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Review Article

Targeting dysregulation of brain iron homeostasis in Parkinson disease by iron chelators

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ABSTRACT

Brain iron accumulation has been implicated in a host of chronic neurological diseases, including Parkinson disease (PD). The elevated iron levels observed in the substantia nigra of PD subjects have been suggested to incite the generation of reactive oxygen species and intracellular α-synuclein aggregation, terminating in the oxidative neuronal destruction of this brain area. Thus, elucidation of the molecular mechanisms involved in iron dysregulation and oxidative stress-induced neurodegeneration is a crucial step in deciphering PD pathology and in developing novel iron-complexing compounds aimed at restoring brain iron homeostasis and attenuating neurodegeneration. This review discusses the involvement of dysregulation of brain iron homeostasis in PD pathology, with an emphasis on the potential effectiveness of naturally occurring and novel iron-chelating/antioxidant therapeutic hybrid molecules, exerting a spectrum of neuroprotective interrelated activities: antioxidant/monoamine oxidase inhibition, activation of the hypoxia-inducible factor (HIF)-1 signaling pathway and induction of HIF-1 target iron-regulatory and antioxidative genes, and inhibition of α-synuclein accumulation and aggregation.

Contents

Abbreviations: 6-OHDA, 6-hydroxydopamine; ALS, amyotrophic lateral sclerosis; AD, Alzheimer disease; BBB, blood–brain barrier; DFO, desferrioxamine; EGCG, epigallocatechin 3-gallate; EPO, erythropoietin; FBXL5, F-box/leucine-rich repeat protein 5, GLUT, glucose transporter; GSH, glutathione; HO-1, heme oxygenase-1; HIF, hypoxia-inducible factor; IRE, iron-responsive element; L-DOPA, l-dihydroxyphenylalanine; MAO, monoamine oxidase; MPTP, *N*-methyl-4-phenyl-1,2,3,6-tertahydropyridine; OS, oxidative stress; PD, Parkinson disease; PHD, prolyl-4-hydroxylase; ROS, reactive oxygen species; SOD, superoxide dismutase; SNpc, substantia nigra pars compacta; Tf, transferrin; TfR, transferrin receptor; TH, tyrosine hydroxylase; UPDRS, Unified Parkinson's Disease Rating Scale; UPS, ubiquitin–proteasome system; VEGF, vascular endothelial growth factor.

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Introduction

In many of the neurodegenerative diseases, such as Alzheimer disease (AD)[1], Parkinson disease (PD), Huntington disease, Friedreich ataxia, and amyotrophic lateral sclerosis (ALS), as well as in the regular aging process, excessive generation of oxidative stress (OS) and accumulation of iron levels and deposition have been observed in specific affected brain regions and thus regarded as contributing factors to the pathogenesis of the diseases [1–7]. In PD, high levels of iron were observed in the degenerative dopaminergic neurons and associated microglia in the substantia nigra (SN) [8].

Iron is a highly reactive element and dysfunction of iron homeostasis is accompanied by concomitant oxidation processes within the living organism. A high concentration of unbound or free iron can induce OS, because of its interaction with hydrogen peroxide (H_2O_2) in the Fenton reaction, resulting in an increased formation of hydroxyl free radicals in the neurodegenerative brain [6,9]. Free radical-related OS causes molecular damage that can then lead to a critical failure of biological functions, protein modification, misfolding, and aggregation and ultimately neuronal death [10–13]. Additionally, iron accumulation might be associated with the neurotoxicity of endogenous or environmental toxins; brain iron dyshomeostasis was reported to be linked to activation of the *N*-methyl-D-aspartic acid receptor, a signaling neurotoxicity cascade that involves nitric oxide synthase and adaptor proteins that interact with ferroportin, such as the divalent metal transporter-1 (DMT1) [14].

This review discusses primarily brain iron dyshomeostasis and toxicity in PD that may be an essential factor in the disease pathology and addresses the potential importance of targeting iron and related cascades as a novel therapeutic strategy. We mainly focus on the potential benefits of selective natural and chimeric iron-chelating compounds as a valuable therapeutic strategy in PD. The molecules in question display an array of interrelated activities relevant to brain neuroprotection; these include antioxidant activity and monoamine oxidase (MAO) inhibition, activation of the hypoxia-inducible factor (HIF)-1 signaling pathway and induction of HIF-1 target iron-regulatory and antioxidative genes, and inhibition of α-synuclein accumulation and aggregation.

Brain iron homeostasis

Iron is an abundant element in all organisms, possessing a vital physiological role due to its simplicity in accepting and donating electrons. In the central nervous system (CNS), iron is essential for multiple processes, including DNA synthesis; neurotransmission; myelination; oxygen transport, storage, and activation; mitochondrial electron transport; and metabolism. Iron also functions as a cofactor for many key enzymes of neurotransmitter biosynthesis, such as dopamine (DA) and noradrenaline [15–17]. In regard to PD, metals can act as cofactors for tyrosine hydroxylase (TH), which is the rate-limiting enzyme in DA synthesis. In vitro studies demonstrated that TH activity was stimulated by iron [18].

Brain iron homeostasis (Fig. 1) seems to rely on comparable proteins and mechanisms that exist in the peripheral organs. Brain iron (Fe) incorporation and transport is regulated by the interaction between the endothelial cells and the astrocytes; brain astrocytes are devoid of transferrin receptors (TfR's), thus suggesting that astrocytes incorporate iron by a mechanism that is not related to TfR [19]. The TfR1 in the luminal membrane of endothelial cells binds ferric iron (Fe^{3+})-loaded transferrin (Tf) and internalizes this complex into the endosomal compartment, where Fe^{3+} is reduced to ferrous (Fe^{2+}) [19]. This is transported

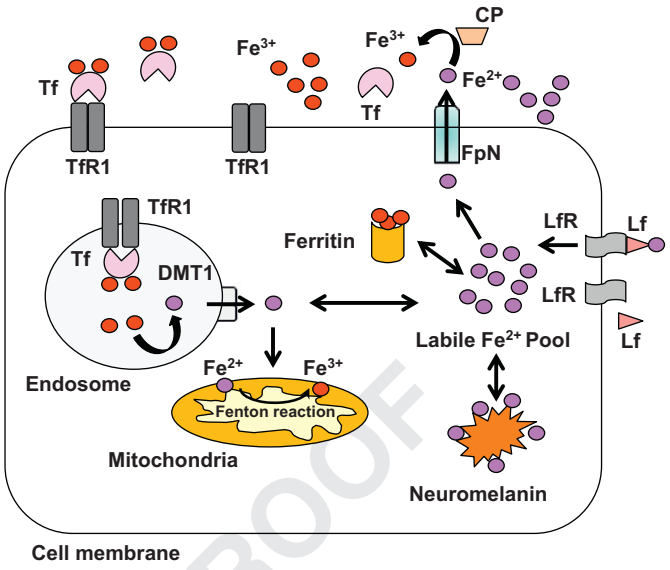

Fig. 1. Schematic illustration of brain iron homeostasis. Transferrin receptor 1 (TfR1) in the luminal membrane of endothelial cells binds ferric (Fe^{3+}) iron-loaded transferrin (Tf) and internalizes this complex into the endosomal compartment, where Fe^{3+} is reduced to ferrous (Fe^{2+}). This is then transported across the endosomal membrane into the cytosol by the divalent metal transporter-1 (DMT1) and exported into the extracellular fluid by ferroportin (FpN). On the other hand, it has been suggested that the Tf–TfR1 complex may be transported from the luminal to the abluminal surface, followed by iron release; Fe^{2+} outside the neuron is oxidized to Fe^{3+} by ceruloplasmin (CP), endorsing its binding to Tf. Lactoferrin (Lf) receptors (LfR) provide another pathway to transport Fe^{2+} across the cell membrane. Neuromelanin in SN dopaminergic neurons is the major neuronal store of iron, whereas ferritin is the main iron storage of the glial cells. Additionally, a high concentration of reactive Fe^{2+} can interact with hydrogen peroxide in the Fenton reaction, resulting in an increased formation of reactive oxygen species in the brain.

across the endosomal membrane into the cytosol by the DMT1 and exported into the extracellular fluid by ferroportin [19]. Alternatively, it has been proposed that the Tf–TfR1 complex may be transported from the luminal to the abluminal surface, followed by iron release [20]; ceruloplasmin, expressed in the astrocytes, oxidizes newly released Fe^{2+} to Fe^{3+}, which binds to Tf in the brain interstitial fluid. Lactoferrin receptors provide another pathway to transport Fe^{3+} across the cell membrane from Fe^{3+}-containing lactoferrin [19–21]. Fe^{2+} can also bind to ATP or citrate and be transported as non-Tf-bound iron, which is the source of iron for astrocytes and oligodendrocytes [19,20]. The iron-storage protein ferritin consists of two subunits, the high (H)-ferritin, a ferroxidase, which is involved in the rapid uptake and reutilization of iron, and the low (L)-ferritin, which is associated with long-term iron storage [21]. In all brain regions, both subunits are expressed, although H-ferritin is more widespread and the ratio of H-ferritin to L-ferritin depends on iron utilization by specific regional cells [21].

The control of cellular iron homeostasis is a posttranscriptional regulatory action that involves two iron-regulatory proteins (IRP), 1 and 2, which play a key role in sensing iron availability. IRPs are cytosolic RNA-binding proteins that bind to iron-responsive elements (IREs) existing in certain mRNAs that encode the proteins involved in iron homeostasis and, thus, regulate the translation or stability of these mRNAs [17]. In an environment of iron deficiency, IRPs bind to IREs and facilitate the regulation of ferritin, ferroportin, TfR1, and DMT1 [17]. In the case of ferritin and ferroportin, binding of IRPs to IREs in the 5′ untranslated region (UTR) of their mRNA prevents the initiation of their translation. For TfR1 and DMT1, the binding of IRPs to their IRE, located at the 3′ UTR of their mRNA, results in upregulation of the synthesis of

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