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Iron and manganese-related CNS toxicity: mechanisms, diagnosis and treatment

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Abstract

Introduction: Iron (Fe) and manganese (Mn) are essential nutrients for humans. They act as cofactors for a variety of enzymes. In the central nervous system (CNS), these two metals are involved in diverse neurological activities. Dyshomeostasis may interfere with the critical enzymatic activities, hence altering the neurophysiological status and resulting in neurological diseases.

Areas covered: In this review, the authors cover the molecular mechanisms of Fe/Mn-induced toxicity and neurological diseases, as well as the diagnosis and potential treatment. Given that both Fe and Mn are abundant in the earth crust, nutritional deficiency is rare. In this review the authors focus on the neurological disorders associated with Mn and Fe overload.

Expert commentary: Oxidative stress and mitochondrial dysfunction are the primary molecular mechanism that mediates Fe/Mn-induced neurotoxicity. Although increased Fe or Mn concentrations have been found in brain of patients, it remains controversial whether the elevated metal amounts are the primary cause or secondary consequence of neurological diseases. Currently, treatments are far from satisfactory, although chelation therapy can significantly decrease brain Fe and Mn levels. Studies to determine the primary cause and establish the molecular mechanism of toxicity may help to adapt more comprehensive and satisfactory treatments in the future.

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Keywords

iron; manganese; neurotoxicity; CNS diseases

1. Introduction

Iron is the second most abundant metal on the earth crust, while manganese is the fifth. They both are transition metals and have similar characteristics and functions. For example, they share similar brain distribution and common cellular transporters, including divalent metal transporter 1 (DMT1) [1], the transferrin (Tf)/transferrin receptor (TfR) system [2, 3, 4, 5] and the Fe exporter, Ferroportin (Fpn) [6]. They are essential cofactors for many proteins involved in the normal function of the brain. Fe is critical for oxygen transport, storage and activation, electron transport, DNA synthesis, mitochondrial respiration, myelin synthesis, neurotransmitter synthesis and metabolism [7, 8, 9]. Mn plays important roles in antioxidant defense, energy production, immune response and regulation of neuronal activities [10, 11, 12]. Ingestion is the primary route for Fe and Mn uptake [9, 10]. In adults, approximately 1–2 mg of Fe [13] and 1.8–2.3 mg of Mn [10] are absorbed daily. The systemic absorption of Fe takes place in the lumen of the small intestine through enterocytes [14]. After absorption by enterocytes, Fe interacts with transporter proteins, such as Tf/TfR and iron regulatory proteins (IRPs), and enters blood stream [8, 9, 15]. The brain-iron intake process involves multiple steps and is similar to Fe intake of enterocytes in the small intestine. The Tf/TfR system plays an important role in brain Fe uptake, which facilitates Fe transport across the blood-brain barrier (BBB) and neurons [14, 16]. Astrocytes have a pivotal role in the regulation of Fe homeostasis, acquiring Fe by DMT1 [14, 16]. Ferroportin mediates Fe export in neurons, while ceruloplasmin plays an important role in astrocytes. As a copper protein, ceruloplasmin can oxidize Fe (II) to Fe (III) and its deficiency leads to neurodegeneration secondary to Fe accumulation [16]. Mn shares similar transport mechanisms to Fe, except IRP [10, 12].

Given the multiple functions of Fe in the brain, insufficient Fe uptake or Fe deficiency is likely to disrupt normal neuronal activities, thus leading to a neurological disorder, referred to as restless legs syndrome (RLS) [17]; while Mn deficiency has been linked to epilepsy [18, 19, 20, 21]. However, excessive Fe and Mn accumulation in the brain is also harmful. High levels of Fe have been associated with Alzheimer's disease (AD), Parkinson's disease (PD), Friedreich's ataxia (FA), Huntington's disease (HD), aceruloplasminemia (ACE), neuroferritinopathy (NF), pantothenate kinase-associated neurodegeneration (PKAN), etc. In turn, Mn exposure has been associated with manganism, PD, attention deficit hyperactivity disorder (ADHD), depression, hepatic encephalopathy (HE), etc. Herein, we will review selected aspects of these neurological disorders focusing on their diagnosis and treatment.

2. Iron and CNS toxicity

Iron is essential for proper physiological activities of all living organisms. It is commonly found in the form of heme containing proteins, as a cofactor in Fe-sulfur cluster containing

proteins, and as Fe ion containing proteins [22]. Hemoglobin, cytochromes, catalases and peroxidases are examples of proteins that consist of heme Fe [23]. Their main function includes oxygen transport, activation and storage, electron transport and cellular respiration [23, 24]. In addition, prosthetic heme is involved in mitochondrial respiration, signal transduction and DNA synthesis [22]. Heme containing proteins that contribute to electron transport chain (ETC) include cytochrome bc1, cytochrome c, cytochrome c oxidase and succinate dehydrogenase [22]. Fe-sulfur clusters, Fe-oxo clusters and mononuclear Fe centers are the predominant forms of non-heme Fe found in proteins [24]. These proteins are vital in DNA synthesis, transcriptional regulation, cell division and differentiation [23, 24]. Brain requires high levels and constant supply of oxygen; thus, optimal Fe levels are critical for its proper function. In addition, Fe regulates neurotransmitter and myelin synthesis [25]. For example, Fe acts as a cofactor of tryptophan hydroxylase, tyrosine hydroxylase and phenylalanine hydroxylase, which are responsible for the synthesis of serotonin, dopamine (DA) and cholinergic neurotransmitters, respectively. Fe plays a role in emotion, cognitive and motor function [26]. Furthermore, Fe also mediates degradative processes associated with these neurotransmitters [27]. Monoamine oxidase (MO), which metabolizes these neurotransmitters, requires Fe for its function [27]. Moreover, oligodendrocytes, which have the highest Fe levels in the brain [25, 26, 28], are responsible for myelin production [26, 28]. Oligodendrocytes take up Fe from proximate blood vessels or from ferritin via its receptors [14, 16]. Researches have shown that Fe is a prerequisite for myelin synthesis [25, 26, 28] and Fe-deficient diets lead to hypomyelination [28]. Iron deficiency has been associated with a neurological disorder, named restless legs syndrome, which will be discussed later.

Despite the important roles of Fe in the brain, there is evidence supporting a strong link between high brain Fe concentrations and Fe-induced neurotoxicity, including several neurodegenerative diseases [29]. Defects in Fe metabolism cause Fe overload or accumulation, leading to high levels of the free metal (Fe(II)) [29]. MRI investigations have documented increased Fe concentrations in the brain of patients with several neurodegenerative diseases, such as AD, PD, FA, ACE, NF, HD, etc [16].

2.1. Molecular mechanisms of Fe-induced toxicity

The mechanism of Fe-induced toxicity is primarily related to oxidative stress. Iron's flexible character and redox potential allows it to easily switch between Fe^{2+} and Fe^{3+} [24]. Nonetheless, this becomes a disadvantage in case of Fe excess, when it becomes the cause of toxicity in aerobic environment [24]. In Fenton's reaction, the interactions between Fe and aerobic respiration products, such as peroxide and superoxide, lead to the formation of free hydroxyl radicals [23, 24]. As a result of oxidative stress, lipid peroxidation and carbonyl formation are upregulated. De Lima et al. investigated the long term effects of Fe treatment in postnatal Wistar rats [30]. Their results showed positive oxidative stress markers in the brain, including lipid peroxidation, mitochondrial superoxide generation and antioxidant enzyme activities [30]. Another group showed that Fe exposure in neonatal stage had an impact on the adult life of rats with incidence of oxidative stress in the brain [31]. A different study using Fe-dextran to analyze acute effect of Fe overload in the brain, showed an increase in total Fe, labile Fe pool, oxidative stress index, nuclear factor-kappaB (NF κ B) deoxyribonucleic acid and catalase activity [32].

Fe overload also results in mitochondrial dysfunction. In postnatal rats treated with excess Fe, mitochondrial dysfunction and superoxide dismutase (SOD) production were observed in brain cells as rats became adults [30]. In addition, excess Fe changed mitochondrial morphology and decreased mitochondrial membrane potential, leading to decreased ATP production [33]. In the mitochondria of rat brain cells, Sripecthwandee *et al.* observed a dose and time dependent mitochondrial swelling, depolarization and reactive oxygen species (ROS) production as a result of ferrous and ferric iron (Fe(II)) overexposure [34]. The ferrous form of iron (Fe(III)) was proven to cause more intense mitochondrial dysfunction [34]. The study also indicated that Fe transport through the mitochondrial calcium uniporter (MCU) might be the main mitochondrial uptake system [34].

Metals such as Cu, Zn, Co, and Mn, are believed to impact Fe metabolism, regulating Fe homeostasis as a competitor for transporters or as a cobalamin cofactor in mitochondrial SOD [35]. In rat neurons, both Fe depletion and loading increased Mn levels, and the interaction between Fe and Mn was synergistic rather than competitive, when they were transported from plasma to the brain [36]. Currently, the mechanism by which Fe influences other metals' homeostasis in the CNS is obscure, but it is known that in AD, abnormally high Fe level can disrupt Cu and Zn transport, and contribute to the aggregation of the biomarker protein amyloid β peptide (A β) [37].

2.2. Neurological Diseases Associated with Iron Deficiency-Restless Legs Syndrome (RLS)

The pivotal role that Fe plays in the development of CNS has been known for centuries, but isolating the effects of Fe deficiency from anemia has been a challenge [38]. It is known that Fe deficiency in the absence of anemia interferes in the development of auditory nerve and a change in velocity conduction [38]. Furthermore, Fe deficiency in RLS may reflect problematic Fe metabolism [39] or insufficient Fe intake that comes from malnutrition, which leads to defects in cognitive development as seen in patients with Fe-deficiency anemia [40].

RLS is a common neurological disorder seen in ~10% of the US population [41]. RLS is characterized by involuntary twitching leg movements either when asleep or awake [42], which is associated with sleep deprivation, anxiety, depression and attention-deficit/hyperactivity disorder (ADHD) symptoms [41, 43]. Moreover, RLS may portend more serious consequences, including hypertension, heart disease and stroke [44, 45, 46, 47]. The pathobiology of RLS has been linked to deficits in dopaminergic (DAergic) function and Fe deficiency. The mismanagement of body Fe affecting the brain Fe intake is one of the main causes [48]. Cerebrospinal fluid, MRI and autopsy studies of RLS patients have consistently revealed Fe deficiency in the brains of both familial and non-familial forms of RLS, particularly in basal ganglia circuits [39, 49]. Its symptoms follow up as consequence of the effects on the dopaminergic neurons of substantia nigra (SN) and other neurotransmitter systems [16, 48]. Fe supplementation has proven to be clinically effective in reducing RLS symptoms [50, 51, 52]. Furthermore, DAergic agonists, pramipexole and ropinirole, have also been approved to treat moderate to severe RLS.

2.3. Neurological Diseases Associated with Iron Overload

2.3.1 Alzheimer's Disease (AD)—AD is a progressive neurodegenerative disorder associated with cognitive decline and memory impairment that involves significant loss of neurons in the cortical and hippocampal regions of the brain[53]. AD represents the most common type of neurodegeneration[54] and accounts for 50–75% of all forms of dementia[55]. The pathological hallmarks of AD include profuse extracellular amyloid β peptide ($A\beta$) plaques, intracellular neurofibrillary tangles of protein tau, and increased Fe in the brain, especially in and around the $A\beta$ plaques[56]. As the major cause of neurodegeneration and synaptic dysfunction, the aggregation of $A\beta$ can be triggered by metal ions, such as Fe, copper and zinc. $A\beta$ readily binds Fe, contributing to both $A\beta$ accumulation and Fe overload. The loss of integrity in AD hippocampal tissue has been associated with increased levels of ferritin and decreased ferroportin, two key proteins involved in regulating Fe homeostasis[57]. The balance of Fe metabolism proteins is also affected by the downregulation of hepcidin and the upregulation of divalent metal transporter 1 (DMT1), transferrin, and lactoferrin[54]. Fe accumulation in AD can be detected by MRI, and can assist with diagnosis and disease monitoring[58].

AD is the most prevalent form of dementia related to the aging processes[57]. During the normal aging process, Fe accumulates in the brain in conjunction with the storage protein, ferritin[56]. In AD, Fe accumulates in the cerebral cortex and the hippocampus without an increase in ferritin, leading to a dangerous surplus of free Fe in the ferrous ion form. The ferrous ion can react with hydrogen peroxide via the Fenton reaction to produce hydroxyl free radical, one of the most potent and destructive forms of ROS, which causes oxidative stress to surrounding biomolecules, such as lipids, protein, and DNA. The brain is particularly sensitive to oxidative damage due to its high oxygen requirements, modest endogenous antioxidant activity, and abundance of polyunsaturated lipids[55]. In addition to oxidative damage caused by the overexposure of Fe alone, Fe-aggregated $A\beta$ can generate a new pool of ROS, impairing the $A\beta$ protein itself and surrounding biomolecules[55, 56]. Fe accumulated within the neurofibrillary tangles and neuritic processes adjoining senile plaques, is correlated with cognitive decline[56]. There are multiple interactions between Fe and $A\beta$ that may contribute to the pathophysiology of AD. In one study, ferritin was reported to be involved in the redox conversion of ferric ions (Fe^{3+}) to the ferrous form (Fe^{2+}) through cooperation with $A\beta$ [59]. In addition, Fe can regulate the generation of $A\beta$ through amyloid precursor protein (APP)[54, 56]. Increases in cytosolic Fe trigger the release of iron response protein 1 (IRP1) from the iron response element (IRE) associated with APP transcripts, upregulating APP expression through translation. APP can then facilitate the efflux of Fe from the neuron via ferroportin (FPN), promoting Fe homeostasis[56]. In the case of Fe overload, however, APP is overexpressed, leading to excess production of $A\beta$. An additional link between Fe and $A\beta$ involves the neuroprotective protein mitochondrial ferritin (FtMt). FtMt expression is enhanced by the presence of $A\beta$, and is amplified in AD as an attempt to sequester excess Fe. Additional signaling pathways involving interactions of Fe and $A\beta$ continue to be explored, including extracellular signal regulated kinases, phospholipase D, the transcription factors Forkhead box O (FoxO) and nuclear factor κ B. Abnormal structural changes within the tau protein represent another key component in the development of AD[57]. Fe instigates the cascade of tau aggregation,

entanglement and oxidative stress. The ferric ion can bind to hyperphosphorylated tau protein, inducing aggregations and neurofibrillary tangles. Excess ferrous ion can then accumulate within the tangles and generate more ferric Fe and ROS, thus creating an environment that perpetuates the process of aggregation, entanglement, and oxidative damage.

Taken together, these multiple signaling pathways, in conjunction with Fe overload, A β aggregation, tau entanglement and oxidative stress, highlight the intricacy of AD etiology. Further investigation is needed to understand the pathophysiology of AD and the role of Fe overload in this complicated and multifactorial disease.

2.3.2. Parkinson's Disease (PD)—PD is the second most common neurodegenerative disease after AD[60]. Genetic factors, such as mutations in genes coding for parkin and α -synuclein, as well as environmental factors, such as pesticides and heavy metals, contribute to the development of PD[61]. Important features of this late onset disease include the progressive degeneration of DAergic neurons in the substantia nigra pars compacta and nigrostriatal tract, the accumulation of brain Fe in specific brain regions, and the aggregation of α -synuclein based inclusions called Lewy bodies[62, 63, 64]. The depletion of striatal dopamine results in movement disorders in PD patients[62]. Epidemiological studies indicate that occupational exposure to Fe in the ferroalloy industry[65] and excessive nonheme Fe intake in the form of Fe supplements[66] can increase the risk for developing PD[61]. A key characteristic of PD is the accumulation of Fe in the substantia nigra (SN) [67]. This has been established by postmortem histology, and by MRI with quantitative susceptibility mapping (QSM)[68]. A critical reservoir for Fe in the SN is neuromelanin. In the SN of PD patients, neuromelanin granules with surplus Fe have been discovered in dopaminergic neurons[67]. The SN also shows a significant decrease in glutathione, allowing ROS to overwhelm dopaminergic neurons in this region. Additionally, Fe can accumulate in Lewy bodies and promote α -synuclein aggregation. Mutations in the α -synuclein gene may also enhance α -synuclein aggregation and Fe overload. To date, it is still unknown whether Fe is a cause or consequence of PD[61]. Fe is abundant in the dopaminergic neurons since it acts as a cofactor for tyrosine hydroxylase, an enzyme required for dopamine synthesis[69]. While the role of Fe in the pathogenesis of PD has been extensively studied, the mechanism of Fe accumulation and its effect on neuronal death is still not fully understood[61]. Some evidence indicates that Fe may trigger events leading to dopaminergic cell death, while other studies suggest that Fe accumulation is secondary to neuronal death.

Based on recent findings, several factors related to Fe regulation in the brain may be involved in the pathogenesis of PD, including upregulated DMT1, decreased ferritin levels, reduced activity of ceruloplasmin, and disrupted transferrin-transferrin receptor2 (Tf/TfR2) function[61, 68, 69]. Amyloid precursor protein, which stabilizes ferroportin on the cell surface, was also found to be reduced in postmortem PD brain tissue[62]. Fe can impair the function of parkin to degrade α -synuclein and DMT1 by ubiquitination[61], which can lead to α -synuclein aggregation and increased influx of Fe into dopaminergic cells through DMT1. This, in turn, causes a depletion of endogenous antioxidants, excessive oxidative damage, and can lead to cell death[61, 68]. The deregulation of IRP1 may also provide a

link between mitochondrial dysfunction and Fe accumulation in PD[70]. Recent studies indicate that astrocytes and microglia could impact Fe metabolism, dopamine neuron degeneration, and PD mechanisms[71, 72]. Ferroptosis, an Fe-dependent cell death pathway that involves the depletion of reduced glutathione antioxidant and increased lipid peroxidation, is also being investigated as a potential cell death mechanism in PD[73, 74]. While these multiple factors and proposed mechanisms highlight the complexity of PD etiology, the common outcome is an overload of Fe and consequent oxidative damage to the brain[62]. Dopamine metabolism also involves the production of neurotoxic metabolites. The oxidation of dopamine by Fe produces a dopamine quinone and 6-hydroxydopamine, both of which may contribute to the production of ROS and oxidative stress, especially under conditions of Fe overload. The interaction of Fe and α -synuclein can exacerbate oxidative stress in PD by propagating a vicious cycle of Fe accumulation and protein aggregation[68]. PD is a complicated and multifaceted disease requiring continued research to understand the precise role of Fe accumulation and neurodegeneration.

2.3.3. Friedreich's Ataxia (FA)—FA is a rare neurodegenerative disease caused by deficient expression of the mitochondrial protein, Frataxin[75]. FA is characterized by lesions in the dorsal root ganglia, dentate nuclei of the cerebellum, corticospinal tracts, and sensory peripheral nerves. Symptoms usually begin between 5 and 15 years of age, but can occur over a wide range of age groups[76]. The first symptom often appears as gait impediments, followed by gradual muscle weakening and loss of sensation in the extremities. In addition to neurodegeneration, FA is also considered a cardio-degenerative disease[75]. Most cases derive from a homozygous GAA trinucleotide repeat expansion on the frataxin gene, *FXN*. Through epigenetics, this GAA expansion results in abnormal DNA confirmations, decreased *FXN* mRNA, and diminished frataxin protein synthesis. FA patients are vulnerable to oxidative stress and Fe accumulation in the mitochondria[76]. It is uncertain whether oxidative stress is a primary cause of FA or a secondary effect. The pathological development of FA can be partially explained by the role of frataxin. The frataxin protein is localized in the mitochondrial matrix and associated with the inner mitochondrial membrane[77]. It is critical for the synthesis of Fe sulfur clusters (ISC) and heme in the mitochondrion[75]. Proteins that incorporate these structures, such as ISC protein complexes in the respiratory chain, Fe responsive element binding protein 1 (IRB1), hemoglobin, and cytochromes, also require Fe for assimilation and proper function[75, 77]. In FA, frataxin deficiency causes disruptions in the assembly of these important biomolecules, resulting in compromised respiratory chain function and Fe accumulation in the mitochondria. Excess hydrogen peroxide production, along with Fe overload, leads to the uncontrolled production of hydroxyl free radicals and consequent cellular oxidative damage. The compromised ISC biogenesis due to frataxin deficiency is presumed to be the major contributing factor in the etiology of FA[75]. Cell degeneration usually begins in the dorsal root ganglia, with evidence of diminishing neurons and reduced myelination of axons[77]. Excess Fe was discovered in the dentate nucleus of FA patients using MRI[75]. Additionally, the expression of proteins involved in Fe homeostasis, including TFR1, ferritin, and FPN1, were altered in the dentate nucleus. Neurodegeneration in FA provides another example of the deleterious effects caused by redox-active Fe overload in the cells, particularly in the mitochondria.

2.3.4. Huntington's Disease (HD)—HD is a progressive autosomal dominant disorder that causes motor and cognitive impairment [78, 79]. The estimated incidence is 1 in 8,000 in individuals of Caucasian European lineage. HD is caused by a trinucleotide CAG repeat on the *HTT* gene, producing mutant huntingtin protein (mHtt) which is expressed in the neurons and glia [78, 79, 80]. Aggregates of mHtt contribute to neurodegeneration and have been described as Fe-dependent centers of oxidative stress[81]. Brain tissue from HD patients has revealed increased levels of Fe, decreased levels of Mn, and evidence of mitochondrial dysfunction, with decreased activity in the electron chain transport complexes II-IV and aconitase [82, 83, 84]. A recent study found accumulated mitochondrial Fe, increased expression of mitoferrin 2, and decreased frataxin in both human and mouse HD brain tissues[80]. As mentioned with FA, a deficiency in frataxin protein will hinder the biogenesis of Fe-sulfur clusters, leading to free Fe accumulation and disrupted function of Fe-dependent proteins. Since Fe is transported into the matrix through mitoferrin 2, increased expression of this protein may exacerbate the accumulation of labile mitochondrial Fe. This condition of Fe overload may instigate oxidative damage and energetic dysfunction in HD, and may also contribute to changes in manganese homeostasis [82, 84]. While evidence of Fe overload and mitochondrial dysfunction may explain the etiology of HD to some degree, the precise physiopathology is still unknown [79]. Glutamate excitotoxicity has been proposed as a possible mechanism for the neurodegeneration that occurs in HD [13, 85, 86]. Excess Fe could increase the rate of this process, since the addition of Fe to neurons leads to increased secretion of glutamate. More research is needed to understand the mechanics of this complex neurodegenerative disease.

2.3.5. Aceruloplasminemia (ACE)—ACE is a rare inherited disease caused by defects in the ceruloplasmin gene [87]. The lack of ceruloplasmin, a protein directly involved in Fe homeostasis, leads to brain Fe accumulation (mainly Fe(II)) and neurodegeneration[88]. This rare disorder has fewer than 100 reported cases worldwide, and is most prevalent in Japan, affecting 1 in 2,000,000 [89]. Compared to other Fe overload disorders, ACE is characterized by both systemic and brain Fe dyshomeostasis. Fe is found to accumulate in the pancreas, liver, heart, thyroid, retina and the brain [87]. ACE can be distinguished from other neurodegenerative disorders by detection of Fe accumulation in the thalamus and caudate nucleus, putamen and globus pallidus of the basal ganglia[88]. Additionally, deformed astrocytes and globular structures were detected in the striatum, which corresponded to significant Fe accumulation and neuronal loss [88, 89]. The precise mechanism of neuronal loss is still under investigation. Genetic defects in the ceruloplasmin gene cause mutations in the protein ferroxidase ceruloplasmin (Cp) [88]. This copper dependent protein plays a key role in maintaining Fe homeostasis, especially in the brain. Cp stabilizes ferroportin and oxidizes ferrous iron (Fe(II)) to the ferric form (Fe(III)), allowing Fe to bind to transferrin for cellular export. In the case of malfunctioning Cp, Fe becomes trapped within the astrocytes, causing Fe accumulation and damage to brain cells[89, 90]. Accumulated Fe(II) can generate dangerous levels of ROS [91], leading to increased oxidative stress and lipid peroxidation, contributing to the neurodegenerative process in ACE. The diagnosis of ACE is determined by the absence of serum Cp and through neuroimaging, and can be confirmed by genetic testing[89]. Patients with ACE have a complete absence of serum Cp and low hepcidin levels[88, 89]. Hepcidin is a peptide

hormone involved in Fe absorption regulation through its interaction with ferroportin. Reduced hepcidin in ACE patients may contribute to cellular Fe accumulation, leading to potential cell damage [89]. While Fe accumulation in the brain is the dominant feature of ACE, systemic Fe overload is common for most patients at the time of diagnosis [88]. Based on autopsy analysis, Fe accumulation has been found in the endocrine portion of the pancreas, accompanied by loss of beta cells. Consequently, ACE may present as diabetes in the early stages of the disease. Retinal degeneration and diabetes often manifest in ACE patients before the symptoms of neurodegeneration occur.

2.3.6 Neuroferritinopathy (NF)—NF is a rare genetic disease caused by mutations in the ferritin light chain 1 gene (*FTL1*), and is the only autosomal dominant neurodegeneration with brain iron accumulation (NBIA) disorder [92]. The proper functioning of ferritin is critical for the maintenance of Fe homeostasis, as it sequesters and stores excess cellular Fe. The dysfunction of ferritin in NF causes Fe accumulation and ferritin aggregates, predominantly in the basal ganglia. Only 90 cases of NF have been identified thus far, with a mean onset age of NF is approximately 40 years old [93]. The most common symptoms of NF include chorea and dystonia, but other clinical features include tremor, Parkinsonism, and cerebellar ataxia. Diagnosis can be made using a combination of low serum ferritin, MRI, and genetic testing. While neuromelanin is the main storage protein for Fe in the substantia nigra and locus coeruleus, ferritin is the major Fe storage protein in the brain and throughout the body. It is present both in the cytosol and the mitochondria. Normal ferritin contains heavy and light chain subunits that work synergistically to effectively store intracellular Fe, maintaining proper Fe homeostasis [90]. In addition to this critical role of Fe storage, the heavy chain in ferritin has a ferroxidase function, which is supported by the light chain. Mutations in the ferritin light domain impair the operation of the ferritin protein, leading to a surplus of Fe in the cytosol and accelerated degradation of ferritin. This excess free Fe(II) induces the production of ROS and promotes oxidative stress, especially in vulnerable brain tissue [94]. Increased intracellular Fe also upregulates the synthesis of ferritin, which can lead to protein aggregates [93]. Fe deposits and ferritin aggregates have been detected in various brain structures, most notably in the globus pallidus and putamen [94]. Abnormal nuclear and cytoplasmic ferritin inclusion bodies and Fe accumulation were found in CNS glia and neurons [91]. Fe and ferritin deposits have been found in other organs and tissues, specifically in the liver, kidneys, skin, and muscle. This suggests that NF could be classified as a systemic disease, and may be referred to as its alternative name, hereditary ferritinopathy [93, 95].

2.3.7 Pantothenate Kinase-Associated Neurodegeneration (PKAN)—PKAN, formerly referred to as Hallervorden-Spatz Syndrome, is the most common type of NBIA representing approximately 50% of NBIA cases [90, 96]. This autosomal recessive disease is caused by mutations in the *PANK2* gene, which disrupts coenzyme A (CoA) biosynthesis and results in neurodegeneration [90, 97]. The classic form of PKAN manifests as early as six years of age, with symptoms such as gait difficulty and postural distortion [90]. The atypical form often occurs in the second decade of life, and may present as speech impediment, myriad psychiatric issues, and cognitive decline. MRI can be used to diagnose both forms of PKAN, using the characteristic “eye of the tiger” signature corresponding to

Fe accumulation in the globus pallidus. PKAN results in neuronal death by mechanisms that have not yet been determined. Excess metal has been discovered in the cytoplasm of astrocytes and in some neurons, and ferritin has been found to accumulate in the astrocytes. MRI studies on pre-symptomatic patients indicate that Fe accumulation occurs after neuronal loss, suggesting that Fe overload is a consequence and not a cause of PKAN [97]. The *PANK2* gene encodes the mitochondrial enzyme PANK2, a pantothenate kinase enzyme that is required as the first rate-limiting step in the biosynthesis of CoA from pantothenate or vitamin B5. CoA is a critical cofactor involved in hundreds of metabolic reactions, such as the citric acid cycle and fatty acid metabolism. Both CoA and acetyl CoA are key regulators of several biological processes, including cell growth and cell death. The connection between disrupted CoA synthesis, Fe overload, and neurodegeneration has not been established; however recent studies show progress in understanding the pathological mechanism. In a recent study, human induced pluripotent stem cells from PKAN patients cultured into neuronal cells exhibited altered oxidative status, cellular Fe dyshomeostasis, and mitochondrial dysfunction, including impairments in energy production, Fe-sulfur cluster synthesis, and heme biosynthesis [98]. Upon CoA administration, these neurons recovered and mitochondrial function was restored, demonstrating a potential therapeutic method. Another study used cultured skin fibroblasts to demonstrate impaired palmitoylation, which could be a result of compromised CoA or fatty acid biosynthesis, and reduced recycling of transferrin receptor 1, which could impact not only PKAN but all NBIAAs [99].

2.4 Treatments for neurological disorders with iron overload

Treatment methods for diseases related to neurodegeneration and Fe overload are currently insufficient [100]. This can be attributed to limited knowledge on the precise pathophysiological mechanisms that control these abundant and varied disorders, which are often complex and multifaceted. Since Fe overload is implicated in the proposed mechanism of oxidative damage leading to neurodegeneration, Fe chelation therapy is a common treatment approach. Unfortunately, several disorders can only be treated symptomatically. The most common therapeutic methods and some experimental treatments for neurodegenerative diseases related to Fe overload are described below, with a focus on therapies that target the restoration of Fe homeostasis.

AD poses a significant healthcare challenge, as no effective treatment method exists [101]. Research has centered around strategies to remove or reduce A β [53]. While this approach seems logical, the results have been disappointing. The U.S. Food and Drug Association (FDA) has approved only five drugs for the symptomatic treatment of AD. Fe chelation techniques are currently being evaluated in preclinical and clinical trials [53, 56, 102]. Deferoxamine (also known as desferrioxamine) was shown to slow disease progression, but does not readily penetrate the blood-brain barrier (BBB) and has had limited efficacy in clinical trials [56]. Clioquinol, a divalent metal chaperone, improved cognitive performance in patients when groups were stratified by level of impairment [102]. A clioquinol derivative, PBT2, did not significantly reduce A β nor improve cognitive performance, but did improve trend toward preserving hippocampal brain volume. Deferiprone is currently tested in clinical trials for the conservative chelation of Fe. This drug can readily cross the

BBB, and forms a neutral, lipophilic complex with Fe that easily exits the cells and redistributes Fe to transferrin. A multitarget Fe chelating drug, M30, has shown therapeutic efficacy in cell and animal studies [103]. Prochelators, which become active in the diseased state, are also being explored [104]. Alternative strategies include the use of diet and supplements to delay the progression of AD [101, 105]. The antioxidant ascorbic acid (Vitamin C) was studied extensively, but was found ineffective in clinical trials [105]. Selenium supplementation has been posited as a method for boosting glutathione peroxidase activity and inhibition of tau hyperphosphorylation [101]. Based on epidemiological evidence, targeted nutrition might be a potential method to epigenetically prevent or slow disease progression. This strategy requires further support through experimental and longitudinal studies to be considered a viable option [105].

Current treatment options for PD may alleviate symptoms, but will not stop disease progression. There is a need to develop disease-modifying therapies that will prevent degeneration of DAergic neurons and protect against oxidative stress [69, 106]. The most effective symptomatic therapy used today is levodopa [106]. Attempts to develop treatments that can regenerate neurons and repair the damage from ROS have not yet been successful. This is likely due to the fact that PD is a complex and heterogeneous disease with many subtypes. Fe chelation therapy that conserves systemic Fe has been a major focus [69]. Low doses of deferiprone have proven efficacy in pilot studies for the reduction of Fe in the SN, and improvement of motor control. Placebo-controlled, randomized control clinical trials are currently underway with this drug. Polyphenols, such as curcumin [107] and epigallocatechin gallate (EGCG) from green tea [108], are also being evaluated as natural Fe chelators and antioxidants for PD patients [68, 109]. A study that assessed food and supplements to decelerate the effects of PD recommends eating fresh fruits and vegetables, nuts, seeds, nonfried fish, and other foods inherent to Mediterranean diets [66]. Food and supplements that were high in Fe (such as beef and multivitamins) were associated with more rapid PD progression. Analysis and optimization of the intestinal microbiome have also been suggested as a potential method to prevent or slow the onset of PD, since gastrointestinal issues often precede neurodegeneration in PD [110].

Currently, there is no FDA-approved treatment for Friedreich's Ataxia in the US [111]. Antioxidant remedies such as idebenone (an analogue of coenzyme Q), coenzyme Q with vitamin E, and resveratrol have been evaluated, but results have been inconclusive. The Fe chelator deferiprone was found to be unsuccessful when used alone; however, the combination of Fe chelators with idebenone has been shown to reduce Fe deposits in the dentate nucleus of FA patients, providing hope for a potential treatment [75]. N-acetylcysteine (NAC) has been recommended as a method to restore glutathione levels, but this requires further investigation. Gene therapy using histone deacetylase (HDAC) inhibitors or interferon gamma is an optimistic potential therapeutic method [111]. HDAC inhibitors, such as nicotinamide (Vitamin B3), work by increasing histone acetylation on *FXN*, potentially increasing the expression of this gene to boost the synthesis of frataxin. Interferon gamma may stimulate frataxin production, also by increasing the transcription of the *FXN* gene. These epigenetic therapies are currently being tested in clinical trials.

Approved therapies for Huntington's disease are limited for treating select symptoms, and are lacking for disease-modification [112]. Tetrabenazine helps to control chorea and other involuntary movements, but does not alleviate the more disabling motor and cognitive features of HD. A new deuterated form of tetrabenazine provides similar relief, with the added benefit of reduced side effects and fewer required doses. Gene therapy for disease modification is being investigated in phase 1 clinical trials. It is recommended that therapeutic strategies and treatment development for disease modification should focus on bioenergetic deficits due to mitochondrial dysfunction and degenerating neural circuits [113]. Fe chelators have been tested in mice with some success [80]; however, no clinical trial information is readily available at this time.

ACE patients have been treated with the Fe chelators deferasirox, deferoxamine and deferiprone with mixed results [100]. Deferasirox and deferoxamine successfully normalized serum ferritin, decreased Fe levels in the heart and liver, and reduced the symptoms of anemia and diabetes in several patients; however, brain Fe was only slightly reduced as confirmed by MRI. Neurological symptoms were improved in only a few cases. Less data is available for deferiprone. In one case study, deferiprone failed to remove Fe from tissues, while another case study using long term treatment prevented neurological symptoms in an asymptomatic patient with the defective Cp gene. The use of these Fe chelators alone or in combination shows promise for the prevention of neurological symptoms when ACE is detected early; however, these studies must be confirmed with time to allow for the assessment of symptoms at the typical age of disease manifestation. Recent treatments using a combination of Fe chelators with fresh frozen plasma (FFP) [114] and ceruloplasmin replacement therapy [87] show potential for reducing neurological symptoms in ACE patients. A clinical trial with deferoxamine, deferiprone, and FFP for 6 months improved serum ferritin levels, gait stability, trunk ataxia, and myoclonus with no side effects [114]. Fe accumulation in the basal ganglia was stabilized, but not reduced. In a preclinical study, Cp-knockout mice were administered human Cp replacement therapy [87]. After 2 months, mice showed partial replacement of Cp levels, increased brain ferroxidase activity, and improved motor coordination. The treatment group also showed a reduction in Fe deposition in the whole brain and choroid plexus epithelium, and reduced neuronal death in the cerebellum.

Fe chelation therapy for NF has not been effective in most clinical trials [100]. Instead, alternative treatments have been recommended for patients based on specific symptoms [93]. Anticholinergics such as trihexphenidyl, and benzodiazepines have had some success to alleviate dystonia. Sulpiride, a D2 receptor blocker, and tetrabenazine, a dopamine depleting agent, provided some relief for chorea. Tetrabenazine was successful in treating chorea and facial tics in one case report. Fe chelation therapy still has potential to prevent Fe accumulation in NP if the disease is detected early in life, but more research is needed to confirm this postulate. NF can be detected by MRI in children and young adults before symptoms present, offering a proactive approach to NF treatment with Fe chelators, antioxidants, or other methods [92]. A recent study using a mouse model showed promising results using the Fe chelator deferiprone to stabilize systemic Fe homeostasis and reduce ferritin aggregation[95]. However, more work is needed to focus on treatments that can reduce or prevent the damage caused by neurodegeneration and the associated clinical symptoms.

The majority of treatments for PKAN remain symptomatic [97]. The Fe chelator deferiprone effectively reduced Fe levels in the globus pallidus of some PKAN patients, but clinical improvement or stabilization was limited [100]. Since Fe accumulation in PKAN is reported to be a secondary effect of the disease, treatment with Fe chelators in general may not be a viable solution. A clinical management guideline reported by Hogarth et al. explains attempted treatments and provides recommendations for the alleviation of PKAN symptoms [96]. To treat dystonia, trihexyphenidyl, clonazepam, and baclofen are recommended. Most Fe chelators were found to deplete systemic Fe. High doses of vitamin B5, pantothenate, have been attempted by patients, but no clinical trials have been performed. Adults with atypical PKAN have anecdotally reported some clinical benefit using pantothenate, however children and patients with classic PKAN have not experienced symptomatic relief using this method. CoA administration shows therapeutic promise in a cell study [98], but this must be corroborated with clinical trials.

3. Mn and CNS Toxicity

Similar to Fe, Mn also acts as a cofactor for many enzymes to support normal physiological activities in cells. These enzymes, such as arginase, pyruvate carboxylase, acetylcholine esterase (AChE), glutamine synthetase (GS) and Mn superoxide dismutase (Mn-SOD) [10, 115], are essential for normal brain function; however, exposure to excess Mn, either through environmental or occupational routes, results in accumulation of this metal in the brain, preferentially in the basal ganglia [116, 117, 118]. High levels of intracellular Mn disrupt normal cellular function, leading to oxidative stress, mitochondrial dysfunction, autophagy dysregulation, apoptosis, protein dyshomeostasis, which eventually alter neurotransmission. All of these impair normal neuronal function and result in a variety of neurological disorders.

3.1. Molecular Mechanisms of Mn-induced neurotoxicity

Although Mn is required for certain antioxidant enzymes (such as Mn-SOD), excess Mn itself actually can result in oxidative stress. In the brain of Mn treated rats, glutathione (GSH) levels were reduced with elevated glutathione disulfide (GSSG) concentrations, indicating Mn exposure increased oxidative stress [115]. The changes of cellular oxidative status by Mn is likely to be the fundamental mechanism for the consequences listed below.

Mitochondria, as the critical organelle for ATP production, are a susceptible target of Mn-induced toxicity. Excess Mn impairs normal mitochondrial function and leads to decreased energy production. Gunter and colleagues showed that high levels of Mn were able to inhibit ATP production in mitochondria isolated from rat liver, heart and brain [119]. Similarly, ATP production was inhibited by Mn in a time- and concentration-dependent manner in PC12 cells [120]. In rat primary neurons, Mn treatment caused dose-dependent losses of mitochondrial membrane potential and complex II activity [121].

Autophagy functions to disassemble and recycle unnecessary or dysfunctional components in cells and its dysregulation has been associated with multiple neurological diseases, such as PD. After injection of Mn in rat brains, researchers found increased number of abnormal lysosomes, concomitant with activated mammalian target of rapamycin (mTOR)/p70

ribosomal protein S6 kinase (p70s6k) signaling, while Beclin1 protein level was decreased, as well as the ratio of microtubule-associated protein 1 light chain 3 (LC3) II over LC3 I, all of which indicated autophagy was inhibited in the rat brain [122].

Mn exposure can activate apoptosis, accounting for Mn-induced cell death or neurodegeneration. In human B lymphocytes, Schrantz *et al.* observed a dose- and time-dependent cell apoptosis in response to Mn treatment, with activation of the apoptotic marker proteins caspase-1 and 3 [123]. In PC12 cells, Mn treatment resulted in internucleosomal DNA fragmentation, a hallmark of apoptosis, and this phenomenon could be inhibited by Bcl-2 overexpression [124]. Mn was also able to induce phosphorylation of c-Jun and SEK1/MKK4 (c-Jun N-terminal kinase kinase, JNK), indicating Mn-induced apoptosis might be mediated through the JNK pathway [124].

Mn exposure also antagonizes protein homeostasis. In the nematode *C. elegans*, Mn exposure induced unfolded protein responses in the endoplasmic reticulum (ER) as well as in the mitochondria, which is aggravated by aging [125].

Mn exposure may significantly alter neurotransmission. In the rats that received Mn injection, Zhang and colleagues found a reduction of dopaminergic (DAergic) neurons in the substantia par compacta (SNpc) and tyrosine hydroxylase (TH) protein, associated decreased dopamine (DA) and D1 DA receptor [122]. An increase of AchE activity and glutamate was observed in rat brain extracts with Mn exposure [115]. In addition, decreased cellular dopamine (DA) and serotonin (5-HT) levels have been reported in PC12 (rat pheochromocytoma) cells [126].

3.2. Neurological Diseases Associated with Mn Deficiency-Epilepsy

As an essential element of various metalloprotein enzymes involved in many physiological processes, Mn deficiency is likely to impair normal brain function. Epilepsy is associated with low Mn levels in the blood. Epilepsy is characterized by seizures, which can vary from almost undetectable episodes to long lasting vigorous convulsions. In most cases, the cause is unknown, although brain injury, infection and tumor, as well as stroke and birth defects may contribute to the development of this disease. Several clinical studies in epilepsy patients revealed significant lower blood Mn concentrations in patients compared with control groups [20, 21, 127, 128]. Similar results were also seen in mice [129] and rats [19, 130]; however, whether Mn deficiency is the cause or the secondary consequence of epilepsy is still not clear. Mn is an important cofactor of glutamine synthetase. The activity of this enzyme is significantly lower in genetically epilepsy-prone rats (GEPRs) and its inhibition causes seizures in animals [19]. Although Mn supplement seems to be potentially effective in epilepsy patients with low blood Mn level, significant improvements were not seen in GEPRs with Mn supplementation [19]. Further studies are needed to determine the relationship between Mn deficiency and development of epilepsy.

3.3. Neurological Diseases Associated with Excess Manganese

3.3.1. Manganism and PD—Increasingly high exposure to Mn in adults is associated with a variety of psychiatric and motor disturbances, such as subclinical parkinsonian

movements and postural instability, increased risk for PD, and at the highest levels with manganism, a parkinsonian-like disorder which is not ameliorated after cessation of exposure [116, 117, 118, 131]. Manganism was found in industrial workers, such as welders, smelter workers and miners, who have been exposed occupationally to high environmental Mn [132]. The early symptoms include anorexia, irritability, mood swings, attention disturbances and reduced response times; as the disease progresses, other symptoms emerge, including hypomimia, rigidity, disturbed speech, bradykinesia and walking difficulty, similar to the symptoms of idiopathic PD; at later stages, patients exhibit abnormal gait associated with rigidity and postural instability [133, 134].

Despite the resemblance in extrapyramidal symptoms between manganism and PD, the two syndromes have different clinical and pathological characteristics, and are considered as distinct and separate disease entities. The differences between Mn-induced Parkinsonism and PD have been highlighted in several review articles [135, 136, 137]. Unlike typical PD, Mn-induced Parkinsonism is not responsive to Levodopa and clinically presents with an absence of resting tremor and more frequent early gait disorders with dystonia [137, 138, 139]. The distinct symptoms likely originate from differences in primary target brain regions [140]. Manganism is characterized by neuronal loss and reactive gliosis in the globus pallidus (GP) and substantia nigra pars reticulata (SNpr) in the absence of Lewy bodies [138, 141, 142], the protein aggregates that distinguish PD. Mn causes abnormal presynaptic dopaminergic signaling and suppression in dopamine release, while the dopamine content within striatum, and the integrity of dopaminergic neurons in the SNpc are unaffected [138, 143]. In contrast, degeneration of SNpc dopaminergic neurons and loss of striatal dopamine are pathologic hallmarks of PD. Because the linkage between manganism and PD is noteworthy, extensive studies have examined the role of Mn in the etiology of PD, which remains to be an area of controversy. Elevated Mn levels in blood [144] and cerebrospinal fluid (CSF) [145] have been found in individuals with PD. Although several studies have reported increased prevalence of PD due to occupational exposure to Mn [146, 147, 148], a 2012 meta-analysis of data from 13 cohort, case-control and mortality studies concluded that there was little evidence for a causal association between manganese exposure and PD in welders [149]. In non-occupational settings, two studies investigating metal exposure through air pollution identified Mn as potential risk factor for PD [150, 151]. In contrast, a recent prospective cohort study of female nurses reported no association between higher exposure to airborne Mn and PD [152]. The discrepancies in these studies may be due to differences in defining PD in their cohorts as well as different methods in assessing exposure levels.

While the connection between Mn intoxication and PD remains inconclusive, the two disorders share broadly similar molecular mechanisms such as mitochondrial dysfunction and oxidative stress, altered protein aggregation, and activation of apoptotic cell death pathways. Several early-onset Parkinsonism genes including PARK2 (parkin) and PARK9 (ATP13A2) are associated with Mn transport and/or toxicity [153, 154, 155]. Overexpression of parkin has been found to attenuate Mn-induced dopaminergic cell death [156], while ATP13A2 confers protection by reducing intracellular Mn concentrations [157]. Variants in the *ATP13A2* gene have been reported to associate with increased susceptibility to Mn

neurotoxicity in humans [158]. Furthermore, Mn exposure promotes α -synuclein expression and oligomerization [159, 160, 161, 162] which enhance cellular toxicity.

3.3.2. Attention Deficit Hyperactivity Disorder (ADHD)—ADHD is the most common childhood neurobehavioral disorder manifested by symptoms of inattention, impulsivity, and hyperactivity [163]. It affects approximately 5% school-age children worldwide and the deficits often persist into adulthood [164, 165]. Although evidence indicates that ADHD is a highly familial disorder, environmental risk factors such as exposure to heavy metals have also been implicated in its etiology [166, 167]. Since an impaired dopaminergic system is implicated in the pathophysiology of both ADHD [168, 169] and Mn neurotoxicity, numerous studies have explored the influence of Mn on children's behavioral disorders and some of them reported positive associations between Mn exposure and behavioral problems. A recent study reported elevated serum concentrations of Mn in treatment-naïve children with ADHD compared with normal controls in Brazil [170]. The results are further supported by a case-control study in the United Arab Emirates [171], and a large sample cross-sectional study in an e-waste recycling area in China [172]. Both studies reported an association between high blood Mn levels and the presence of ADHD. A pilot study by Bouchard *et al.* found that hair Mn levels in children were associated with increased oppositional behaviors and hyperactivity in Quebec, Canada [173]. In a following study, the same group recruited 375 children and observed a significant association with poorer attention function, but not hyperactivity, which may attribute to lower Mn exposure [174]. In addition, Mn concentrations in drinking water were positively associated with both internalizing and externalizing behavior scores in Bangladeshi children [175]. A small-sample study used Mn levels in tooth enamel as a biomarker reported positive correlations between Mn and ADHD-related behaviors [176]. However, a more recent study based on a larger sample size of 266 children contradicted the previous finding, reporting no significant relationship between dental Mn levels and behavioral deficits [177]. Consistent with this study, a study on school-age children living near a ferroalloy plant in Italy reported no association between Mn exposure and behavioral functions [178]. Taken together, these studies provide some evidence of a link between Mn exposure and ADHD-like symptoms in children but the results are inconclusive. The discrepancies may result from the differences in age of onset, duration, and concentration of exposure as well as different sample sizes, choices of exposure biomarkers, and analytical methods.

3.3.3. Depression—Perturbations to the Dopaminergic neurotransmission compromise the major pathophysiological mechanism of Mn-induced parkinsonism. In addition, reduced levels of serotonin (5-HT) and its metabolite 5-HIAA have been reported in both rodents and nonhuman primates exposed to Mn [138]. Modulations of dopamine and serotonin pathways play a major role in the pathogenesis of depression [179, 180]. Indeed, anxiety/depression is described as one of the initial psychiatric manifestations in manganese poisoning [181]. Mn-exposed workers display a dose-effect relationship between exposure level and neuropsychiatric symptoms including depression [182, 183]. Further, a decrease in level of urinary 5-HIAA has been found in welders with long-term Mn exposure [184].

A few recent clinical studies have examined the association between Mn and depressive disorders in populations without occupational exposure. A cross-sectional study in 2015 has reported that higher level of urinary Mn is associated with adult depression after adjusting for confounders [185]. However, it is noted that urinary Mn is not a reliable biomarker since Mn is mainly eliminated through the biliary system [186]. Abadalian *et al.* assessed the effect of Mn supplementation in patients on long-term parenteral nutrition [187]. Among a total of 16 patients, 66% reported depression. Additionally, Hong *et al.* found a significant interaction between blood Mn level and occurrence of anxiety/depression in children with ADHD [188]. On the other hand, two recent cross-sectional studies have reported an inverse association between dietary Mn intake and prevalence of depressive symptoms. One study found mean intake level of Mn was lower in school aged Spanish children who had depressive symptoms than those did not [189]. The other study in Japanese women demonstrated higher Mn intake was independently associated with a lower prevalence of depressive symptoms during pregnancy [190]. More observational studies and randomized clinical trials are warranted to investigate the association between Mn deficiency/overexposure and depressive disorders.

3.3.4. Hepatic Encephalopathy (HE)—HE refers to a spectrum of neuropsychiatric abnormalities occurring in patients with liver dysfunction [191, 192]. Clinically, HE is characterized by a number of neurologic and psychiatric symptoms such as changes in personality, impaired sleep-wake cycle, cognitive decline, and alterations in motor functions [192]. A common pathogenic notion is that HE is caused by the accumulation of toxic substances normally metabolized or removed by the liver [193, 194]. Mn is primarily eliminated via the hepatobiliary route; consequently insufficient liver detoxification increases Mn body burdens, including the CNS [195]. Indeed, Mn concentration are elevated in blood [196, 197, 198], CSF [197] and post-mortem brain tissue [199] of cirrhotic patients. T1-weighted MRI in patients with chronic hepatic diseases reveal bilateral signal hyperintensities in the globus pallidus, which has been attributed to Mn deposition [196, 197, 200, 201]. The hyperintensity of the T1 signal parallels high incidence of extrapyramidal dysfunction, characterized by rigidity, tremor and akinesia in HE patients [198]. In addition to the well-established dopaminergic toxicity, Mn has been postulated to act synergistically with ammonia, the main factor in the pathogenesis of HE [202, 203]. Both ammonia and Mn can enhance neurosteroid synthesis through induction of peripheral-type benzodiazepine receptor [204, 205, 206]. Neurosteroids are potent agonists of the GABA_A receptor, and increased GABA-mediated neurotransmission, which in turn contributes to motor function impairment and decreased consciousness in HE [194, 206]. Moreover, Mn may act synergistically with ammonia to promote Alzheimer type II astrocytosis, inhibit astrocytic glutamate uptake, increase glutamine accumulation, produce excess free radicals and impair cerebral energy metabolism [202, 207, 208].

3.4. Diagnosis of Mn intoxication

Diagnosis of Mn intoxication relies primarily on the neurological presentations, occupational exposure history, MRI brain appearances, and Mn analysis in biological samples. Since Mn is homeostatically regulated to maintain optimal tissue level [209], its concentration in biological samples is poorly related to external exposure levels [186, 210].

Currently, there are no reliable biomarkers of cumulative Mn exposure, nor are there predictive biomarkers of its neurotoxic effects. While less than an ideal indicator, blood Mn is analyzed in patients who demonstrate extrapyramidal movement disorder and are at risk of Mn overload [143]. There are a number of studies investigating the use of Mn concentration in the blood compartment (i.e., Mn in whole blood, plasma, or serum) as a biomarker of Mn exposure in human subjects (reviewed in [186]). In general, these studies suggest that blood Mn level serves as a suitable indicator of exposure at the group (exposed vs. control subjects), but not individual level. Moreover, due to its relatively short elimination half-life [211], blood Mn reflects recent exposures and cannot be used to estimate cumulative exposure or body burden [186]. Other biomarkers such as Mn in hair, nail [212, 213, 214, 215, 216], or the Mn:Fe ratio in plasma or erythrocytes [217, 218] have been investigated in an attempt to develop accurate biomarkers to reflect the body burden to Mn exposure. In addition, multiple studies have reported a positive correlation between Mn exposure and serum prolactin in both occupationally and environmentally exposed populations [219, 220, 221, 222, 223]. It is well established that dopamine inhibits prolactin secretion from the anterior pituitary gland [224]. Mn overexposure induces dopaminergic disturbance, therefore indirectly disinhibits prolactin secretion, causing an increase in circulating prolactin levels [225]. In this regard, peripheral prolactin level may serve as an effect-rate biomarker that reflects Mn-induced dopaminergic dysfunction.

MRI is a particularly sensitive non-invasive technique for detecting Mn in the brain. Patients with Mn intoxication usually exhibit a bilateral symmetrical hyperintense signal in T1-weighted MRI typically in GP and midbrain [137, 226, 227], while T2-weighted images are generally normal. This finding is because the paramagnetic properties of Mn results in shortening of T1 relaxation time, leading to T1 signal hyperintensity in the affected brain regions [228, 229]. Brain Mn content can be semi-quantitatively estimated using Pallidal Index (PI) [229, 230], which is defined as the ratio of the T1 signal intensity in the GP to that in the frontal white matter. The PI is generally considered as a good biomarker for external Mn exposure even before the appearance of neurological symptoms [231]. However, using PI to assess brain Mn levels may lead to underestimation of pallidal Mn content because Mn can also accumulate in the frontal white matter [232, 233]. Therefore, several recent studies have suggested that direct measures of the T1 relaxation time may be a more sensitive indicator of tissue Mn level as it is not confounded by Mn deposition in frontal white matter [229, 234, 235]. It is noteworthy that the MRI can only reflect recent exposure. The hyperintense signal usually resolves about 6 months after cessation of exposure [231, 236, 237], despite the persistence of symptoms in untreated patients. The T1 signal hyperintensity is not observed in PD patients, which may be helpful in differential diagnosis [142].

Mn-induced parkinsonism and PD can also be differentiated by other neuroimaging modalities such as positron tomography (PET) and single-photon emission computed tomography (SPECT) [136, 137, 238]. In PD patients, PET scan shows reduced striatal uptake of ^{18}F -fluorodopa, while SPECT imaging reveals diminished dopamine transporters (DAT) uptake in the striatum. In contrast, patients with Mn-induced parkinsonism generally show normal ^{18}F -dopa PET and DAT SPECT.

Magnetic resonance spectroscopy (MRS) has been used to monitor Mn-induced neurochemical metabolites changes in the brain. MRS can be used to quantify ratio of N-acetyl-aspartate (NAA)/total creatine (tCr), choline (Cho)/tCr, glutamine plus glutamate (Glx)/tCr along with many other brain metabolites. Different groups have reported conflicting results using MRS. While some studies found no significant differences of NAA/tCr, Glx/tCr or Cho/tCr between welders and controls [239, 240], Dydak et al. showed a significant decrease of NAA:tCr in the frontal cortex and an increase of GABA in the thalamus of Mn-exposed smelters [241]. MRS may become a promising tool for detecting early pathogenic effects of Mn exposure with further clinical studies employing larger sample sizes.

3.5. Treatment for neurological disorders with Mn overload

Lack of treatment for manganism has been the major barrier in clinical management of Mn intoxication. The foremost therapeutic strategy is removal of the source of Mn exposure [242, 243]. Levodopa is considered ineffective in manganism [142, 244], presumably because the nigrostriatal pathway remains intact. Chelation therapy has been suggested in order to reduce the body burden of Mn in severe cases of Mn intoxication [242]. Chelating therapy with intravenous ethylene-diamine-tetra-acetic acid (EDTA) has been shown to successfully increase Mn elimination in urine and decrease Mn concentrations in blood [242, 245]; however, its efficacy to ameliorate clinical symptoms is questionable [243, 246]. Chelation therapy has been found to alleviate parkinsonian symptoms in patients with inherited hypermanganesemia [117, 247]. Nonetheless, other studies reported lack of symptomatic improvements after EDTA chelation [142, 246]. The limited benefits of EDTA in the late stage of Mn intoxication may result from its low brain bioavailability [248].

In addition to EDTA, para-aminosalicylic acid (PAS), an anti-tuberculosis drug has been used successfully for treatment of severe manganism in Chinese patients with a promising long-term prognosis [248]. The therapeutic effectiveness of PAS has been attributed to its chelating function [249]. Unlike EDTA, PAS is able to pass across the blood-CSF barrier and reduce Mn from brain tissue [249]. It is noteworthy that most studies on chelation therapies are single or series case reports. Thus, large controlled clinical trials would be needed to evaluate the effectiveness of treatment strategies.

Fe supplementation is another arm of treatment. Fe is a competitive inhibitor of Mn intestinal absorption [143]. In a case of inherited hypermanganesemia, a combination of Fe supplementation and chelation therapy effectively lowered the blood Mn and reduced the body Mn load, leading to significant improvements of neurologic symptoms [250].

Conclusions

Iron and manganese are essential nutrients for human, as cofactors of various enzymes and proteins. In the brain, they are involved in oxygen transport, redox reactions, electron transport, cellular respiration, ATP synthesis, as well as metabolism of neurotransmitters. Deficiency of iron and manganese has been associated with restless legs syndrome [17] and epilepsy [21, 127, 129, 130], respectively; however, it remains unclear whether the lack of

these two metals is the primary cause or the secondary consequences of these diseases. Further research is needed to define the roles of iron and manganese in these diseases.

As environmentally abundant metals, iron and manganese overload is much more prevalent than deficiency. High levels of Fe and Mn can disrupt normal cell function and induce toxicity. Due to rigorous physiological activities and metabolism in the brain, Fe and Mn tend to accumulate in the CNS, which results in neurotoxicity. The molecular mechanisms under excessive conditions include oxidative stress, mitochondrial dysfunction, metal dyshomeostasis, inflammation, apoptosis, autophagy dysregulation and protein dyshomeostasis. Currently, high levels of iron have been associated with AD, PD, HD, FA, NF, ACE and PKAN. Excess manganese has been linked to managanism, PD, depression, ADHD and HE. Analysis of metal concentrations in biological samples, occupational exposure history and MRI can be applied to diagnose whether these diseases or syndromes are caused by Fe or Mn intoxication. If levels are abnormally increased, chelation therapy might be considered; however, these treatments may be symptomatic or have poor efficacy, since: 1) it remains unclear whether excess Fe and Mn are the primary or the secondary cause of neurodegeneration; 2) the neurological functions altered by Fe and Mn intoxication cannot be restored by removal of the metal overload; 3) neurodegeneration cannot be reversed. Limited treatment efficacy remains a common shortcoming in these neurological diseases. Thus the search for more efficient and long-term therapies should be further advanced.

Expert Opinion

Fe and Mn are required for proper physiological functions in the brain, but they also play important roles in the pathology of the neurological disorders mentioned above. Currently, there is a limited number of studies directly investigating the amount of Fe and Mn in the brain of patients afflicted the neurological diseases mentioned above. Understanding the impact of Fe/Mn on these diseases is the first step. Next it will be important to investigate whether these patients have elevated metals in their brains by means of MRI. Contemporarily, this represents a challenge given the high cost that would be associated with clinical trials. However, given the scientific link between Fe/Mn overload and those neurological diseases, these types of studies should be able to impart critical information on disease etiology. Simultaneously, future developments should also be focused on novel and cost-effective methods for the monitoring of brain Fe/Mn content. Novel Fe/Mn transporter proteins and/or homeostasis regulators will also be identified in future years. This should stimulate research into novel small molecule modifiers and the screening of large libraries for compounds that can regulate Mn/Fe levels in diverse tissues, including the CNS. Novel pharmacological modalities will contribute to these neurological disorders, enabling clinicians to focus more directly on individual needs for the control of metal homeostasis. In addition, new chelators or compounds should be developed to treat these metal-induced diseases. There is a debate among researchers as to whether chelator therapy is beneficial or harmful to patients, as chelators possibly remove essential trace metals during treatment. Moreover, the time of chelation cessation is difficult to ascertain, as blood metal levels might not be representative of their brain concentrations. Again, this reminds us to prioritize the development of new methods to accurately monitor brain Fe/Mn levels. Last

but not the least, superoxide dismutase (SOD) mimetics recently have been shown to protect against oral mucositis in cancer patients and also be protective in animal models of AD and PD. Mn is contained in all these SOD mimetics. One of these mimetics-GC4419 is already under Phase 1b/2a trial to reduce chemoradiotherapy-induced severe oral mucositis in patients with oral cavity or oropharyngeal cancer. However, potential risks of Mn intoxication exist due to the intravenous delivery method, which bypasses the regulation of intestine and liver. Thus, the metal-induced toxicity of these novel pharmacological compounds has to be evaluated clinically before release.

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Abbreviations

ACE	aceruloplasminemia
AD	Alzheimer's disease
ADHD	attention deficit hyperactivity disorder
APP	amyloid precursor protein
BBB	blood-brain barrier
CNS	central nervous system
DAergic	dopaminergic
DMT1	divalent metal transporter 1
ETC	electron transport chain
FA	Friedreich's ataxia
Fe	iron
HD	Huntington's disease
IPR	iron regulatory protein
Mn	manganese
NBIA	neurodegeneration with brain iron accumulation
NF	neuroferritinopathy
PD	Parkinson's disease
PKAN	pantothenate kinase-associated neurodegeneration
RLS	restless legs syndrome

ROS	reactive oxygen species
SOD	superoxide dismutase
Tf/TfR	transferrin/ transferrin receptor

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Key issues

- Fe and Mn both are essential elements for human. In the brain, their main function includes oxygen transport, activation and storage, electron transport, mitochondrial respiration, ATP production, signal transduction, DNA synthesis, redox reaction, neurotransmitter synthesis and metabolism, myelin production, etc. Given their critical roles in the CNS, Fe and Mn deficiency has been associated with RLS and epilepsy, respectively, although it is still under debate whether deficiency is the cause of these symptoms or the secondary consequence.
- Despite their indispensable roles in human physiology, Fe and Mn are environmentally abundant. Overexposure or excess amounts of these two metals is detrimental to the CNS. The molecular mechanisms include oxidative stress, mitochondrial dysfunction, autophagy dysregulation, apoptosis, protein and metal dyshomeostasis, which eventually result in neurodegeneration in the brain.
- Fe and Mn overload has become a serious health concern. Currently studies have shown strong links between excess Fe and neurological disorders, including AD, PD, HD, FA, ACE, NF and PKAN. Similarly, Mn overload is associated with manganism, PD, ADHD, He and depression.
- Currently, there are insufficient or unsatisfactory treatments for these diseases, with most of them only symptomatically effective, largely due to limited knowledge on the precise pathophysiological mechanisms of these disorders.