Chapter 5
The Critical Roleplay of Iron Neurochemistry in Progression of Parkinson's Disease

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1 Introduction

Metals such as sodium (Na), potassium (K), calcium (Ca), zinc (Zn), copper (Cu), manganese (Mn), iron (Fe), Aluminium (Al), nickel (Ni), and others played a role in human evolution. For the human body, iron is a vital trace element and a crucial component of metalloprotein. (Evstatiev & Gasche, 2012). It is also vital for normal physiological and metabolic functions of normal human functioning, such as transport of oxygen, synthesis of DNA, iron-sulphur cluster production, synthesis of neurotransmitter, and transfer of electron in the electron transport reaction, due to its specific chemical reaction features (Conway & Henderson, 2019; Lane et al., 2018; Ashraf et al., 2018). Iron is found in 3–5 g in the normal adult human being (Evstatiev & Gasche, 2012). Not only for the body, but Iron is also equally necessary for the appropriate development and activity of the brain. In body it is required for cell proliferation, DNA synthesis, the mitochondrial respiratory chain, and the generation of myelin and neurotransmitters (Connor & Menzies, 1996; Hoepken et al., 2004). Oligodendrocytes act as the storehouse for the most iron for myelin production in the neurons of the locus niger and surrounding areas (Connor & Menzies, 1996). Microglia, which operate as the brain's scavenger cells, have been found to collect iron and may contribute to neuronal cell death prevention (Oshiro et al., 2008; Toku et al., 1998). Astrocytes in comparison retain a lower physiological level of iron, have significant unutilized iron storage capacity, and might play a neuroprotective role from oxidative stress (Toku et al., 1998). When compared to astrocytes, oligodendrocytes, and microglia, research shows that

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neurons are more vulnerable to both iron shortage (Sengstock et al., 1992; LaVaute et al., 2001; Kress et al., 2002) and excess (Moos et al., 1998).

The iron spreading in the brain seem to be somewhat uneven, and those levels have been linked to age. As per histological and biochemical research, the Substantia Nigra and globus pallidus in normal human brains, as well as rats and monkeys brain, have the richest quantities of iron. A recent research that measured iron levels directly in typical human brain cells discovered that the putamen and globus pallidus had the greatest amounts, and that there was a powerful affirmative tie-up between iron levels in the basal ganglia and age.

Iron is plentiful in dopaminergic neurons of Substantia nigra as a fundamental part of tyrosine hydroxylase-dependent dopamine synthesis because it is required for tyrosine hydroxylase-dependent dopamine production as well as other enzymatic and non-enzymatic dopaminergic metabolic pathways (Hare & Double, 2016). Iron's accelerating function in the creation of harmful ROS through Fenton reaction comporising hydrogen peroxide might be explained by the discovery of significant brain labile nonheme high-spin complexes, which grow with age (Holmes-Hampton et al., 2012). This is due in part to monoamine oxidase's oxidative deamination of dopamine and the creation of smectic iron-dopamine complexes, which cause dopamine auto-oxidation and quinone generation. The Substantia nigra has a particular pigmentation due to the trapping of numerous potentially harmful compounds by neuromelanin. However, because the neuromelanin is site for toxins is eliminated in Parkinson's disease, (Hare & Double, 2016). The instable endogenous autooxidation byproducts of dopamine can severely disrupt mitochondrial complexes I and IV respiration. Due to the excessive energy requirement of independent pacemaking, the Substantia nigra may be particularly vulnerable to labile iron imbalances and ultimately resulting in ROS generation.

In recent years, an increasing number of researchers working on exploring the pathophysiology of Parkinson's disease (PD) have shown that oxidative stress caused by iron metabolism disorders, as well as the creation of reactive oxygen species (ROS), are linked to the degenerative process of the disease.

The second most reccurent neurodegenerative disease is Parkinson's disease. Older age is the sole definite prospect for development of the disease (Tanner & Goldman, 1996). In populations of European heritage, the male to female ratio appears to be more than one (de Lau & Breteler, 2006). loss of dopaminergic neurons (DA) in the Substantia nigra (SN) pars compacta (Forno, 1996), buildup of aggregates of protein synuclein known as Lewy neurites or Lewy bodies in the SN (Spillantini et al., 1997), and brain iron cumulation further on seen in non-PD brains of comparable age are all characteristic traits of Parkinson's disease (Sofic et al., 1988). Iron deposits have been seen in major brain areas, including the substantia nigra and globus pallidus, in both postmortem and imaging investigations. Noninvasive imaging investigations of PD patients verified elevated iron congregation in the SN and connected the size of the accumulated protein to the extremity of the disease (Gorell et al., 1995). Exposure to iron through food, work environment, habitation or other ways has been studied for its link to PD for these and other reasons.

This chapter summarizes the role played by iron in progressing pathology of PD, with a specific focus on the oxidative stress caused by normal iron heamostasis and its dysregulation, particularly abnormal expression of iron transporters, transferring receptors, and divalent metal transporter 1 (DMT1), as well as their relationship with PD pathological markers like Senile plaque.

2 Brain Iron Transport

2.1 Overview of Iron Movement across Brain

The blood-brain barrier and the blood-cerebrospinal barrier restrict the protein transferrin from reaching the brain under normal conditions (Jefferies et al., 1984; Crowe & Morgan, 1992). As a result, transferrin generated by oligodendrocytes and choroid plexus epithelial cells facilitates iron transport in the brain (Bloch et al., 1985; Bloch et al., 1987), with transferrin expression being prominent all through the brain. Transferrin in the bloodstream supplies iron to the brain via endothelial cells' transferrin receptor 1 at these cerebral barriers (Jefferies et al., 1984; Crowe & Morgan, 1992), and transferrin transport through these brain barriers is very slow compared to iron (Moos & Morgan, 1998). Iron absorption from transferrin in the rat brain is controlled at the entire animal level, with greater or decreased iron utilization by the tissues of the brain depending on whether the animal is iron deficient or iron loaded (Taylor et al., 1991). The modulation of transferrin receptor 1 transcription on the luminal endothelial cells of capillaries that constitute the blood-brain barrier is held responsible for this impact (Taylor et al., 1991). Iron fails to deposit in the brain under iron overload settings where non-transferrin-bound iron is present in the plasma, as revealed in a mouse hemochromatosis model (Moos & Morgan, 2000), as well as in hemochromatosis humans . Non-transferrin bound iron might bind to transferrin released by oligodendrocytes and choroid plexus epithelial cells in the outer cavity of the brain (Bloch et al., 1985, Bloch et al., 1987). Because neurons ingest diferric transferrin via receptor-mediated endocytosis, this binding is probably important. Non-neuronal cell types, such as astrocytes and oligodendrocytes, express relatively little transferrin receptor 1 in vivo, and may take up non-transferrin-bound iron by a non-transferrin receptor 1-mediated pathway. In vitro, however, enriched cultures of astrocytes, neurons, and glia were all able to absorb iron through non-transferrin-bound iron. Iron concentrations in the CSF fluid appeared to surpass transferrin's iron-binding capability, implying the existence of possibly hazardous non-transferrin-bound iron (Ma et al., 2021) . These findings were verified in rats, where anti-transferrin antibodies pretty much entirely precipitated iron in the plasma, a considerable fraction of iron was not precipitated in the cerebral fluid (Moos & Morgan, 1998). Anti-transferrin antibodies absorbed 80–93% of iron in cerebral fluid, while anti-ferritin antibodies absorbed 1–5% of it, depending on the age of the animal. When the rats were 15 days, 20 days, and 56 days old, no iron in the blood plasma went through a 30,000 molecular weight

cut-off filter, whereas the proportion of iron in the cerebrospinal fluid passed through the filter was 5%, 10%, and 15%, respectively (Ma et al., 2021). As glia (astrocytes, microglia and oligodendrocytes) have been indicated to be involved in brain iron utilization and the pathogenesis of PD, a brief overview of their roles is described below.

2.2 Astrocyte Iron Movement

Astrocytes are the most plentiful type of cells in the CNS, performing a range of biological functions such as cellular aid throughout CNS growth, ion homeostasis, neurochemical utilisation, neuromodulation, and neuroprotective effects, as well as being important stimulators of synaptic, neuronal, and cognitive function (Vasile et al., 2017). Astrocytes are thought to span 95% of the capillary surface of the blood-brain barrier, acting as an iron transport channel into the brain as well as regulating the process (Ma et al., 2021). DMT1 has been found in the end foot processes of astrocytes that come into touch with endothelial cells (Wang et al., 2001). The potential of astrocytes to receive iron through active contact with endothelial cells has been presented as a possible explanation for their apparent lack (or extremely low levels) of transferrin receptor 1 expression (Moos & Morgan, 2004; Moos et al., 2007). While DMT1 is implicated in iron uptake from non-transferrin iron substrates in working astrocytes (Pelizzoni et al., 2013), the Zn + 2 transporter ZIP14 [280] and resident transient receptor potential channels (TRPCs) in resting astrocytes (Pelizzoni et al., 2013) are two further non-transferrin-mediated iron uptake mechanisms in astrocytes. Because iron extent in the brain surpass transferrin's iron-binding capability, considerable nontransferrin-bound iron occurs (Moos & Morgan, 1998). 2 Transferrin is a protein that binds two iron atoms and distributes iron from the bloodstream to all parts of the body save sanctuary locations like the brain (Ponka et al., 1998). The blood-brain barrier and the bloodcerebrospinal barrier prevent transferrin from getting into the brain from the blood (Jefferies et al., 1984; Crowe & Morgan, 1992). Transferrin is generated locally in the brain (Richardson & Ponka, 1997). 3 The majority of iron absorption by cells is mediated through the interaction of diferric transferrin with the transferrin receptor 1, which is mediated by transferrin-bound iron uptake. While transferrin cannot pass the blood-brain barrier, DMT1 is involved in non-transferrin-bound iron absorption by astroglia in the brain. Other routes of non-transferrin-bound uptake, like via the Zn^{+2} transporter ZIP14, might potentially play a role. Iron is taken up by neuronal cells in the brain from locally produced transferrin (Bloch et al., 1985; Bloch et al., 1987). 4 Transferrin is initially generated by the liver to maintain iron homeostasis in the body. Transferrin is exclusively found in the brain since it is made by oligodendrocytes and choroid plexus epithelial cells (Bloch et al., 1985; Bloch et al., 1987). 5 Ascorbic acid levels in the blood are generally modest (approx 50 M) (Lane & Richardson, 2014. The levels of ascorbic acid in mammalian brains is believed to be up to 8 times that of plasma iron levels (200–400 M) (Covarrubias-

Pinto et al., 2015). By retaining ferrous iron, which limits redox cycling, this may reduce the toxicity associated with high non-transferrin-bound iron (Covarrubias-Pinto et al., 2015) 6 Ceruloplasmin, a ferroxidase found in the blood, is involved in systemic iron mobilisation. In the brain, a glycosylphosphatidyl inositol link connects a distinct ceruloplasmin to the plasma membrane, and it plays a role in iron efflux from astrocytes. Decreased iron release from astroglia caused by a conditional deletion of FPN1 inhibited oligodendrocyte precursor cell re-myelination. In addition, reduced iron release from astrocytes reduced the production of cytokines in microglial cells, which are implicated in re-myelination . Depending on the stimulation, astrocytes can become activated to protect or harm the body, with the chemicals produced by these cells having neurotrophic or inflammatory effects. In fact, astroglias have exhibited immunological and inflammatory functions that are comparable to those of microglia. The stimulation of astrocytes causes reactive astrogliosis, which can be common in atypical PD, and can be interfered by extracellular α-synuclein binding. Reactive astrogliosis serves to restrict disease and help repair. Astrocytes have also displayed qualities to remove and absorb extracellular α-synuclein, which may be helpful for SNpc neurons but may potentially lead to increased production of inflammatory cytokines such as interleukin-1 and tumour necrosis factor-1. High quantities of iron have been displayed to activate microglia and astrocytes, which may then act on dopaminergic neurons, causing neurodegeneration (Ma et al., 2021.

2.3 Oligodendrocytes (Transferrin Secretion)

When it comes to oligodendrocytes, it's widely known that they have an involvement in myelin production, and immunohistochemical investigations have shown that they not only express transferrin and ferritin, but they're also the major cells in the brain that stain for iron (Gerber & Connor, 1989; Todorich et al., 2009). There's additional evidence that oligodendrocytes can receive iron from ferritin in the interstitial fluid or cerebrospinal fluid via T cell immunoglobulin and mucin domain-containing protein 2 (Tim 2) (Todorich et al., 2008) however the relative relevance of this route vs transferrin is unclear. As a matter of fact, transferrin was found in oligodendrocytes, however no transferrin receptor 1 expression has been observed in these cells (Hill et al., 1985). However, reports of transferrin being discovered in oligodendrocytes in humans, rats, and chickens (Oh et al., 1986; Stagaard & Saunders, 1987; Connor & Fine, 1986; Connor & Fine, 1987) contradict this. This last result might indicate that transferrin is present within endosomes, or that these cells produce transferrin. It has been claimed that while oligodendrocytes can produce transferrin, it is not secreted, leaving only the choroid plexus to perform this job (Leitner & Connor, 2012). Transferrin, like transferrin receptor 1, is extensively distributed throughout the brain, and the distribution of transferrin receptors measured by 125Iodine-labeled transferrin and anti-transferrin receptor monoclonal antibody binding is nearly identical (Hill et al., 1985). Iron shortage causes hypo-

myelination regardless of the route of iron absorption by oligodendrocytes, suggesting that iron plays a key part in this process (Bae et al., 2020), with myelinating neurons and motor coordination improved in transferrin over-expressing transgenic mice (Saleh et al., 2003). Furthermore, it is well recognised that iron shortage throughout human development results in motor and behavioural problems that last into adult age, highlighting iron's critical role in the CNS (Kim & Wessling-Resnick, 2014). This is because of the pivotal role of iron in neuron activity, as evidenced by the existence of transferrin receptors (Moos et al., 1998).

2.4 Microglia

Microglia are macrophage-like cells that contribute to dopaminergic neuron degeneration in Parkinson's disease (PD) through inflammatory activation (Banati et al., 1998), which can occur after exposure to mutant and overexpressed α-synuclein (Su et al., 2009) or other inflammatory mediators like lipocalin 2 (Jang et al., 2013). Activated microglia, on the other hand, can play a neuroprotective role, with the two effects being reliant on distinct activation states, specifically the conventional M1 phenotype, which produces pro-inflammatory cytokines, and the M2 anti-inflammatory phenotype (Colton, 2009; Cherry et al., 2014). In rat neuron-microglia-astroglia cultures, iron has exhibited to cause particular and continuous dopaminergic neurotoxicity. Higher transcription and translation levels of the p47 and gp91 subunits of the superoxide producing enzyme, NADPH oxidase 2 (NOX2), result in increased ROS when microglia are activated by increasing iron levels. This reaction is noteworthy because iron exhaustion rather than iron loading has been playing a role up-regulate NOX2 expression in other cell types via a hypoxia-inducible factor-1 (HIF-1)-mediated mechanism (Yuan et al., 2011). Based on these findings, it's reasonable to assume that NOX2 expression is regulated differently depending on the type of cell.

3 Iron Metabolism in Brain

3.1 Absorption

Neurons and glia are the major types of cells that make up the brain. Neuromelanin is shown to retain iron ions for a extended period, and ferritin is the chief protein for iron storage in neurons. Astrocytes and microglia manufacture L-ferritin to stock iron ions in glial cells, while oligodendrocytes express L- and H-ferritin (Jiang et al., 2017). Nutrients, including iron ions, do not come into direct touch with cells in the Central Nervous System (CNS). The blood–brain barrier (BBB) and the blood–brain spinal cord barrier (BBSCB) distinguish the CNS from the systemic circulation. The BBB is a unique structure made up of ancillary foot of capillary endothelial cells,

peripheral skin cells, and astrocytes that rigorously controls what enters the CNS (Daneman & Prat, 2015; Camandola & Mattson, 2017). Holo-Transferrin (Holo-TF) is prevented from accessing the nervous system by the hydrophobic BBB. To cross the BBB, Holo-TF must get via the brain capillary endothelial cells. Holo-TF binds to the TfR1 TF receptor on the luminal surface of brain capillary endothelial cells and passes them via the bloodstream. The Fe^{2+} is transported out of the capillary endothelial cells via the FPN on the abluminal surface, where Fe^{2+} is oxidised to Fe^{3+} by ceruloplasmin (CP) (Rouault, 2013; Rouault & Cooperman, 2006). The transit of FPN-exported ferrous iron is aided by CP, which is expressed in astrocytes. TF is produced and released by glial cells in nerve cells, and plica choroidae cells drain iron ions into interstitial fluid and cerebrospinal fluid, which permeate across brain parenchymal tissue and interact to the TfR1 receptor on neuronal membranes. (Patel et al., 2002). Apo-Transferrin (Apo-TF) enters the bloodstream via arachnoid villi after releasing iron ions. Ferroportin (FPN) is managed by hepcidin in the system, though the origin of hepcidin inside the brain is unknown. It may penetrate the BBB into the brain to regulate iron metabolism (Fig. 5.1) (Daneman & Prat, 2015).

3.2 Storage

Iron Regulatory Proteins (IREBs) regulate the expression of related proteins at the cellular level to maintain brain iron homeostasis. The reduction in IRP2 expression causes an imbalance in iron levels of brain, although myelin iron remains unaffected. Brain iron balance will be disrupted by mutations in genes governing iron metabolism, which will impact myelin production. As discussed above the origin of hepcidin generation is unknown. It is unclear if it is generated in the brain or it permeates through the BBB after its production in hepatic cells. In a model of an inflammatory cell signalling cascade, inflammation stimulates microglia and increases the production of hepcidin by astrocytes; this signal obstructs the liberation of iron ions in neurons and finally making way for the neuronal cell death which further augment the discharge of different anti-inflammatory and pro-inflammatory substances at the same time, there is no activation of normal human microglia, and there is no signaling cascade between cells (Fig. 5.1) (Gerlach et al., 1994; Zecca et al., 2004; Peng et al., 2021).

3.3 Brain Iron Toxicity and Accumulation

With ageing, iron ions start to deposit in the CNS. The ferritin protein and the substantia nigra are the principal targets of iron ions. Iron ion buildup can cause

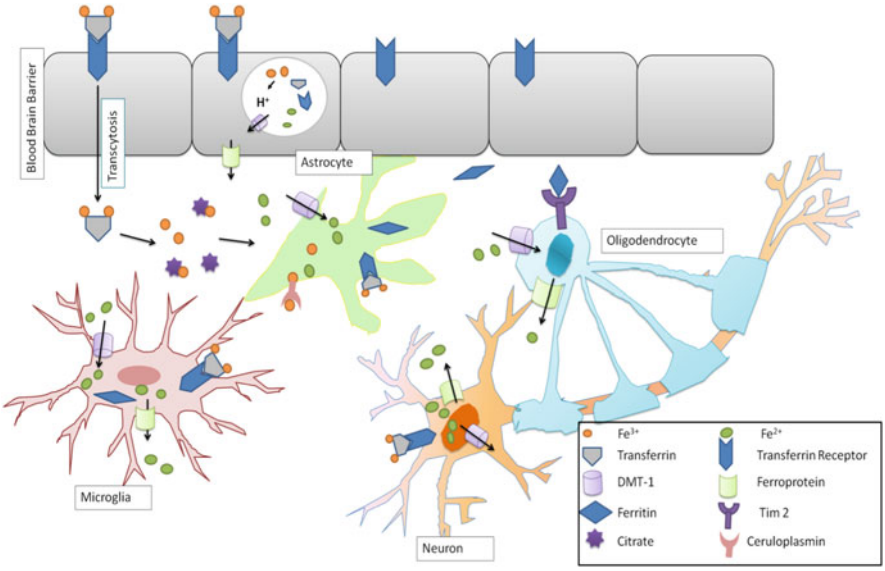

Fig. 5.1 Brain's iron metabolism. The Transferrin receptor (TfR) on the inner membrane of endothelial cells takes up transferrin (Tf) coupled to ferric iron (Fe^{3+}), and the Fe^{3+} bound Tf and TfR complex is internalised into endosomes. Duodenal cytochrome b converts Fe^{3+}-bound Tf to ferrous iron (Fe^{2+}). The divalent metal transporter l (DMT1) in the endosome membrane transports Fe^{2+} to the cytosol, and ferroportin l exports it into the extracellular matrix (FPN1). Tf is regenerated after Fe^{2+} release to bind to Fe^{3+} in the circulation. **1. Astrocytes:** Tf-TfR1 might allow astrocytes to absorb Fe^{3+}. Fe^{2+} absorption is aided by DMT1, Zip14, and TRPC. Cp may oxidise Fe^{2+} to Fe^{3+} and subsequently stimulate Fe^{2+} release via FPN1. Iron may be efficiently stored in ferritin. **2. Microglia:** DMT1-mediated iron import and FPN1-mediated iron export could transport Fe^{2+} in microglia. Microglia can also stock iron in ferritin and transfer Fe^{3+} ions to neurons via the Lf/LfR pathway. **3. Oligodendrocytes:** Oligodendrocytes store iron mostly in the form of ferritin or Tf. Oligodendrocytes have the ability to release Tf. The major mechanism for iron absorption is Tim2-induced ferritin uptake. **4. Neuron:** Tf-bound and non-Tf-bound iron (NTBI) are taken up by neurons. NTBI may also bind to citrate and ATP produced from astrocytes, allowing oligodendrocytes and astrocytes to get iron

neurotoxicity through a variety of methods. Excessive iron ion buildup will increase BBB permeability, cause inflammation, influence iron ion redistribution in the brain, and ultimately modify brain iron metabolism. When iron ions start to accumulate in the brain, they can act both as the electrophiles and neutrophiles., Fenton and Haber–Weiss chemical processes will create reactive oxygen free radicals. Protein oxidation, membrane lipid peroxidation, and nucleotide change can all be caused by free radicals. Oxidative stress occurs when ROS levels exceed the antioxidant capacity of organelles, causing damage to neurons and, in extreme situations, tissue deterioration. (Peng et al., 2021).

4 Gut Microbiota: A Bridging Stone Between Iron Metabolism and Neurodegeneration

In mammals, oxidized or reduced iron is absorbed mostly through the duodenum, which has a stringent absorption regulatory system. Remaining iron that escapes absorption in duodenum reaches the colon, which is abode to the number of gut microbiome, a collection of bacteria. Iron plays a pivotal role in the growth of intestinal microorganisms because it is a ferritin cofactor in redox processes, metabolic pathways, and respiratory chain of bacteria. As a result, the amount of iron ions in the colon cavity influences the configuration, multiplication, and living status of intestinal microorganisms, and changes in intestinal microbes have an effect on the host's health. The gut-brain axis, which includes neuronal, immunological, and metabolite-mediated pathways, has been found to interact between the digestive tract and the central nervous system in a rising number of studies. Preclinical and clinical research has revealed that the gut microbiota is important in the gut-brain interface, and that changes in gut microbiota composition are linked to the etiology of neurological illnesses, particularly neurodegenerative diseases (Peng et al., 2021). Studies have shown a correlation amongst the host microbiota (including bacteria of mouth and gut), neuroinflammation and neurodegenerative disease, which might be produced directly by invading microbes of the brain owing to barrier leakage, toxin and inflammatory factor production, or indirectly by immune responses being modulated. Furthermore, the microbiota composition influenced the deposition of α-synuclein (Mulak & Bonaz, 2015).

5 Biochemical Pathways Accelerating Iron Aggregation

5.1 Disabled Iron Discharge

Intoxication with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA) depletes ferroportin in parkinsonian models (Ward et al., 2014) tau function are depleted in the Substantia nigra in Parkinson's disease, culminating in neural iron accumulation and iron-dependent death of nigral neurons. (Ayton et al., 2013;, Lei et al., 2012) Ceruloplasmin may aid cellular iron outflow by ferroportin, and mice lacking this enzyme suffer deferiprone (DFP) rescuable age-dependent iron elevation and parkinsonism. (Ayton et al., 2013) Low ceruloplasmin activity has been seen in the Substantia nigra, cerebrospinal fluid, and serum of PD patients. (Ward et al., 2014) In Parkinson's disease, genetic variants in the ceruloplasmin gene are linked to parkinsonism (Lei et al., 2015) and SN hyperechogenicity (Ayton et al., 2013; Hochstrasser et al., 2005).

5.2 *Modified Iron Deposition*

Neuromelanin is expressed as an alternate "iron sink" to supplement neurons' restricted ability to store extra iron into ferritin molecules (Ward et al., 2014; Belaidi & Bush, 2016) However, in PD, such capabilities may be surpassed, resulting in increased ferritin immunoreactivity in Substantia nigra microglia (Belaidi & Bush, 2016 By functioning as a metastable storehouse for iron, enhanced concentrations of iron-loaded ferritin may contribute to age-related neurodegeneration. (Ward et al., 2014; Belaidi & Bush, 2016).

5.3 *Enhanced Iron Influx*

Single-nucleotide variations in Transferrin (Tf) and its receptor (TfR) discovered in PD case reports may have a protective role by altering Tf linked iron transportation into the cell. (Rhodes et al., 2014) Lactoferrin and its target might possibly be involved. (Faucheux et al., 1995a, b) Finally, elevated levels of the iron importer divalent metal transporter correlate with iron buildup in the Substantia nigra of patients and MPTP incuced model of PD mice. (Salazar et al., 2008).

6 Altered Neurobiology of Iron in PD

Many metabolic processes at cellular level are thought to be defective or disrupted in PD, including α-synuclein aggregation, Lewy body formation, ubiquitin–proteasome system malfunction, and oxidative stress, may be affected by iron.

6.1 *Abnormal Iron Homeostasis under Pathophysiological Condition of PD*

The pathophysiological mechanism of Parkinson's disease is regarded to have a significant impact on the mechanism of transport and storage of iron. A large number of data suggests that systemic metabolism of iron is aberrant in Parkinson's disease. In PD, serum markers of iron transport, such as transferrin or lactoferrin, are seen to be diminished, albeit the details of which transporter is changed vary between reports ((Logroscino et al., 1997; Grau et al., 2001). Iron culminated greater in the substantia nigra region in PD patients than in control cases in the brain (Martin et al., 1998). Because transferrin and lactoferrin are involved in iron absorption, researchers looked at their expression in Parkinson's disease. In individuals with PD, lactoferrin immunoreactivity is higher in afflicted dopamine releasing neurons in

comparison to normal controls, although transferrin levels are lower (Faucheux et al., 1995a, b). The increased immunoreactivity is only seen in locations where there is neurodegeneration, and it is not shown in cholinergic neurons in people with Parkinson's disease. The imprudent buildup of iron in dopaminergic neurons in individuals with PD might be due to enhanced levels of lactoferrin in the dopamine releasing neurons of substantia nigra. The significance of variations in systemic iron transport is unclear, although systemic abnormalities might readily indicate a core issue with iron homeostasis in PD. In Parkinson's disease, ferritin levels are also affected. The level of ferritin isoforms and their H/L ratio fluctuates depending on the pathological situation. Because of no established link between PD and changes in iron levels, the changes in PD are startling. Despite higher iron concentration in the brain region responsible for PD(substantia nigra), individuals with PD had decreased extent of both ferritin subunits (relative to similar aged control individuals) but no change in the H/L ratio in the substantia nigra was found (Connor et al., 1995). Increased iron absorption by another species in the substantia nigra in PD (such as neuromelanin or α-synuclein, as described below) or altered regulation of iron storage proteins as part of the pathophysiology of PD could define the absence of homeostatic adjustments in ferritin levels in response to changes in iron content.

6.2 *Interconnection Between Iron and Alpha Synuclein*

Lewy bodies, the hallmark characteristic of sporadic as well as familial PD, are made up mostly of alpha synuclein. Familial PD is caused by pathogenic translational mutations in the Syn gene (PARK1) and multiplication (duplications and triplications) of the Syn gene (PARK4). Syn had been discovered to have a special binding pocket for metals such as iron which are divalent in nature. Overexpression of Syn causes higher iron levels intracellular and iron redistribution from the cytoplasm to the perinuclear area within α-synuclein-rich inclusions in neuronal cells susceptible to excessive iron. Iron may bind directly to Syn in ferrous Fe^{2+} as well as ferric Fe^{3+} forms, however the ferric form has been shown to be more powerful in speeding up the rate of Syn aggregation and fibril formation (Wolozin & Golts, 2002; Ma et al., 2021).

6.3 *Ubiquitin–Proteasome System Induced Cell Death*

One of the primary pathways for the degeneration of cellular, nonmembrane-bound proteins is the ubiquitin–proteasome system (UPS), whose role is to establish adequate cellular concentrations of shortlived regulatory/functional proteins and to destroy unusual, misfolded, damaged, or toxic proteins reviewed in. Defects in, or overloading of, the UPS may result in harmful protein buildup, biological malfunction, or death. Under investigational circumstances of enhanced oxidative stress

and/or mitochondrial complex I inhibition, UPS overload or malfunction seems to develop (e.g., the rotenone rat model of PD). Furthermore, because Lewy bodies and Lewy neurites include not just α-synuclein aggregates, but also ubiquitin, parkin, and torsin A(an ATPase), there is some evidence that dysregulated UPS activity is at least a part of PD pathogenesis. The iron chelator desferrioxamine lowers the presence of ubiquitin-positive intracellular inclusions in the SN of mice, which suggests that iron may have a part in UPS dysfunction (Zhang et al., 2005). Furthermore, IREBs appear to modulate the mRNA of a 75-kDa mitochondrial complex I protein (Lin et al., 2001), which might impact function of mitochondrial complex-1, which is widely recognised for its harmful role in Parkinson's disease (Chen et al., 2019).

6.4 How Oxidative Stress Is Linked to Iron Imbalance

Dopamine oxidation produces hydrogen peroxide (H2O2). Iron is a powerful redox agent, and when it encounters H_2O_2, ferrous iron (Fe^{2+}) catalyses the Fenton reaction, which produces oxygen radicals (ROS) that raise the burden of cell's oxidative stress (Gerlach et al., 1994). In fact, when rat neuron cultures were exposed to the combination of Fe^{2+} and H_2O_2, cell survival was lower and free radical levels were higher than when the cultures were treated with a vehicle. The presence of free radicals is known to cause protein degradation, misfolding, and aggregation. Scientists have assessed the interconnection between free oxygen radicles and the human encephalon in depth, Because of its intensive usage of oxygen for different anabolic and catabolic activities and its relative lack of antioxidant and regeneration qualities compared to other organs, the brain is considered to be particularly vulnerable to free-radical buildup, particularly oxygen radicals (Andersen, 2004; Sayre et al., 2005; Mancuso et al., 2007).

ROS are produced by a variety of standard and deteriorated cellular pathways, including auto-oxidation of dopamine, disordered mitochondrial complex I, incorrect integration of extrinsic toxic substances, insufficient glutathione availability, and poorly stored or excess iron concentrations. Uncontrollable ROS manufacturing can cause damage to nuclear and mitochondrial DNA, lipid peroxidation, damaged or misfolded proteins, and aggregated proteins undetected by the UPS owing to incorrect ubiquitination. Iron may have a role in oxidative stress on several levels, including direct ROS generation, α-synuclein aggregation, interference with the UPS system's function, and other cellular processes in the brain (Carocci et al., 2018).

7 Ferroptosis —Cell Death Pathway in PD Utilizing Iron

A recently discovered iron-dependent cell death mechanism has important implications for Parkinson's disease pathophysiology. Ferroptosis appears to be caused by an iron-dependent strategy that incorporates lipid oxidation, glutathione peroxidases-4 depletion to modify glutathione defence, mitochondriopathy, and various morphological changes that are distinctive from other cell death mechanisms (e.g., apoptosis, necrosis, and autophagy) (Dixon et al., 2012) enhanced intracellular iron is related to enhanced transport of iron inside transferrin (Tf) via transferrin receptor (TfR) endocytosis, which is aided by α-synuclein, and increased import of Fe via the divalent metal transporter 1 (DMT1) (Zecca et al., 2005). Furthermore, b-amyloid precursor protein (APP) or ceruloplasmin destabilise ferroportin on the cell surface, impairing iron export (CP). The labile pool of iron is boosted when the storage proteins neuromelanin and ferritin are no longer able to securely store intracellular iron, which acts as a catalyst for the manufacture of phospholipid hydroperoxides. Glutathione biosynthesis requires cysteine absorption via the Xc antiporter (in oxidative circumstances) or the alanine, serine, cysteine–preferring (ASC) system (in reducing conditions) (GSH). Glutathione peroxidase 4 (Gpx4) reduces phospholipid hydroperoxides to their corresponding lipid-alcohols with the help of two GSH molecules, creating H2O and glutathione disulfide (GSSG) as side products. Increased intracellular iron levels combined with Gpx4 depletion, as shown in PD models, stimulate the formation of phospholipid hydroperoxides, resulting in membrane breakdown via a ferroptotic pathway. Depleting phospholipid hydroperoxides (ie, liproxstatin-1 or ferrostatin-1) or reducing the labile iron pool (ie, deferiprone) are therefore attractive strategies for suppressing ferroptosis in PD pathogenesis (Moreau et al., 2018).

8 Treatment Strategies for Parkinson's Disease Targeting Iron Homeostasis

8.1 Iron Chelators: A Promising Treatment for PD

Chelation of iron using different chelators has been proposed as a possible treatment strategy for the cure of neurodegenerative disorders with iron excess symptoms, such as Parkinson's disease. Previous studies have shown that the Fe^{3+} chelator deferoxamine (DFO) reduced the harmful effect of the iron–melanin complex in nigrostriatal co-cultures (Mochizuki et al., 1993). Therapy with DFO was also recognized to effectively cure behavioural abnormalities and enhance the survival rate of dopamine releasing neurons in the SN and striatum in mouse model of MPTP induced PD, by upregulation of the expression of proteins including HIF1, TH, vascular endothelial growth factor (VEGF), and growth associated protein 43 (GAP-43) and downregulating the expression of α-synuclein, DMT, and Tf

receptor. However, due to its poor pharmacokinetic profile orally, shorter half-life, and poor penetration in brain. Another artificial chelating agent, deferiprone (DFP), was discovered, which has been shown to be effective in an MPTP-model of PD. Developing PD patients on stable dopamine treatments were included in a 12-month single-center research using DFP in a pilot double-blind, placebo-controlled randomised clinical trial. Early-start patients reacted to therapy more sooner and more stable than late patients based on substantia nigra iron deposits and UPDRS scores, while safety preserved all through the trial. (Devos et al., 2014). Some 8-hydroxyquinoline analogues have indeed showed potential in the therapy of Parkinson's disease neurodegeneration. Clioquinol, an iron chelator with lipophilic properties, has been shown to revert iron buildup in the SN of MPTP-induced Parkinson's disease animal models (Kaur et al., 2003). Furthermore, clioquinol treatment of genetically modified mice model overexpressing A53T Syn prevents an iron–Syn interplay, Syn aggregate clustration, Syn-related neuronal loss in the SN, dendrites spine density reduction in hippocampus and caudate putamen intermediate spiny neurons, and movement and cognition decline. Another iron chelator which can penetrate brain, VK-28, was able to preserve neurons in 6-OHDA induced PD like symptoms in rats (Ben-Shachar et al., 2004). Increased iron in nigra region of brain and monoamine oxidase B (MAO-B) activity are both hallmarks of PD and hence therapeutic markers. Rasagiline has a powerful MAO-B inhibitory and neuroprotective effect due to the propargylamine moiety (Youdim et al., 2001). Because of propargylamines' neuroprotective properties, various bifunctional iron chelators with propargylamine moiety (HLA-20 and M30) were developed from the typical iron chelator, VK-28. These agents have properties to chelate iron like DFO, as well as MAO-A and B selectively inhibition and neuroprotection properties (Youdim et al., 2005; Zheng et al., 2005a, 2005b, 2005c; Gal et al., 2005, 2010). These chemicals provide neuroprotection, via dual mechanism i.e. iron chelating and MAO-B inhibitory action, might be used in treatment of Parkinson's disease. Summary of these compounds is discussed in Table 5.1.

9 Conclusions and Future Prospects

In the earth's crust, iron is a plentiful metal element. Iron's redox characteristics enable efficient electron transport, which is useful to a wide range of biological processes. However, When the adequate iron homeostasis is interrupted, such responsive qualities of iron may increase the production of reactive oxygen species (ROS), resulting in an overabundance of metal ions in the system. As an outcome, precise framework exists in organisms for iron uptake, stockpiling, and dispersion. Excessive iron buildup causes oxidative stress events, in high quantities, it can be hazardous to cellular components, especially body tissues and organs. Furthermore, iron is necessary for the creation of a myelin sheath in neurons as well as aerobic respiration in mitochondria. Whenever brain iron homeostasis is disrupted, iron is concentrated in various areas of the brain, causing oxidative stress, mediating

Table 5.1 Studies showing different iron chelators in treatment of PD

S. no	Compound	Nature	Phase of study	Conclusion	Reference
1.	Deferiprone	Synthetic	Phase-3 (NCT01539887)	Effective. Reduces iron levels but may not necessarily provide symptomatic relief.	Clinicaltrial.gov
2.	Deferoxamine	Synthetic	Pre-clinical	Efficacious against MPTP, 6-OHDA and rotenone and $FeSO_4$ induced PD like symptoms	Sangchot et al. (2002)
3.	Apomorphine	Synthetic	Completed (NCT02006121)	Effective. Reduces iron levels but may not necessarily provide symptomatic relief.	Clinicaltrial.Gov
4.	VK-28	Synthetic	Pre-clinical	Protects neuronal cells from the toxicity caused by 6-ohda. Additionally protects against lipid peroxidation caused by iron	Zheng et al. (2005a, 2005b, 2005c)
5.	Clioquinol	Synthetic	Pre-clinical	MAO inhibitory activity, in MPTP-induced Parkinson's disease, rescues iron-induced toxicity.	Kaur et al. (2003)
6.	M30	Synthetic	Pre-clinical	Protective effect due to MAO inhibition in 6-OHDopamine, MPTP and Lactacystine induced Parkinson disease	Gal et al. (2005)
7.	1-hydroxypyridin-2one	Synthetic	Pre-clinical	Neuroprotective effects due to hydroxamic acid in 6-OHDA induced Parkinson disease	Workman et al. (2015)
8.	HLA-20	Synthetic	Pre-clinical	Selective MAO-B inhibitor, neuroprotection in P-12 cell ines against 6-OHDA induced toxicity.	Zheng et al. (2005a, 2005b, 2005c)
9.	Quercitin	Natural	Pre-clinical	Neuroprotective effects in 6-OHDA	Lesjak et al., 2014,

(continued)

Table 5.1 (continued)

S. no	Compound	Nature	Phase of study	Conclusion	Reference
				induced Parkinson disease	Costa et al. (2016)
10.	Epigallocatachin gallate			Efficacious against MPTP, induced PD like symptoms	Reznichenko et al. (2010) Leaver et al. (2009)
11.	Curcumin	Natural	Pre-clinical	Neuroprotective effects in fisetin and 6-OHDA induced Parkinson disease	Singh et al. (2013)
12.	Silibinin	Natural	Pre-clinical	Efficacious against MPTP, induced PD like symptoms Inhibited alpha-synuclein oligomer toxicity in OLN-93 cell line	Lu et al. (2009)
13.	Phytic acid	Natural	Pre-clinical	Protects against MPP+ and 6-OHDA toxicity in normal and excess iron condition	Xu et al. (2008, 2011)

synuclein production via the Ubiquitin–proteasome pathway, and eventually leading to the development of Parkinson's disease. In Parkinson's disease, oxidative stress induced by iron buildup in neurons encourages the formation of Lewy body and alpha synuclein, which damages neurons and causes motor function losses, among other things. Although adopting iron-chelating techniques has shown some promise in terms of alleviating PD symptoms, further study is needed before the findings can be translated into clinical practise for the treatment of PD. Nonetheless, there has been little genetic research on iron-reduction measures in Parkinson's disease patients. There is a lot of room for more investigation into this type of treatment, given the expanding number of iron chelating drugs with potential disease-improving effects, as well as the availability of markers of iron load in MRI and CSF. Furthermore, genetic studies in model animals on the control of several critical genes in iron homeostasis have revealed the possibility of more efficient and accurate therapy. Iron's part in the pathogenesis of Parkinson's disease is generally acknowledged. Iron not only exacerbates the buildup of alpha synuclein and lewy bodies, but it also results in oxidative stress to neurons. Given the uniqueness and relevance of iron in the process of ferroptosis, future study should focus on determining how ferroptosis has a position in the molecular physiology of PD, which might lead to new insights into the illness and therapeutic suggestions. In light of the current discovery of a possible connection between iron, the host microbiota, and Parkinson's disease, it is expected that by research on the body's and brain's iron

metabolic mechanisms in greater depth, to improve or cure the condition, new and effective targeting and treatment procedures are needed. Will be discovered (Peng et al., 2021).

Conflict of Interests Authors declare no conflict of interests.

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