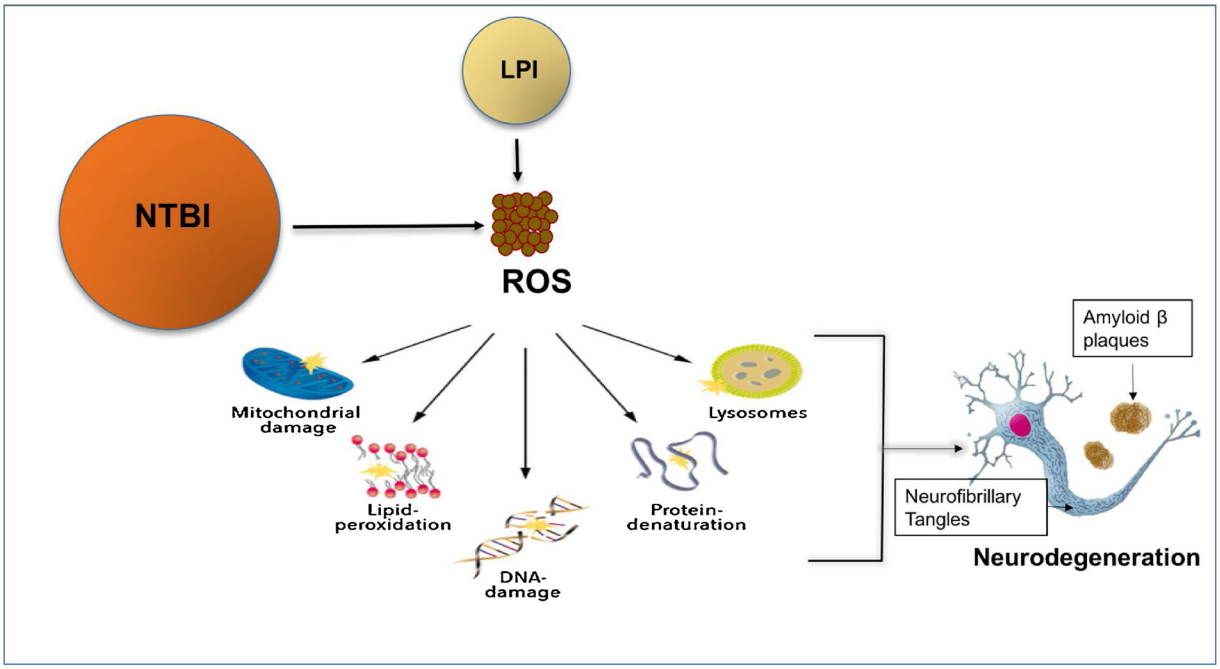
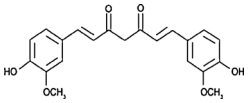
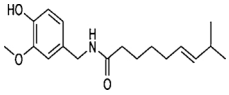
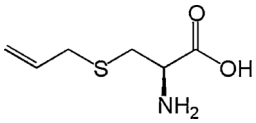
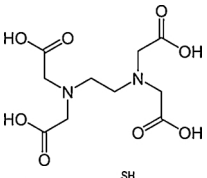
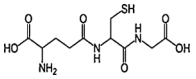
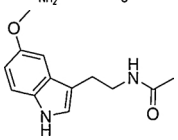


Fig. 1. Intracellular damage caused by Reactive oxygen species. (Gutteridge and Halliwell, 2018; Cheignon et al., 2018). Abbreviations: NTBI-Non-transferrin-bound serum iron; LPI: Labile plasma iron; ROS: Reactive oxygen species.

Table 1
Natural Anti-oxidants reducing brain iron.

Natural Anti-oxidants	Chemical structure	Oxidation potential	Fe^{+2} Chelating activity (%) in brain	Role in Brain	References
Curcumin		0.41	39	Curcumin has shown to decrease oxidative stress in rat brain induced by sodium fluoride	(Kiran Kumar et al., 2018)
Capsaicin		0.37	29	Capsaicin has shown reduction in oxidative stress and increase in dopamine in drosophila model of Parkinson's disease	(Siddique et al., 2018)
S-allylcysteine		—	17	Low temperature-aged garlic extract has shown positive effects in oxidative stress response in brain	(Hwang et al., 2019)
EDTA		—	78	EDTA chelation therapy has ameliorated neurotoxicity	(Alessandro and Elena, 2019)
Glutathione		0.60	—	Glutathione has shown to bind with copper ions thus reducing cytotoxicity and oxidative stress	(Saporito-Magriñá et al., 2018)
Melatonin		0.64	—	Melatonin has alleviated secondary brain injury induced by intracerebral haemorrhage via suppressing oxidative stress and inflammation	(Wang et al., 2018)

in the amyloid plaques. It is also reported that Fe^{+3}-Aβ complex is not stable, therefore it is converted to $Fe^{+3}(HO)_3$ and precipitate is formed. However, the Fe^{+2}-Aβ complex is stable and thus leads to ROS production (Smith et al., 1997). Anti-oxidants which can cross the Blood brain barrier (BBB) can be utilized for alleviating the oxidative stress caused by iron overload. Natural antioxidants like curcumin, capsaicin, epigallocatechin gallate, S-allyl cysteine etc. can be beneficial in the reduction of oxidative stress (Table 1).

Recent research has demonstrated the anti-oxidant effects of capsaicin, curcumin and S-allyl cysteine in rat brain homogenate. Ferrozine assay and electrochemistry were employed for testing the Fe^{+2} and Fe^{+3} chelation respectively. It was studied that; these compounds were effective in mitigating the lipid peroxidation induced by Fe^{+2} (Dairam et al., 2008). These compounds can be further tested for the treatment

Table 2
Function of Fe-S cluster regulating proteins in the brain.

Protein	Gene	Location	Function	Diseased condition	Brain research	References
Frataxin	FXN	Chromosome 9	Assists in the assembly of iron-sulfur clusters	Friedreich's ataxia	Delivering frataxin to the tissues by coupling the protein to trans-activator of transcription (TAT) peptides-mitochondrial targeting sequence (MTS)-Frataxin (FXN) (TAT-MTScs-FXN) decreased neurite degeneration	(Britti et al., 2018)
Glutaredoxin 5	GLRX5	Chromosome 14	Bio-genesis of iron-sulfur clusters	Pyridoxine-refractory sideroblastic anemia	Upregulation of Glutaredoxin-1 leads to activation of Microglia and Promotes Neurodegeneration	(Gorelenkova Miller et al., 2016)
Iron-sulfur cluster assembly enzyme	ISCU	Chromosome 12	Encodes Fe-S cluster protein involved in [2Fe-2S] and [4Fe-4S] cluster synthesis and maturation	Exercise intolerance	Hypoxia Rescues the loss of Frataxin by Restoring the Fe-s Cluster Biogenesis	(Ast et al., 2019)
Mitochondrial 70 kDa heat shock protein/ Mortalin	HSPA9	Chromosome 5	Encodes a heat-shock cognate protein which helps in cell proliferation and maintenance of mitochondria	Even-Plus Syndrome, Sideroblastic anemia.	Mortalin levels are downregulated in astrocytes and other brain tissues in Parkinson's disease	(Singh et al., 2018)
Cysteine desulfurase	NFS1	Chromosome 20	Supplies inorganic sulfur to form Fe-S clusters	Combined Oxidative Phosphorylation Deficiency 19 and Xanthinuria.	Zinc (II) binding on human *WT* ISCU and Met140 variants modulate NFS1 desulfurase activity	(Fox et al., 2018)
LYR Motif Containing 4	LYRM4	Chromosome 6	Functionalization of NFS1 by forming tight functional complex	Combined Oxidative Phosphorylation Deficiency and Friedreich Ataxia.	Disruption of this gene negatively impacts mitochondrial and cytosolic iron homeostasis	(Fox et al., 2018)

of neurodegenerative disorders.

3. Aggravation of apoptotic pathway by Iron overload

Toxicity led by iron in the brain can cause the generation of reactive oxygen species, which in turn damages the mitochondria. Due to iron accumulation, there is a decrease in the Fe-S cluster synthesis, FPN1 expression, glutathione levels and an increase in activation of DMT1, TfR1 expression, ROS. Due to an increase in oxidative stress and decrease in glutathione levels, the complex 1 of mitochondria is blocked. Also, levels of inflammatory cytokines increase, which in turn induce mitochondrial dysfunction and iron accumulation. Thus, increase in overall oxidative damage irreversibly results in apoptotic death. Mitochondrial complex I dysfunction through a positive feedback loop triggers the apoptotic pathway leading to the production of pro-inflammatory cytokines. These cytokines (lL6, IL-1β and, TNF-α) in excess cause further damage and aggravate the apoptotic pathway (Urrutia et al., 2014). A recent study has shown anti-apoptotic effect of Dexmedetomidine (Dex), a highly selective α-2-adrenoceptor agonist on $FeCl_2$-treated SH-SY5Y cells. 20 μM Dex has exhibited down-regulation of pro-apoptotic proteins, activation of Caspase 3 and an increase in the levels of the anti-apoptotic proteins (Hu et al., 2019). Therefore, further research has to be conducted on compounds like Dex for the prohibition of neuronal apoptosis. This will, in turn, decrease neuronal death and prevent neurodegeneration.

Latest preclinical research utilized "Cannabidiol (CBD)" as a potential drug for the reversal of iron-induced neurodegenerative effects in neonatal and adult rats. Iron overload increased the levels of Caspase 3, Caspase 9, Apoptotic peptidase activating factor 1 (APAF1), Cytochrome c and cleaved poly ADP ribose polymerase (PARP). It was found that CBD withdrew iron-induced effects by recovering the levels of Caspase 3, Caspase 9, APAF1 and cleaved PARP as compared to the negative control group (da Silva et al., 2018). PI3K/AKT/mTOR pathway was found to be inactivated by iron overload. Compounds like Icariin have been tested, and have proved to attenuate PI3K/AKT/mTOR pathway which was inactivated by iron overload. It was stated that 1 μM Icariin was able to attenuate the elevated levels of Caspase-3 and BAX protein, induced by ferric ammonium citrate Guo and Ye, 2019.

Therefore, iron overload plays an important role in the maintenance of the apoptotic pathway. Increased levels of iron can cause dysregulation of apoptosis, in turn causing neuronal death.

4. Mitochondrial damage due to iron overload in brain

Mitochondrial respiratory chain which is located in the inner mitochondrial membrane is the main functional part of the mitochondria. This respiratory chain is responsible to carry out many metabolic activities. The complexes I-V present in the mitochondria are responsible for the phosphorylation of ADP to ATP by electron transfer mechanism (Bhat et al., 2015). Under normal physiologic processes, less than 5 % of ROS is generated mostly by the mitochondria. The ROS in the mitochondria are produced in the electron-transport chain at NADH complex and ubiquinone-cytochrome c reductase complex Nissanka and Moraes, 2018. The latter being main site for the production of ROS, these ROS produced in the mitochondria can damage the macromolecules like DNA, proteins, lipids etc. (Islam, 2017). Once the ROS damages the mitochondrial DNA, it becomes target for oxidative damage thus decreasing the expressions of specific proteins which are important for electron transport chain. Due to this, there is damage produced to the cell organelles, thus forming a vicious cycle and leading to cell apoptosis. Excessive oxidative stress on the mitochondria can also lead to disruption of Fe–S clusters thus subsequently lowering the mitochondrial energy production (Ghezzi and Zeviani, 2012).

Mitochondrial dysfunction plays an important role in the pathogenesis of neurodegenerative disorders like Alzheimer's disease,

Table 3
Genes responsible for neurodegeneration with brain iron accumulation disorders.

Gene	Functions	Involvement in neurodegeneration	Human disorders	References
PANK2	Present in the mitochondria, responsible for regulation of Coenzyme A formation. It is also utilized for fatty acid metabolism	Overexpressed mutations in human PANK2 proteins affected development and motor behavior of zebrafish embryos	1. PANK2 associated neurodegeneration mimic Tourette syndrome. 2. Hallervorden–Spatz Syndrome	(Rohani et al., 2018)
PLA2G6	arachidonic acid release, phospholipid remodeling, synthesis of leukotriene and prostaglandin, fas-mediated apoptosis, and transmembrane ion flux in glucose-stimulated β-cells.	Mutations in the Drosophila homolog of human PLA2G6 exacerbates psychomotor activity and neurodegeneration associated with age	1. PLA2G6 affects Vps26 and Vps35, retromer function and ceramide levels. 2. autosomal recessive neuroaxonal dystrophy	https://www.ncbi.nlm.nih.gov/gene/8398 (Iliadi et al., 2018; Lin et al., 2018)
C19orf12	encodes small transmembrane proteins, Ubiquitous expression in fat and brain	Heterozygous Mutation in C19orf12 cause Levodopa Induced Dyskinesia in Neurodegeneration with Brain Iron Accumulation	1. Spastic paraplegia 2. pallido-pyramidal syndrome 3. autosomal recessive Neurodegeneration with brain iron accumulation	https://www.ncbi.nlm.nih.gov/gene/83636#gene-expression (Blackstone, 2018; Hedera, 1993; Kruer et al., 2014)
COASY	Involved in membrane trafficking and signal transduction This gene encodes protein coenzyme A synthase (CoAsy) to carry out the biosynthesis of CoA from pantothenic acid	Down-regulation of COASY aids in the reduction of Bmp signaling, disturbs dorso-ventral patterning and modifies neuronal development in zebrafish	Pontocerebellar hypoplasia, type 12	https://www.omim.org/entry/614297 Khatri et al., 2016; Levi and Tiranti, 2019; van Dijk et al., 2018)
FA2H	Encoding of a protein which catalyzes the synthesis of 2-hydroxysphingolipids	Interaction between genetic mutations in PARK2 and FA2H causes a novel phenotype in childhood-onset movement disorder	1. Spastic paraplegia 2. leukodystrophy 3. Atherosclerosis	MIM#611026 (González-González et al., 2018; ; Köhler et al., 2018)
ATP13A2	Lysosomal cation pump; auto phagosome formation	Complete loss of ATP13A2 in mice causes sensorimotor deficits and accumulation of α-synuclein	1.Early onset parkinsonism, 2. dementia 3. Kufor-Rakeb syndrome 4. Neuronal Ceroid Lipofuscinosis	MIM#610513 (Inzelberg et al., 2018; Suleiman et al., 2018)
WDR45	Protein-protein interaction; Early autophagosome formation	Mutation in WDR45 causes neurological deterioration, early onset of parkinsonism, cognitive decline and seizures	β-propeller-associated neurodegeneration (BPAN)	MIM#300526
FTL1	exhibit ferroxidase activity which prevents undesirable oxidative stress, nucleation and mineralization of the iron stores	Dysfunction of FTL1 leads to iron deposition in motor cortex, basal ganglia, cerebellar and cerebral atrophy, parkinsonism	1. Neuro-ferritinopathy 2. Hyperferritinemia-cataract syndrome	MIM#134790 (Cadenas et al., 2019; Kuwata et al., 2019)
CP	An acute phase α2-glycoprotein regulates body iron homeostasis	progressive accumulation of iron in basal ganglia, Substantia Nigra, and the retina. Transgenic mice with Cp gene deletion exhibit age-dependent accumulation of non-heme iron in the brain.	Aceruloplasminemia	(Patel et al., 2002)
DCAF17	It is a nuclear transmembrane protein associated with damaged DNA binding protein 1 ubiquitin ligase complex.	Iron accumulation in Globus pallidus and in white matter	Woodhouse-Sakati syndrome	(Bettencourt et al., 2016)
GTPBP2	GTP-binding protein; a member of the GTPase superfamily is efficient in the binding of GTP or GDP	mutation in GTPBP2 in mice causes neurodegeneration, and retinal damage by iron accumulation	JABERI-ELAHI syndrome	(Jaberi et al., 2015)
SCP2	Intracellular lipid transfer protein	SCP2 mutations cause neurodegeneration with brain iron accumulation	Zellweger syndrome, Leukoencephalopathy	(Horvath et al., 2015; Levi and Tiranti, 2019)

Parkinson's disease, amyotrophic lateral sclerosis and Huntington's disease (Franco-Iborra et al., 2018). Pathological iron overload in the mitochondria can cause various diseases ranging from sideroblastic anemia to genetic defects such as mitochondrial protein translation. The Fe-S clusters in the mitochondria are responsible for various cellular functions for almost all cell types (Table 2). The iron levels in the cytosol are highly regulated by the iron regulatory proteins IRP1 and IRP2 (Angelova and Abramov, 2018). These proteins regulate the iron by sensing the levels of iron in the cell and binding to mRNA, to carry out metabolism of iron. An iron storage heteropolymer; ferritin and iron uptake protein; transferrin receptor 1, help in the regulation of iron. Mitochondria expresses mitoferrins which are iron uptake proteins belonging to mitochondrial carrier family.

MFRN1 is the mitoferrin responsible for the iron uptake in the mitochondria of erythroidal cells whereas, MFRN2 accounts for the iron uptake in the non-erythroidal cells [42]. Frataxin which is present in the mitochondria plays a role in the regulation of Fe-S cluster synthesis (Puccio et al., 2001). Mitochondrial dysfunction due to disruption of frataxin is also responsible to cause a disease called as Friedreich's ataxia. In the brain, it can affect the deep cerebellar nuclei adversely. A recent study on downregulation of mitoferrin expression in the Drosophila model decreased mitochondrial iron accumulation and reversal in neurodegeneration (Navarro et al., 2015). Iron chelators are being studied for its action on reduction in the mitochondrial iron. Mitochondria is the center of iron accumulation with the ability to generate free radical species by Fenton reaction. Iron chelators assist in chelation of accumulated iron and decrease the labile iron pool (Nuñez and Chana-Cuevas, 2018).

Therefore, iron chelators can be conjugated with the molecules having mitochondrial affinity to give a site-specific action. A recent study on the conjugate of Triphenylphosphonium (TPP) and desferrioxamine (DFO) has shown good iron chelation and anti-oxidant activity in comparison to DFO alone. TPP is a lipophilic cation with mitochondrial affinity which assists DFO, an iron chelator for achieving mitochondrial iron reduction (Alta et al., 2017). Similar strategy can be applied by conducting a comparative study between TPP and various iron chelators to evaluate which conjugate displays better action with less toxic effects.

5. Neurodegeneration with brain iron accumulation disorders (NBIA)

NBIA are neurodegenerative diseases which are genetically predisposed by the accumulation of iron deposition in the brain (Gregory and Hayflick, 1993). The targeted regions are mainly in the basal ganglia, like substantia nigra and globus pallidus (Arber et al., 2016). Also, other brain regions such as cortex and cerebellum can have iron deposits. NBIA are typically autosomal recessive, X-linked or autosomal dominant. The extrapyramidal symptoms include cognitive impairment, parkinsonism, dystonia, spasticity, neuropsychiatric abnormalities and retinal degeneration. NBIA causing genes are 15 in number, out of which 2 genes are exclusively carry out iron homeostasis, the other 13 genes are involved in subsequent metabolic pathways (Levi and Tiranti, 2019).

Aceruloplasminemia caused by alteration in the ceruloplasmin (CP) gene is the first ever disease to be discovered to cause neurodegeneration due to alteration in the iron regulation (Mukhopadhyay et al., 1998). It is an autosomal recessive disease affective 1 in 2,000,000 people. Aceruloplasminemia can be caused due to 50–51 different mutations in the CP gene. The location of CP gene is at chromosome no. 3q21-24 which encodes CP, functioning as a cellular iron exporter mediated by ferroportin (Kono and Miyajima, 2014). This disease is characterized by its typical hallmark of very low, undetectable levels of CP and high levels of serum ferritin (Gonzalez-Cuyar et al., 2008). Iron accumulation in neuronal and glial cells has been demonstrated in some neuropathological investigations (Kaneko et al., 2012). A recent clinical case report of a neurological patient in his 50 s diagnosed with aceruloplasminemia is suspected to have a novel homozygous mutation of the CP gene at exon 6 (c.1192-1196del, p.Leu398Serfs). Brain magnetic resonance imaging showed accumulation of iron in the basal ganglia, cortex, thalami and dentate nuclei. Laboratory tests showed low levels of haemoglobin, CP, transferrin and iron. Plasma ferritin levels were elevated beyond normal (Stelten et al., 2019). CP is responsible to regulate iron levels in the brain and prevents damage due to free radicals (Patel et al., 2002). Enzyme replacement therapy with CP is a recent strategy been researched for the treatment of aceruloplasminemia.

A preclinical research on CP-/- mice was conducted by administration of human CP to the mice. It was observed that, the essential proteins in the brain were restored leading to reduction in cerebral iron and improvement in motor co-ordination. This suggests that, enzyme replacement therapy can be a novel strategy for the treatment of aceruloplasminemia (Zanardi et al., 2018). The other genes with their potential role in the human brain is given is Table 3.

6. Role of Iron chelators for the treatment of iron overload induced neurodegeneration

Over the past decade, the use of iron chelators for the treatment of neurodegenerative diseases has gained attention. The mechanism of iron chelators is to chelate/bind iron and remove excess iron from the body. Therefore, same mechanism is applied in brain by keeping iron overload induced neurodegeneration into consideration. The iron chelators desferrioxamine, deferiprone and desferasirox which have been approved for its clinical use in β-thalassaemia are been expended for the treatment of neurodegeneration (Ward et al., 2015). There are several preclinical and clinical studies (Table 4), which have expended these iron chelators for the treatment of neurodegeneration. The dose of iron chelators should be minimum, so that it does not affect the iron levels in the other body tissues. The brain iron level should be monitored with the help of T2* MRI technique, while treating with iron chelators (Schenck et al., 2006). The iron chelators which are used, should have ability to cross the BBB, should be target specific to the site of iron accumulation and also should be capable of transferring the iron to biological proteins like transferrin.

7. Future implications

The mechanisms of iron mediated neurodegeneration in disease like AD needs to be explored further. Iron accumulation in the brain might be responsible for the induction of cognitive impairment, but the levels of iron in the brain do not typically rise to the levels observed in NBIAs. Ayton et al. describes that, there is a faster decline in cognition in AD brains with relatively higher iron levels but within normal ranges (Ayton et al., 2019). Therefore, in depth research has to be performed for finding the role of iron in the prognosis of neurodegeneration. Iron chelators have been utilised currently for the amelioration of accumulated iron (Alcalde et al., 2018). Good pre-clinical results are displayed for the same, but there are many drawbacks like non-specificity and excessive depletion of brain iron. Iron chelators can be conjugated with the compounds which can cross the blood brain barrier, so as to ease the entry of the drug in the brain. Also, mitochondrial specific cations like TPP can be conjugated with iron chelators to attain mitochondrial specific activity (Alta et al., 2017). As discussed previously, TPP and DFO conjugated molecule has shown good results in brain mitochondrial iron chelation as compared to DFO alone. TPP can be conjugated with naturally occurring low molecular weight which act as iron chelators as well as anti-oxidants, viz. flavonoids (Genistein, Flavan-3-ol), quinoline derivatives (8-Hydroxyquinoline, menadiol) etc.

Table 4
Iron chelators for the treatment of iron overload induced neurodegeneration.

Compound	Chemical Structure	Marketed name	Current use	Preclinical Studies	Clinical Studies	References
Desferriox amine		Desferal, DFO	Acute iron poisoning, Iron Chelation therapy for chronic iron overload due to blood transfusions for eg: in β-thalassaemia patients, Sickle cell leg ulcer (Orphan drug).	Intranasal formulation; 1. Improved cognition (dose 2.5 mg) in APP/PS1 mice 2. Decreased loss of memory (dose 0.24 mg), soluble Aβ40 and Aβ42 in cortex and hippocampus and GSK3β in APP/PS1 mice 3. Supressed iron induced tau phosphorylation (dose 6 mg) in APP/PS1 mice	An interventional, open-label, safety, tolerability, and dose-finding study for iron accumulation in the brain after brain haemorrhage with continuous reassessment (dose 7 mg/kg to 125 mg/kg) by IV Infusion. (NCT00598572)	Hanson et al., 2012; Fine et al., 2015; Guo et al., 2013; Clinicaltrials.gov, NCT00598572
Deferiprone		Ferriprox, L_1	Iron Chelation therapy for chronic iron overload	Oral solution of Deferiprone mitigated brain iron overload, neurotoxicity mediated by iron, oxidative stress, brain mitochondrial dysfunction, glial activation and hallmarks of Alzheimers (75 mg/kg/day).	A clinical trial is ongoing to investigate if Deferiprone (15 mg/kg BID orally) slows decline in cognition in the AD patients. (NCT03234686).Another trial on 38 (18 M/20 F) participants with superficial siderosis have shown that Deferiprone mitigated Hemosiderin Deposition in 8 participants (dose 30 mg/kg/day). (NCT01284127)	Sripetchwandee et al., 2019; Clinicaltrials.gov, NCT03234686; Clinicaltrials.gov, NCT01284127.
Deferasirox		Exjade, ICL670	Iron Chelation therapy for chronic iron overload	Invitro studies of Cyclodextrin-desferasirox conjugate have shown improvement in anti-oxidant activity and inhibition of metal (iron) induced protein aggregation with less cytotoxicity.	A non-randomized, single group assignment safety and efficacy study was carried out on patients with iron overload resulting from hereditary hemochromatosis. No results have been reported yet. (NCT00395629)	Gascon et al., 2019, Clinicaltrials.gov, NCT00395629

8. Conclusion

Iron accumulation has become a significant contributing factor leading to neurodegeneration. The factors include genetic and pathological predispositions which contribute to cognitive impairment. Treatment for the diseases like Alzheimer's and Parkinson's are now strategically implied by keeping iron chelation into consideration. Several preclinical models have been tested on these diseases, by keeping iron chelation into consideration.

The research on finding the treatment for Alzheimer disease is now not only limited to the hallmarks of Alzheimer's i.e Amyloid β plaques and Neurofibrillary tangles but, the newly emerging strategies include; mitochondrial regulation, anti-oxidant therapy, GSK3β inhibition, and iron chelation strategies etc. As, iron overload is also responsible for α-synuclein aggregation in parkinsonism, molecules like Rosmarinic acid, Hesperidin and nicotine are being tested positive for depletion of these aggregations (Getachew et al., 2019; Pinto et al., 2018; Swerdlow, 2018)

Gene targeted therapies can also be utilised for the amelioration of brain accumulated iron. Gene replacement or gene transfer approaches can be applied for targeted treatment approach (Hayflick et al., 2018).Gene silencing can be done by using novel drug delivery system methodology. Newer strategies like oral siRNA-encapsulated nanoparticles-in-microspheres can be tested for silencing the genes responsible for iron overload (Attarwala et al., 2018).

Immense research is being carried out for the amelioration of iron accumulation in the brain to treat neurodegeneration. Surprisingly, there are only handful of strategies that have successfully transitioned to clinical studies. Novel and clinically reliable approaches are necessary for the fruitful advancement in this area.

Declaration of Competing Interest

The authors declare no conflict of interest.

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