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Review Article

Iron and Mechanisms of Neurotoxicity

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The accumulation of transition metals (e.g., copper, zinc, and iron) and the dysregulation of their metabolism are a hallmark in the pathogenesis of several neurodegenerative diseases. This paper will be focused on the mechanism of neurotoxicity mediated by iron. This metal progressively accumulates in the brain both during normal aging and neurodegenerative processes. High iron concentrations in the brain have been consistently observed in Alzheimer's (AD) and Parkinson's (PD) diseases. In this connection, metalloneurobiology has become extremely important in establishing the role of iron in the onset and progression of neurodegenerative diseases. Neurons have developed several protective mechanisms against oxidative stress, among them, the activation of cellular signaling pathways. The final response will depend on the identity, intensity, and persistence of the oxidative insult. The characterization of the mechanisms mediating the effects of iron-induced increase in neuronal dysfunction and death is central to understanding the pathology of a number of neurodegenerative disorders.

1. Introduction

The so-called "biometals" (e.g., iron, copper, or zinc) are known to play a fundamental role in numerous essential metabolic processes, thus being considered as essential for life. Metal ion homeostasis is maintained through highly regulated mechanisms of uptake, storage, and secretion [1]. A specific set of transporters functions in each cellular compartment to provide a strict balance of transport activities across their membranes. Nonbound copper and iron are potentially harmful mainly due to their redox activities. Normally, under healthy conditions, these metal ions are bound to ligands (e.g., transferrin, ceruloplasmin), and they are not found as free species. However, the release of free ionic or exchangeable zinc and copper has been reported in the synaptic cleft. In addition, zinc is also being increasingly involved in several cellular reactions like calcium, and it has been proposed as a new class of second messenger.

A loss or an abnormal metal homeostasis might cause cellular death or severe dysfunction, and it has been recognized as a triggering factor for different neurodegenerative disorders such as Alzheimer's (AD), Parkinson's (PD), and Huntington's (HD) diseases as well as amyotrophic lateral sclerosis (ALS) [2–6]. Although the etiology of these diseases is still largely unknown, oxidative damage mediated by metals has been thought to be a significant contributor since metals such as iron, aluminum, zinc, and copper have been observed to be dysregulated and/or increased in AD brains and prone to generate a pro-oxidative environment [7–11]. Taking into account the great amount of information regarding the role of transition metals in cell biology, this paper will be mainly focused on the role of iron in neurodegeneration.

Loss of iron may cause neurological disease, and, in opposition, its accumulation or abnormal interaction with cellular components such as proteins, lipids, or nucleic acids may also contribute to neurodegenerative disorders. The intracellular pool of free iron, the labile iron pool (LIP), has been well established to modulate the expression of various proteins, including the amyloid precursor protein (APP) [12, 13].

In the brain, the movement of metals across the blood-brain barrier is highly regulated, and there is no passive flux of metals from the circulation to the brain [1, 14].

While iron, copper, and zinc are being increasingly implicated in interactions with the major protein components of neurodegenerative diseases, this is not merely due to increased (e.g., toxicological) exposure to metals but rather because of a breakdown in the homeostatic mechanisms that compartmentalize and regulate metals [7].

The ability of iron to accept and donate electrons can lead to the formation of reactive nitrogen and oxygen species (the latter named "ROS" in this paper) which may trigger the oxidative attack of tissue components, therefore contributing to disease and perhaps aging itself [15, 16]. Increasing age is the main risk factor associated with the appearance of neurodegenerative diseases. Several studies in animals and humans have reported a rise in brain iron as a function of ageing [17, 18]. The vulnerability of the brain to abnormal iron regulation has been demonstrated by the relationship between the failure of ferroxidases, ceruloplasmin [19, 20], ferritin [18, 21, 22], and frataxin [23, 24], iron accumulation (IA), and the onset of neurodegenerative diseases.

2. Iron Accumulation in Neurodegenerative Diseases

The accumulation of transition metals in the nervous system is a common observation in different neurodegenerative diseases that support a role of metals in these disorders [25, 26]. Particularly, iron homeostasis has shown to be altered [26, 27]. Excessive iron deposition has been reported to occur in the central nervous system (CNS) in a number of neurodegenerative pathologies such as AD, PD, ALS, and neuroferritinopathies, among others [4, 28–33].

ALS is a neurodegenerative disorder characterized by progressive paralysis of skeletal muscles and degeneration of motor neurons in the spinal cord, brainstem, and cortex. High levels of iron in the CNS of both familial and sporadic forms of ALS have been reported [32, 34, 35]. However, neither the mechanisms underlying iron accumulation nor its complete role in the pathogenesis of the disease are clear.

Neuroferritinopathies, like neurodegeneration with brain iron accumulation (NBIA), are defined as extrapyramidal disorders [33] characterized by radiographic evidence of focal iron accumulation in the brain [36]. These diseases are progressive movement disorders caused by nucleotide insertions in exon 4 of the ferritin light chain gene [37]. These patients show low levels of serum ferritin [22] and abundant spherical inclusions in the brain, skin, kidney, liver, and muscle [33] that are positive for iron, ferritin, and ubiquitin staining [38].

Moreover, abnormal accumulation of iron is also considered to be involved in the pathogenesis of myelin diseases such as multiple sclerosis (MS). Histochemical studies have shown that abnormal iron deposits are observed in reactive microglia, axons, neurons, and oligodendrocytes in patients with MS [39, 40]. Indeed, ferritin levels are increased in the CNS of mice with experimental autoimmune encephalomyelitis, an animal model of MS [41], and in the cerebrospinal fluid of MS patients [42, 43]. Since the synthesis of ferritin can reduce toxic ferrous iron (Fe^{2+}), the elevated level of ferritin in autoimmune encephalomyelitis mice and MS patients is considered to be cytoprotective [40].

Although iron has been demonstrated to have a potential role in many diseases of the CNS, this paper will focus mainly on the information regarding the role of iron in AD. It is well known that transition metals provoke oxidative stress by generating ROS through the Fenton reaction, thus causing brain lipid peroxidation [44] and protein oxidation [45, 46]. Interestingly, not only has iron been involved in lipid and protein oxidation but also in DNA damage. It has been shown that iron is able to oxidize DNA bases, and it has been suggested that the accumulation of this transition metal observed in some neurodegenerative disorders could act by both increasing oxidative genome damage and also preventing its repair [47]. Iron itself has been related to neurotoxicity, and its accumulation, mainly in the hippocampus and cortex, has been observed to occur before AD lesions are detectable. Moreover, it has been also demonstrated to accumulate both in AD senile plaques [48] and in amyloid deposits in AβPP2576 transgenic mouse model of AD [49]. Interestingly, Aβ insoluble aggregates have been shown to be dissolved by metal chelators [50].

Oxidative stress is considered to be the earliest change in the pathogenesis of AD, and high levels of oxidative stress have been demonstrated to occur in the clinical precursor of AD, known as mild cognitive impairment (MCI) [51, 52]. Coincidently, increased iron levels were found both in the cortex and cerebellum from the preclinical AD/MCI cases. Moreover, iron concentrations have been found to be increased in the bilateral hippocampus, parietal cortex, frontal white matter, putamen, caudate nucleus, thalamus, red nucleus, substantia nigra, and dentate nucleus subregions of patients with diagnosed AD and in normal elderly patients [53, 54]. It is important to note that these brain iron concentrations, particularly those in the parietal cortex at the early stages of AD, have been found to positively correlate with the severity of patients' cognitive impairment [53]. Although extensive evidence links the dysregulation of iron homeostasis and AD, relatively little is known about the resulting forms of iron that accumulate in the brain. Numerous techniques have been developed in order to characterize, locate, and quantify iron species and iron-containing compounds in AD. For example, the use of iron fluorescence together with synchrotron X-ray absorption spectroscopy showed *in situ* iron accumulations containing high concentrations of ferritin and magnetite in AD brain tissue sections [55].

Alterations in iron metabolism with age have been described, and they may involve iron uptake and release, storage, and intracellular metabolism [56–59]. Although some issues remain unclear, it is well known that the dyshomeostasis of brain iron metabolism is one of the initial events that trigger neuronal death in some neurodegenerative disorders [60–63]. Existing evidence shows that these mechanisms may well be altered by the ageing process with increased (IA) in the brain as the final outcome [64–66]. Age-induced IA has shown to be a consequence of the accumulation of different iron-containing molecules in different brain regions known to be particularly affected in disorders such

as AD and PD [18, 56]. Cellular studies have shown that iron is specifically accumulated in microglia and astrocytes in the cerebral cortex, cerebellum, substantia nigra, and hippocampus, and it is believed that this metal ion would be involved in the neuroinflammation observed in AD and PD [28]. The mechanism underlying IA in the brain is unclear yet. However, one hypothesis holds that it is the blood brain barrier dysfunction that is responsible for the exudation of serum components, with iron among them [67]. Another hypothesis with strong experimental support proposes that IA is a consequence of the dysregulation of proteins that govern metal homeostasis. Among candidates, it has been demonstrated that the iron regulatory proteins (IREG) participate in neuronal IA. Increased expression of IREG1 has been related with neuronal survival during IA [68]. In addition, IREG2 knockout (Ireb2(−/−)) mice develop IA in white matter tracts and nuclei in different brain areas and display neurodegeneration signs in Purkinje cells [69]. Mutations in the divalent metal transporter 1 (DMT1) have been shown to impair iron transport and to protect rodents against neurotoxins like 6-hydroxydopamine, supporting a critical role for DMT1 in iron-mediated neurodegeneration [70]. Mitochondrial IA, loss of iron-sulfur cluster-containing enzymes, and increased oxidative damage are known to occur in yeast and mouse frataxin-depleted mutants as well as in tissues and cell lines from Friedrich's ataxia (FRDA) patients, suggesting that frataxin may be involved in the export of iron from the mitochondria, the synthesis of iron-sulfur clusters, and/or the protection from oxidative damage [71]. The use of Deferiprone (DFP, a chelator in clinical use for treating iron overload) in FRDA cells has been found to reduce the mitochondrial LIP increased by frataxin deficiency [72]. A new recently reported mitochondrial ferritin (MtFt) specifically expresses in high energy-consuming cells, including neurons. The overexpression of MtFt has been observed to lead to a cytosolic iron deficiency and to significantly prevent the alteration of iron redistribution and, consequently, neuronal toxicity induced by 6-hydrodopamine [69].

Although the existing data clearly show a relationship between iron metabolism, aging, and neurodegeneration, more and deeper studies are needed to completely understand the role of this transition metal in the onset and progression of neurodegenerative diseases and neurological age-related disorders.

3. Iron Interaction with Amyloid Beta (Aβ) Peptide

Interestingly, IA, as well as oxidative stress in AD brains, has been linked to altered Aβ deposition. It is well known that Aβ accumulates in senile plaques in AD, and it has also been demonstrated to participate in a positive feedback loop, where oxidative stress leads to increased Aβ generation, and, conversely, the mechanism of Aβ polymerization generates oxidative stress which in turn enhances Aβ production [73]. Additionally, Aβ has been characterized as a metalloprotein able to bind transition metals (e.g., zinc, iron, copper) via 3 histidine (positions 6, 13, and 14) and 1 tyrosine (position 10) residues located in the hydrophilic N-terminal part of the peptide [74, 75], and in so doing Aβ would prevent these potentially redox-active ions from causing oxidative stress. Notably, the redox potential of iron is significantly attenuated by Aβ, supporting a neuroprotective chelating role for Aβ in AD pathogenesis [76, 77]. This particular feature of Aβ could, at least in part, explain the enrichment of these transition metals in AD plaques [48]. It has been shown that not only ROS production induces Aβ aggregation but also its ability to bind metal ions as well. Augmented iron concentrations and oxidative stress have been found to correlate with changes in the concentration of both soluble and deposited Aβ [78]. Interestingly, the metal-dependent generation of ROS by Aβ may be a good target for therapeutics. For example, chelation therapy with desferrioxamine and clioquinol (which are iron and copper/zinc chelators, resp.) has shown to induce clinical improvement in patients with AD [79, 80]. Moreover, coincubation of Aβ from postmortem AD brains with metal chelators has shown to dissolve Aβ deposits [81]. In addition, both animal and human studies with clioquinol have been found to reverse Aβ deposition, improve cognition, general behavior and health, and lower plasma Aβ levels [79, 82, 83].

Taken together, all these data clearly demonstrate that a deeper understanding of the metal-related mechanisms operating in neurodegenerative disorders such as AD is needed, since it may provide insights into new therapeutic approaches.

4. Neuronal Signaling during Iron-Induced Neurotoxicity

Neurons have developed several mechanisms in response to oxidative injury; one of them is the activation of signaling pathways that promote death or survival. The extent and duration of the oxidative insult as well as the cell type injured are crucial factors in determining which pathways are activated, their prevalence, and, in consequence, the final cellular fate [84, 85]. In this aspect, metal-induced oxidative stress has been implicated as the triggering factor of several protective and proapoptotic signaling pathways in neurons [7, 86].

Synapses are sites where the first manifestations of neurodegenerative processes are likely to appear. Their vulnerability to iron-induced oxidative stress has been largely demonstrated by the presence of membrane lipid peroxidation, impairment of membrane ion-motive ATPases, glucose and glutamate transport, and mitochondrial function [87]. In this regard, several key components of signaling pathways like extracellular signal-regulated kinase (ERK), phosphoinositide 3-kinase (PI3K), Akt, and glycogen synthase kinase 3β (GSK3β) are activated in situ in isolated synaptic endings exposed to iron-induced oxidative injury [88, 89]. Moreover, several key biochemical events that are known to occur in intact neurons undergoing apoptosis (i.e., exposure of phosphatidylserine on the plasma membrane surface, activation of caspase-3, mitochondrial calcium uptake, and ROS accumulation) also occur in isolated synaptosomes

exposed to iron-induced oxidative stress [90]. Synapse loss, a key event in neurodegenerative disorders, might also involve in situ apoptotic cascades that might occur before, or independently of, neuronal death. This assumption is supported by the appearance of degenerative morphological changes in synapses preceding amyloid deposition and neuronal degeneration [91]. However, mechanisms whereby apoptotic events triggered by iron-induced oxidative stress in synapses propagate to the cell body remain unknown.

Some cellular signaling pathways are clearly linked to enhanced survival, while others are associated with cell death. Hence, it has been suggested that the balance between the magnitude of ERK and Jun kinase (JNK) activation is key to determining survival. While this idea is still generally accepted, more recent evidence suggests that ERK can exert apoptotic influences, and JNK can exert antiapoptotic influences during the cellular response to oxidative stress.

The presence of iron and Aβ provokes a marked decrease in protein kinase C isoforms, reduced Akt serine/threonine kinase activity, Bcl-2-associated death promoter (BAD) phosphorylation, and enhanced p38 mitogen-activated protein kinase (MAPK) and caspase-9 and caspase-3 activation [92–94]. In isolated synaptic endings, the coincubation with iron and Aβ triggers the activation of Akt and ERK signaling in an oxidation-dependent manner [95]. The phosphorylation and subsequent inhibition of GSK3β mediated by AMP-activated protein kinase (AMPK) contributes to protecting mitochondria against iron-catalyzed oxidative stress [96]. In AD, abnormal activation of GSK3β pathway might play an important role in neurodegeneration, and compounds such as lithium that modulate GSK3β activity have been shown to reduce Aβ production and tau phosphorylation in APP transgenic mice [97].

Deferoxamine, a known iron chelator, has been shown to block all the proapoptotic signaling events triggered by Aβ-Fe. Moreover, Aβ alone has been shown not to activate proapoptotic signaling, thus demonstrating that apoptotic cell death can be only triggered by the presence of iron in vitro [92–94].

Iron has been found to be required for long-term potentiation in hippocampal CA1 neurons, and it is known to participate in the stimulation of calcium release through ROS produced via the Fenton reaction triggering the stimulation of the ERK signaling pathway. These results support a coordinated action between iron and calcium in synaptic plasticity and raise the possibility that elevated iron levels may contribute to neuronal degeneration through excessive intracellular calcium increase caused by iron-induced oxidative stress [98].

As previously mentioned, iron (alone or in combination with Aβ) is able to activate different signaling cascades. The activation of these signaling pathways is, in most cases, a necessary upstream event for the activation of several transcription factors (TFs). These TFs regulate the expression of specific genes that participate in cellular events such as survival or death. Nuclear factor kappa B (NF-κB) plays crucial roles in cellular resistance to oxidants and survival. Although the knowledge of NF-κB gene targets in neurons is limited, it has been demonstrated that this TF can promote their survival and regulate synaptic plasticity [99]. The involvement of NF-κB in the inhibition of apoptosis has been well established [100]. NF-κB plays a central role in the induction of neuroprotective antiapoptotic gene products, such as MnSOD and Bcl-2 that are known to contribute to ischemic tolerance [101]. Activation of NF-κB has also been associated with increased resistance of neurons to apoptosis induced by iron exposure [102]. Levels of p65 immunoreactivity have been reported to be increased in neurons and astrocytes associated with Aβ plaques in the brains of AD patients, suggesting an increased NF-κB activation [103]. Exposure of cultured neurons to Aβ or a secreted form of amyloid precursor protein (sAPP) has shown to induce NF-κB activation, thus suggesting a role for proteolytic products of APP in NF-κB activation in AD [104]. Levels of NF-κB activity have been reported to be increased in cholinergic neurons in the basal forebrain of AD patients [105]. Others have established a correlation between increased NF-κB activity and COX-2 gene transcription in brain regions affected in AD patients [106]. In addition, the inhibition of NF-κB transcriptional activity results in increased vulnerability of neurons to death induced by Aβ [107].

Hypoxia-inducible factor (HIF) is a TF that regulates the expression of more than 60 genes. The expression of genes relevant to iron metabolism such as ceruloplasmin, transferrin receptor, transferrin, and heme-oxygenase 1 has been shown to be regulated by HIF [108–111]. Iron chelation therapy that reduces the size of LIP has been reported to induce the activity of this TF. Moreover, a new multifunctional nontoxic, brain permeable iron chelator, M30, has shown to activate the HIF-1alpha signaling pathway in rat primary culture of cortical cells. M30 has also been found to increase the expression levels of the transcripts of brain-derived neurotrophic factor (BDNF) and growth-associated protein-43 (GAP-43). In connection with AD, M30 has been reported to enhance the levels of phospho-Akt (Ser473) and phospho-GSK3β (Ser9) and to attenuate Tau phosphorylation [112].

The activator protein-1 (AP-1) is another redox-sensitive TF. AP-1 is known to participate in critical cellular processes such as proliferation, differentiation, and survival. Strong evidence supports the involvement of AP-1 in oxidative stress signaling in neurons. In rat cortical neurons and astrocytes, H_2O_2 has been demonstrated to activate MAPK cascade [113]. Upstream of AP-1, c-Jun-N-terminal kinase (JNK), and p38 (two stress-related MAPK) has also shown to be activated by increases in the intracellular levels of oxidants [114–116]. Both MAPK and AP-1 are implicated in normal physiological functions of the brain. c-Jun, a component of AP-1, has been recently attributed a dual role: it is believed to mediate neurodegeneration and cell death as well as participate in plasticity and repair mechanisms. Moreover, upregulation of iron regulatory proteins and DMT-1 isoforms after neuronal injury induced by kainate has been found to be modulated by AP-1 in rat hippocampus [117].

Activation of JNK signaling in neurons has shown to increase stress resistance and to extend life span by the

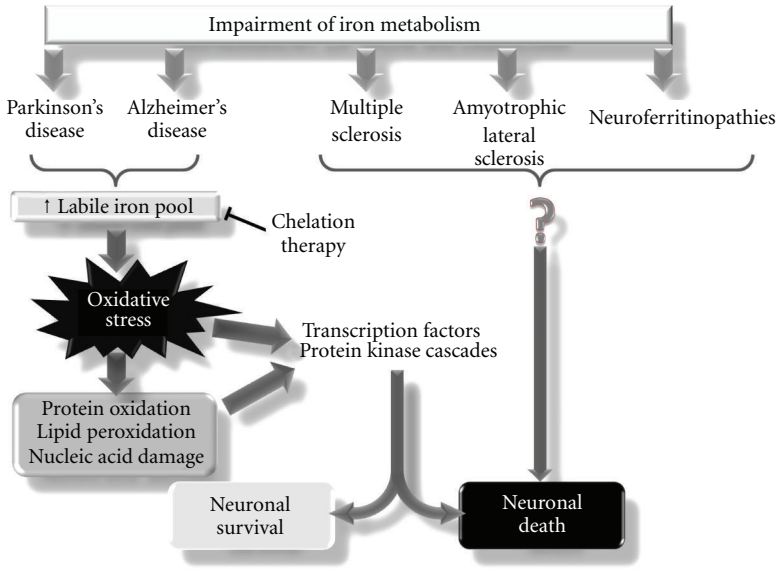

Figure 1: Relationship between the impairment of iron metabolism and neurodegenerative diseases. Impaired iron metabolism is a hallmark in several neurodegenerative diseases such as Parkinson's (PD) and Alzheimer's (AD) diseases, multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), and neuroferritinopathies. In the case of PD and AD, iron has been shown to play a key role in neuronal fate: depending on the extent and intensity of the oxidative stress caused by the increase in the labile iron pool, it affects transcriptional activity and signaling cascades that could participate in neuronal survival or death. Although a role for iron has also been observed in MS, ALS, and neuroferritinopathies, the molecular events that lead to neuronal death are not fully understood.

activation of the forkhead transcription factor (FOXO) family in Drosophila [118]. Recent studies have suggested that MST1 mediates oxidative stress-induced neuronal cell death by phosphorylating the transcription factor FOXO3 at serine 207, a site that is conserved in other FOXO family members [119, 120]. All these data support the hypothesis that FOXO signaling extends life span via amelioration of oxidative damage and mitochondrial dysfunction in neurons. However, to date, there is no link between FOXO signaling and iron-induced oxidative stress in neurons. Understanding signal transduction networks that participate in iron-induced neurotoxicity constitutes one essential objective for the discovery of new drugs and treatments aimed at the improvement and delay of AD symptoms.

5. Concluding Remarks

In this paper, we summarize the latest knowledge about the role of iron in neurodegeneration processes. Iron, a redox-active transition metal, has been proposed as an important contributing factor to the neuropathology of Alzheimer's disease. Even though increasing evidence points towards iron participation in oxidative stress events and protein aggregation, we are still far from totally comprehending the role of this transition metal in the onset and progression of neurodegenerative disorders (Figure 1). The advancement in this field will be fundamental for the establishment of new therapies intended for neuronal protection during iron mismanagement conditions.

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