Iron Homeostasis

Subjects: Clinical Neurology

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Iron accumulation and neuroinflammation are pathological conditions found in several neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD). Iron and inflammation are intertwined in a bidirectional relationship, where iron modifies the inflammatory phenotype of microglia and infiltrating macrophages, and in turn, these cells secrete diffusible mediators that reshape neuronal iron homeostasis and regulate iron entry into the brain.

Keywords: neuroinflammation ; iron ; Parkinson´s disease ; Alzheimer´s disease

1. Introduction

Iron is a crucial element in many cellular processes in the brain, such as mitochondrial respiration, myelin synthesis, DNA synthesis, oxygen transportation, neurotransmitter synthesis, and cellular metabolism. In the central nervous system, iron can be found in a variety of cell types, including neurons, oligodendrocytes, astroglia, and microglia.[1] Brain iron overload in neurodegeneration-prone areas and in neuroinflammation has been broadly recognized as a pathological hallmark of neurodegenerative diseases, such Alzheimer's disease (AD) and Parkinson's disease (PD). Neuroinflammation refers to the inflammatory responses mediated by the innate immune system that take place in the central nervous system (CNS). Although it shares many features with peripheral inflammation, the coexistence of CNS specialized cell types, such as microglia, astrocytes, neurons, endothelial cells, and pericytes, confers unique characteristics to brain inflammation. Furthermore, the loss of integrity of the blood–brain barrier (BBB) found in neuroinflammatory conditions allows the infiltration of peripheral inflammatory cells, such as macrophages [2].

The initiation of the progressive inflammatory process in AD and PD can be traced to the neurodegeneration of noradrenergic (NA) neurons in the locus coeruleus (LC), which is the earliest and more severely affected area in PD (Braak stage 2), followed by dopaminergic neurons of substantia nigra (SN; Braak stage 3) and ultimately, by the neurodegeneration of hippocampal and cortical neurons (Braak stage 5) [3]. Interestingly, in the most recent Braak staging of AD, tau pathology is first observed in the LC, later spreading to the entorhinal cortex and finally to other neocortical regions [4][5][6], suggesting shared molecular mechanisms with PD [7].

The selective vulnerability of LC-NA neurons correlates with their higher production of reactive oxygen species (ROS) under physiological conditions, which is significantly potentiated by peripheral inflammation, resulting in mitochondrial damage. An elevated expression of neuronal NADPH oxidase (NOX), which catalyzes the production of the superoxide radical (O_2^-), plays an important role in the selective susceptibility of LC-NA neurons [8]. Interestingly, LC neurodegeneration can be triggered by an intraperitoneal lipopolysaccharide (LPS) injection [9], suggesting that a gut–brain axis may play a significative role in PD pathogenesis, probably associated with a "body-first" PD subtype [10].

In the brain, norepinephrine (NE) significantly contributes to the suppression of neuroinflammatory responses, by attenuating microglial surveillance and activation, reducing the secretion of proinflammatory factors, and decreasing phagocytic NOX2-mediated $\cdot O_2^-$ production [11][12][13][14][15]. Accordingly, the use of N-(2-chloroethyl)-N-ethyl-2-bromo-benzylamine (DSP-4), which is a selective NE toxin, potentiates neuroinflammation induced by amyloid β $(Aβ)_{1–42}$ aggregates [16] or bacterial endotoxin lipopolysaccharide (LPS) [17][18] and promotes AD and PD pathogenesis in several animal models [17][19][20][21][22][23][24][25][26][27].

Microglia/macrophage activation can be followed during the progression of neurodegeneration by non-invasive techniques, such as positron emission tomography (PET), using radiotracers specifically designed for targeting the mitochondrial translocator protein 18-kDa (TSPO), which is a protein highly expressed in activated microglia/macrophages. Microglial/macrophage activation has been observed using PET in monkeys injected with the mitochondrial complex I inhibitor 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which is a toxin that selectively kills dopaminergic neurons [28][29], and in rats expressing human A53T mutated α-synuclein in SN [30][31] or injected with the highly oxidable dopamine analog 6-hydroxydopamine (6-OHDA) [32][33]. Altered glial immune responses have also

been observed in animal models of familial PD [34][35] and in transgenic mice expressing AD-associated mutant proteins [36][37]. An increase in TSPO binding has been consistently observed in studies with AD [38] and PD [39] patients. However, there are several concerns about potential artifacts in microglial TSPO PET imaging, including binding to multiple cell types, such as astrocytes and endothelial cells [40][41]; differential tracer affinity in TSPO Ala147Thr polymorphism carriers [42]; and other confounding factors [43][44]. Therefore, the conclusions of these studies should be interpreted with caution. Interestingly, a recent study on AD transgenic rats shows TSPO upregulation in astrocytes before microglia [45], urging the development of more specific tracers for studying the respective contributions of astrogliosis and microgliosis to the neurodegenerative process. Overall, the reported evidence points to a central role of neuroinflammation in the initiation and progression of neurodegenerative processes.

The activation of microglial cells triggers the release of diffusible mediators, including cytokines, ROS, and reactive nitrogen species (RNS). Remarkably, ROS/RNS generation is supported by two enzymatic systems: The NOX2 enzyme complex that synthesizes $\cdot O_2^-$, which, through its dismutation, generates hydrogen peroxide (H_2O_2), and the inducible form of nitric oxide synthase (iNOS), which generates ·NO. These enzymatic systems play a crucial role in AD- and PD-associated neurodegeneration, as revealed by the neuroprotection achieved by the pharmacological or genetic inhibition of NOX2 or iNOS reported in animal models of AD [46][47] and PD [48][49][50][51].

Clinical evidence from patients displaying chronic use of non-steroidal anti-inflammatory drugs (NSAID) shows a reduced risk for AD [52][53] and PD [54]. Based on these epidemiological observations and the beneficial effects of NSAID in AD animal models, several clinical trials have been conducted to assess their efficacy in AD and dementia. Unfortunately, these studies have shown no significant effects on the cognitive performance in AD patients, prompting improvement of the therapeutic window and the use of more selective inhibitors in future clinical trials (reviewed in [55]).

Recently, neuroinflammation has been associated with the alteration of iron homeostasis, and at the same time, iron dyshomeostasis has been shown to play a pivotal role in the neuroinflammatory phenotype. As a result, neuroinflammation and iron are entangled in a circuit that amplifies ROS production, leading to neuronal death. An analysis of postmortem tissue from PD patients shows significant elevations in the concentration of iron in the SN, where degenerating neuromelanin-bearing dopaminergic neurons reside [56][57]. Similarly, iron is concentrated in and around AD senile plaques [58][59], in Huntington's disease basal ganglia [60], and in the spinal cord of sporadic amyotrophic lateral sclerosis patients [61]. Due to its paramagnetic property, iron's content can be estimated in specific brain areas using magnetic resonance imaging (MRI), by measuring the R2* relaxation rate, phase changes in susceptibility-weighted imaging (SWI), or susceptivity values upon quantitative susceptibility mapping (QSM) [62][63][64]. Neuromelanin-sensitive MRI has also been proposed as a diagnostic tool for PD [65]. Significant increases in iron levels are measured in vivo by iron-sensitive MRI, even in the early stages of AD and PD patients, showing a good correlation with the severity of their symptoms [64][66][67]. Patients with familial PD-associated mutations also display increased brain iron deposition by MRI, even in asymptomatic stages [68], suggesting that iron accumulation plays a role in the progression of the idiopathic and genetic forms of PD.

Iron overload is also associated with several animal models of AD and PD. Transgenic mice for Amyloid precursor protein/presenilin-1 (APP/PS1) [69][70][71][72] and 5xFAD [73] exhibit increased brain iron levels. Moreover, an injection of MPTP, rotenone, or 6-OHDA phenocopies many aspects of PD in rodents, including iron accumulation in the SN [74][75][76]. Supporting a causal role of iron accumulation in neurodegeneration, neonatal iron supplementation in mice triggers the progressive neurodegeneration of SN dopaminergic neurons, reduces striatal dopamine levels, and increases the responsiveness to MPTP insult [77]. Moreover, chronic oral administration of iron induces iron accumulation in specific brain regions, including the SN and caudate/putamen. Iron accumulation is associated with oxidative stress-related dopaminergic neuronal apoptosis in the SN and with motor and cognitive deficits [78]. Consequently, iron chelation prevents neuronal death in several animal models of AD and PD [79][80][81][82][83] and iron chelation has recently been introduced as a new therapeutic concept for the treatment of PD [84][85]. Nevertheless, the results on the use of iron chelation treatment demonstrate that it slows that disease progression [86]. Due to the multifactorial nature of the neurodegenerative process in PD, a single target treatment, such as the use of chelators, may not fully stop the neurodegenerative process. Accordingly, treatment with multifunctional compounds with an iron chelating capacity and aimed at reducing two or more of the pathological events associated with the progress of the disease (a "multi-target" approach) may be better suited for the treatment of PD [86][87].

Aging is the main risk factor for the development of sporadic forms of AD and PD, and both iron accumulation and neuroinflammation exhibit an age-synchronous increment in the brain. Iron levels and microglial and astrocytic numbers are positively correlated in aged mice basal ganglia [88] and iron-retentive microglia concurring with elevated iron levels

and oxidative stress in aged non-human primates [89]. Interestingly, a genetic predisposition to neuroinflammation aggravates the striatal iron-related poor cognitive switching ability in aged humans [90], highlighting the intimate relationship between iron and neuroinflammation during aging (reviewed in [91]).

2. Iron Homeostasis in the CNS

Iron is an essential protein cofactor that performs a myriad of unique functions in the CNS, including ribosome assembly, DNA repair, mitochondrial energy production, metabolite catabolism, myelination, and neurotransmitter anabolism and catabolism [92]. In excess, however, iron is linked to cellular death, causing sustained cellular oxidative stress by the iron-mediated catalytic conversion of H_2O_2 and $\cdot O_2^-$ into toxic hydroxyl radicals as a result of Fenton and Haber–Weiss chemistry, respectively [93]. Accordingly, iron homeostasis must be tightly controlled.

Transferrin (Tf), which is a glycoprotein that possesses two high-affinity iron (III)-binding sites, is the primary iron transporter into the CNS and thus plays an essential role in cellular iron uptake. Following transferrin binding to its surface receptor, TfR1, the Tf-TfR1 complex is endocytosed through clathrin-dependent pathways into the early endosome, in which its low pH induces iron dissociation from Tf. The ferrireductase Steap2 reduces Fe^{3+} to Fe^{2+}, which is transported into the cytoplasm by the divalent metal transporter-1 (DMT1). The apoTf/TfR1 complex returns to the plasma membrane, where the neutral pH induces its dissociation [94][95].

In the cytoplasm, iron is incorporated into the cytosolic labile iron pool (cLIP), which is distributed to three destinations: (i) To mitochondria, for the synthesis of iron-sulfur (Fe-S) clusters and heme prosthetic groups; (ii) to the cytoplasmic iron storage protein ferritin (Fn); or (iii) back to the extracellular fluid through the iron exporter, Fpn1. Ferritin is a multimeric protein assembled by 24 subunits of H and L monomers in a variable ratio, depending on the cellular type. The H subunit contains ferroxidase activity, while the L subunit is responsible for iron turnover at the ferroxidase site and iron nucleation within the Fn core [96].

Iron delivery to the brain is tightly regulated at the level of the BBB [95], composed of tight junction-adhered endothelial cells that safeguard the free access of molecules to the brain. Iron transport across the BBB is mediated by three mechanisms. Overall, the mechanism of iron transport across the BBB involves two transmembrane steps: Iron uptake at the luminal membrane of the brain capillary endothelial cells, followed by iron efflux into the brain interstitium at the abluminal membrane. The predominant mechanism involves the transcellular transport of iron through Tf endocytosis, DMT1-mediated transport from the endosome lumen into the cytoplasm, and Fpn1-mediated extrusion at the abluminal membrane [97][98][99]. A second mechanism involves Tf/TfR1 complex transcytosis across the endothelial cell and the release of Tf into the parenchyma at the abluminal membrane [100]. A third mechanism is dependent on Fn, which is present in blood serum and cerebrospinal fluid (CSF) [101][102][103]. Serum Fn is mainly composed of L subunits with one or two H subunits [95]. Both in vitro and in vivo studies have shown the transport of Fn across the BBB, utilizing different receptors [104][105][106]. The Scara5 receptor recognizes L-Fn [107], while H-Fn binds to TfR1 [108].

Iron released by brain vascular endothelial cells is quickly captured by nearby astrocytes, which play a critical role in regulating brain iron absorption at the abluminal side. Astrocytes do not express TfR1; however, DMT1 expression is highly polarized in astrocytes, in which DMT1 is mainly found in the end-foot processes associated with the BBB [109]. Therefore, iron released by the endothelial cells is probably taken up by nearby astrocytes through DMT1 and distributed to the brain parenchyma through Fpn1 [110]. The concentration of iron in the CSF ranges between 0.2 and 1.1 µM, whereas the concentration of Tf is about 0.24 µM [111][112]. Therefore, CSF iron levels often exceed the binding capacity of Tf [113] and iron is incorporated by neurons and glia from two sources: Transferrin-bound iron (TBI), through the Tf-TfR1 system, and non-transferrin bound iron (NTBI), through DMT1 or other iron transporters.

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