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Review

The neurotoxicity of iron, copper and manganese in Parkinson's and Wilson's diseases

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ABSTRACT

Impaired cellular homeostasis of metals, particularly of Cu, Fe and Mn may trigger neurodegeneration through various mechanisms, notably induction of oxidative stress, promotion of α-synuclein aggregation and fibril formation, activation of microglial cells leading to inflammation and impaired production of metalloproteins. In this article we review available studies concerning Fe, Cu and Mn in Parkinson's disease and Wilson's disease. In Parkinson's disease local dysregulation of iron metabolism in the substantia nigra (SN) seems to be related to neurodegeneration with an increase in SN iron concentration, accompanied by decreased SN Cu and ceruloplasmin concentrations and increased free Cu concentrations and decreased ferroxidase activity in the cerebrospinal fluid. Available data in Wilson's disease suggest that substantial increases in CNS Cu concentrations persist for a long time during chelating treatment and that local accumulation of Fe in certain brain nuclei may occur during the course of the disease. Consequences for chelating treatment strategies are discussed.

Contents

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Introduction

Impaired cellular homeostasis of metals may initiate neurodegeneration through various mechanisms. Of these, oxidative stress induced by the formation of free radicals is the best established [1]. Other possible mechanisms are impaired production of metalloproteins [2,3], activation of microglial cells leading to inflammation [4] and promotion of aggregation and fibril formation of α-synuclein, a highly conserved protein with unknown function. This protein is the major constituent of Lewy bodies found as intracytoplasmatic inclusions in Parkinson's disease (PD) neurons [5]. Recent in vitro studies have shown that mutant α-synuclein interacts with metals and that iron (Fe) and copper (Cu) seem to aggravate the toxicity caused by the α-synuclein [6,7]. It has been suggested that α-synuclein is a Cu binding protein acting as a cellular ferrireductase [8,9]. Lewy bodies contain reactive iron along with aggregated proteins and oxidized lipid material [10].

Our knowledge regarding cellular metal homeostasis has improved substantially over the last years. Several proteins involved in cellular import, export, trafficking and storage of Fe, Cu and manganese (Mn) have been identified [11–13]. Among those, two novel Mn carriers involved in intracellular Mn transport into lysosomes and Golgi, ATP13A2 and SLC30A10 respectively, have been found. Other recent findings include roles of the copper transporter protein 1 (CTR1) in Cu uptake, of Cu chaperones in synthesis of specific cuproproteins, and of ceruloplasmin in cellular Fe export [14]. Mechanisms of metal transport across the blood–brain barrier (BBB) and the blood–cerebrospinal fluid barrier (BCB) have been thoroughly investigated [11,15,16]. While the brain seems to be protected against high plasma Fe concentrations as documented in hereditary hemochromatosis [17], this is apparently not true for Mn and Cu. Thus, increased plasma Cu and Mn concentrations may lead to brain deposits and CNS damage [18]. It was recently suggested that Mn enters the CNS predominantly through the BCB and that high Mn concentration impairs the integrity of this barrier [19]. There is ongoing research on the roles of Mn species and their transporter molecules in brain Mn influx; Mn-citrate was suggested as the species with the highest influx rate [20], and is presumably also the major Mn species in the CSF [21,22]. This is in contrast to Fe and Cu which are present in CSF mainly as high molecular weight species [18]. Mn and Fe share the transport pathway using the transferrin receptor (TfR) [23,24] and it has been suggested that Fe deficit may increase brain accumulation of Mn [25,26]. Some authors argue that Fe deficiency may lead to divalent metal transporter 1 (DMT1) upregulation leading to increased Mn uptake [27,28]. There is however controversy to what extent the DMT1 is involved in Mn transport [16,29]. Interestingly, DMT1 is supposedly implicated in Mn uptake by the olfactory tract which is another possible route for brain Mn accumulation [30]. In addition to Fe and Mn interdependencies, interactions between Fe and Cu [31] as well as between Fe and calcium [32] metabolism have been reported. Comprehensive discussions of Mn, Fe and Cu transport across BBB and BCB can be found in recent reviews [11,15,16,33].

Despite these advances, it is still unclear to what extent impaired metal metabolism affects the pathophysiology of particular neurodegenerative disorders. The aim of this article is to review current literature covering association between metal dyshomeostasis and neurodegeneration, particularly studies measuring concentrations of Fe, Cu and Mn in the cerebrospinal fluid (CSF) or brain tissues of patients with PD and Wilson's disease (WD) as well as studies examining the pathophysiology of metal abnormalities. PD is a common neurodegenerative disorder with largely unknown pathophysiology, while WD is a rare disorder with well described pathophysiology involving Cu toxicosis where established chelating therapy exists.

Parkinson's disease (PD)

Accumulation of several metals, including Fe, Cu and Mn in substantia nigra (SN) has been suggested to play a causative role in the pathophysiology of PD [34]. Metal related PD hypotheses are based on:

(1) Epidemiological studies assessing the relationship between environmental exposure to metals and the risk of PD.
(2) Clinical observations that disorders with brain metal accumulation such as WD, manganism or the syndromes of neurodegeneration with brain iron accumulation (NBIA) may manifest with parkinsonism.
(3) Animal studies examining exposure to high levels of metals and the effects of chelation treatment.
(4) Measurements of metal concentrations and metal regulatory protein expression in post-mortem brain tissue samples.
(5) Measurements of metal concentrations and metal regulatory proteins in the CSF.

Several of these empirical observations are discussed in the following sections.

Environmental exposure

Effects of Fe and Cu exposure have been sparsely studied and a large environmental survey lent little support for an association between environmental exposure to Fe or Cu and PD [35]. However, combined exposure to Cu and Fe [36] or Mn and Fe [37] lasting for two to three decades have been reported to significantly increase the risk of PD. Also, toxic effects of Mn have been extensively studied [38,39] and excessive Mn intake leads to a specific condition with motor, cognitive and psychiatric symptoms known as manganism, with many similarities to PD. Manganism has been described largely in workers in mining, welding and smelting industries and in battery factories, but has also been reported in communities using drinking water with high Mn concentrations. Manganism may also arise from intravenous Mn intake, as in long-term parenteral nutrition or in methcathinon (ephedron) abusers who use potassium permanganate for the synthesis of the drug [12]. Similar clinical symptoms as in manganism have been described in end-stage liver diseases and due to mutations in the Mn transporter gene *SLC30A10* associated with insufficient biliary excretion of Mn [40]. Clinical symptoms, neuroimaging findings, pathological examination [41] and lack of response to dopaminergic drugs [42] suggest that manganism is not caused by dysfunction of dopaminergic neurons in the SN and that it is pathophysiologically different from idiopathic PD. It has been suggested that chronic Mn exposure in doses insufficient to induce manganism may be toxic to the SN rather than the globus pallidus (GP) and can increase the risk of developing idiopathic PD [43]. Several epidemiological studies have found an association between Mn exposure and risk of idiopathic PD [36,37,44–49], however other studies do not support such an association [35,50,51]. Some reviews [52,53] and one meta-analysis [54] concluded that available data argue against a relationship between Mn exposure and PD. The latter analysis used strict inclusion criteria leading to exclusion of all studies favoring the role of Mn in PD pathophysiology and the topic is still subject to debate. Efforts to establish a firm conclusion are partly hampered by difficulties in differentiating between idiopathic PD and manganism-related atypical parkinsonism in large scale epidemiological studies [55]. Several factors may increase individual susceptibility to PD-related Mn toxicity, e.g. age, ATP13A2 mutations, liver dysfunction or iron deficiency [12]. Epidemiological studies of the relationship between Mn exposure and PD should take these factors into account [43].