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Review

The role of zinc, copper, manganese and iron in neurodegenerative diseases

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ABSTRACT

Metals are involved in different pathophysiological mechanisms associated with neurodegenerative diseases (NDDs), including Alzheimer's disease (AD), Parkinson's disease (PD) and multiple sclerosis (MS). The aim of this study was to review the effects of the essential metals zinc (Zn), copper (Cu), manganese (Mn) and iron (Fe) on the central nervous system (CNS), as well as the mechanisms involved in their neurotoxicity. Low levels of Zn as well as high levels of Cu, Mn, and Fe participate in the activation of signaling pathways of the inflammatory, oxidative and nitrosative stress (IO&NS) response, including nuclear factor kappa B and activator protein-1. The imbalance of these metals impairs the structural, regulatory, and catalytic functions of different enzymes, proteins, receptors, and transporters. Neurodegeneration occurs via association of metals with proteins and subsequent induction of aggregate formation creating a vicious cycle by disrupting mitochondrial function, which depletes adenosine triphosphate and induces IO&NS, cell death by apoptotic and/or necrotic mechanisms. In AD, at low levels, Zn suppresses β-amyloid-induced neurotoxicity by selectively precipitating aggregation intermediates; however, at high levels, the binding of Zn to β-amyloid may enhance formation of fibrillar β-amyloid aggregation, leading to neurodegeneration. High levels of Cu, Mn and Fe participate in the formation α-synuclein aggregates in intracellular inclusions, called Lewy Body, that result in synaptic dysfunction and interruption of axonal transport. In PD, there is focal accumulation of Fe in the substantia nigra, while in AD a diffuse accumulation of Fe occurs in various regions, such as cortex and hippocampus, with Fe marginally increased in the senile plaques. Zn deficiency induces an imbalance between T helper (Th)1 and Th2 cell functions and a failure of Th17 down-regulation, contributing to the pathogenesis of MS. In MS, elevated levels of Fe occur in certain brain regions, such as thalamus and striatum, which may be due to inflammatory processes disrupting the blood-brain barrier and attracting Fe-rich macrophages. Delineating the specific mechanisms by which metals alter redox homeostasis is essential to understand the pathophysiology of AD, PD, and MS and may provide possible new targets for their prevention and treatment of the patients affected by these NDDs.

Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; Al, aluminum; AP-1, activator protein-1; APP, amyloid precursor protein; ATP7A, adenyl pyrophosphatase copper transporting alpha; ATP, adenosine triphosphate; BBB, blood brain barrier; CAT, catalase; Cd, cadmium; cIAP, cellular inhibitors of apoptosis; CNS, central nervous system; Co, cobalt; Cr, chromium; Cu, copper; COX-2, cyclooxygenase 2; CRT1, copper transport protein; CSF, cerebrospinal fluid; DA, dopamine; DCYTB, duodenal cytochrome B; DNA, deoxyribonucleic acid; DMT1, divalent metal transporter-1; Fe, iron; GABA, aminobutyric-acid; GPx, glutathione peroxidase; GR, glutathione reductase; H_2O_2, hidrogen peroxide; GS, glutamine synthetase; IFN-γ, interferon gamma; IL, interleukin; iNOS, inducible nitric oxide synthase; IO&NS, inflammatory, oxidative and nitrosative stress; Pb, lead; Mn, manganese; MnSOD, manganese superoxide dismutase; MBP, myelin basic protein; MMP, matrix metalloproteinase; Mo, molybdenum; MS, multiple sclerosis; NADPH, dicotinamide adenine dinucleotide phosphate; NDDs, neurodegenerative diseases; NK, natural killers; NF-kB, nuclear factor kappa B; NMDA, N-methyl-D-aspartate receptor; PD, Parkinson's disease; PKC-δ, protein kinase C δ; RNS, reactive nitrogen species; ROS, reactive oxygen species; RRMS, relapsing-remitting multiple sclerosis; SH, sulfhydryl groups; SOD, superoxide dismutase; STEAP2, six-transmembrane epithelial antigen of the prostate-2 metalloreductase; Th, T helper; Tf, transferrin; TNF-α, tumor necrosis factor alpha; TrF, transferrin receptor; V, vanadium; Zn, zinc; ZIP, Zrt-and-Irt-related protein; ZnT, Zn transporter; Zrt, Zn transporter proteins

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1. Introduction

Trace metals are defined as essential elements to life and, in general, are present in low concentration in human organism. Essential metals, such as zinc (Zn), copper (Cu), manganese (Mn) and iron (Fe) play a role as cofactors in the activity of a wide range of physiological processes involved in cellular homeostasis and survival, as well as during organ and tissue development (Hsu et al., 2018; Zoroddu et al., 2019).

It is well recognized that alterations in the homeostasis of oligoelements may result in damage of the central nervous system (CNS), with neurodegeneration, disability and neuroinflammation, contributing to the development of several neurodegenerative diseases (NDDs) (Garza-Lombó et al., 2018). NDDs are characterized by progressive dysfunction and loss of neurons with involvement of different functional systems and a wide spectrum of clinical presentations. There are several pathways which contribute to the damage of neurons. A fundamental phenomenon in most NDDs is the deposition of proteins with altered physicochemical properties, as has been shown for Alzheimer disease (AD), Parkinson disease (PD), Wilson disease, prion disease, tauopathies, and other forms of proteinopathies Chronic excitotoxicity has been discussed for progressive long-term NDDs (Kovacs, 2016). Moreover, microglia activation, neuroinflammation, formation of reactive oxygen species (ROS), reactive nitrogen species (RNS), mitochondrial dysfunctions, autoimmunity and demyelination are other mechanisms involved in the neurodegeneration, as have been shown for multiple sclerosis (MS) (Kumar and Abboud, 2019). MS is a disabling disease of the CNS with features of autoimmunity and neurodegeneration. Both the components of immune system (innate and adaptive immunity) play important role in the generation of neuroinflammation in different NDDs, including PD and MS (Gelders et al., 2018). These different pathways interact with others, such as those of energetic dysregulation, molecular damage, metabolic changes, dysregulation of ion homeostasis, and adaptation (von Bernhardi and Eugenín, 2012).

The large majority of the NDDs has a multifactorial etiology with interactions between genetic, lifestyle and environmental factors (Cicero et al., 2017). Among environmental risk factors of NDDs, xenobiotic metals are gaining increasing attention because a larger percentage of population is exposed to industrial pollution through food, air and water (Kawahara et al., 2017; Pandey et al., 2018).

Neurotoxicity of metals has been demonstrated *in vitro*, as well as *in vivo* experimental and epidemiological studies carried out on different populations exposed to trace elements and it is likely that each metal could be toxic through specific mechanisms (Islam, 2017). Excessive metal accumulation in the CNS may be toxic, inducing oxidative stress, disrupting mitochondrial function, and impairing the activity of numerous enzymes with important structural, regulatory, and catalytic functions in different types of proteins, receptors, and transporters. Moreover, alteration in essential metal homeostasis has been suggested to cause neurodegeneration, e.g. in AD via association of metals with proteins and subsequent induction of aggregate formation. Metals can cause neurodegeneration in PD, AD and MS through a vicious cycle by disrupting mitochondrial function, which depletes adenosine triphosphate (ATP) and induces ROS production. Through these mechanisms, metals cause cell death by apoptotic and/or necrotic mechanisms (Garza-Lombó et al., 2018).

In this review, we discuss the role of these essential metals (Zn, Cu, Mn and Fe) on the pathophysiology of some NDDs, including AD, PD and MS, as well as the mechanisms involved in their neurotoxicity.

2. Essential metals responsible for neurodegenerative diseases

The inflammatory immune response and oxidative and nitrosative stress (IO&NS) are the main pathways of ROS and RNS production, which are responsible for a serious and persistent imbalance between the production of highly oxidative compounds and antioxidant defenses that leads to tissue damage, including CNS (Bhat, 2015). The antioxidant defense system has the function of inhibiting and/or reducing the damage caused by the deleterious free radicals and/or non-radical ROS. The antioxidant defense is divided into enzymatic system, such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx), as well as nonenzymatic system through a variety of antioxidant substances, which may be endogenous or dietary, such as ascorbic acid (vitamin C), alpha-tocopherol (vitamin E), carotenoids, and flavonoids. As an integral part of their active sites, two major antioxidant enzymes, SOD and CAT, contain metal ions to battle against toxic effects of metal-induced free radicals (Liu et al., 2017).

Some NDD, including AD, PD and MS, as well as the aging process show that the blood brain barrier (BBB) is more vulnerable than it seems (Kempuraj et al., 2016) and protects the CNS against chemical insults through different complementary mechanisms. Toxic metal molecules can either bypass these mechanisms or be sequestered in and, therefore, potentially be deleterious to BBB. Supportive evidence suggests that damage to blood–brain interfaces can lead to chemical-induced neurotoxicity induced by metals (Chen et al., 2014).

The Fig. 1 shows the role of Zn, Cu, Mn and Fe in the mechanisms of IO&NS in the CNS.

2.1. Mechanisms of Zn neurotoxicity on AD, PD and MS

Zn is the second most abundant transition metal after Fe and is required for humans and many other living organisms. Dietary Zn is absorbed in the small intestine (duodenum and jejunum) and then distributed to peripheral tissues. The Zn excess is excreted through gastrointestinal secretion, sloughing mucosal cells, and in tegument (Kambe et al., 2015).

Zn has an impact on the immune system and possesses neuroprotective properties and changes in plasma levels have consequences, particularly, on the CNS and the immune systems (Bredholt and Frederiksen, 2016). Zn is a cofactor for over 300 enzymes and metalloproteins, including matrix metalloproteinases (MMP). MMP are a group of proteases dependent of Zn for their proteolytic activity and involved in remodeling of the extracellular matrix and modifying cell–matrix interactions. Zn is a component of an even greater amount of proteins including myelin basic protein (MBP), regulating gene transcription and the antioxidant response. The redox inert metal Zn is an essential component of numerous proteins involved in the defense against oxidative stress and depletion of its metal may enhance DNA damage via impairments of DNA repair mechanisms (Kambe et al., 2015).

Zn is widely used as a structural element in proteins than any other transition metal ion, is a catalytic component of many enzymes, and acts as a cellular signaling mediator. The majority of Zn is in the testes, muscle, liver, and brain (Chen et al., 2016). Following the uptake of Zn by cells, it is distributed within the cytoplasm (50%), nucleus (30%–40%), and cell membrane (10%). Cellular Zn is then available as four pools. First, it can bind tightly to metalloproteins, as a structural component or to metalloenzymes as a cofactor; second, Zn binds to metallothioneins with a low affinity, which can occupy 5%–15% of the total cellular Zn pool; third, it can be compartmentalized into intracellular organelles and vesicles for Zn storage and as a supply for Zn-dependent proteins, which is mediated by Zn transporters; and fourth, a pool of cytosolic free Zn is maintained at a very low concentration (Lee, 2018).

The importance of Zn to the function of the CNS is increasingly being established and has been suggested as a key factor in the development of several NDDs, such as AD, PD and MS. In the CNS, Zn occurs in two forms: the first being tightly bound to proteins and, secondly, the free, cytoplasmic, or extracellular form found in presynaptic vesicles. Under normal conditions, Zn released from the synaptic vesicles modulates both ionotropic and metabotropic post-synaptic receptors. For Zn to perform its diverse bioactive roles, a number of specific systems to transport Zn across the biological membrane are required (Kimura and Kambe, 2016).

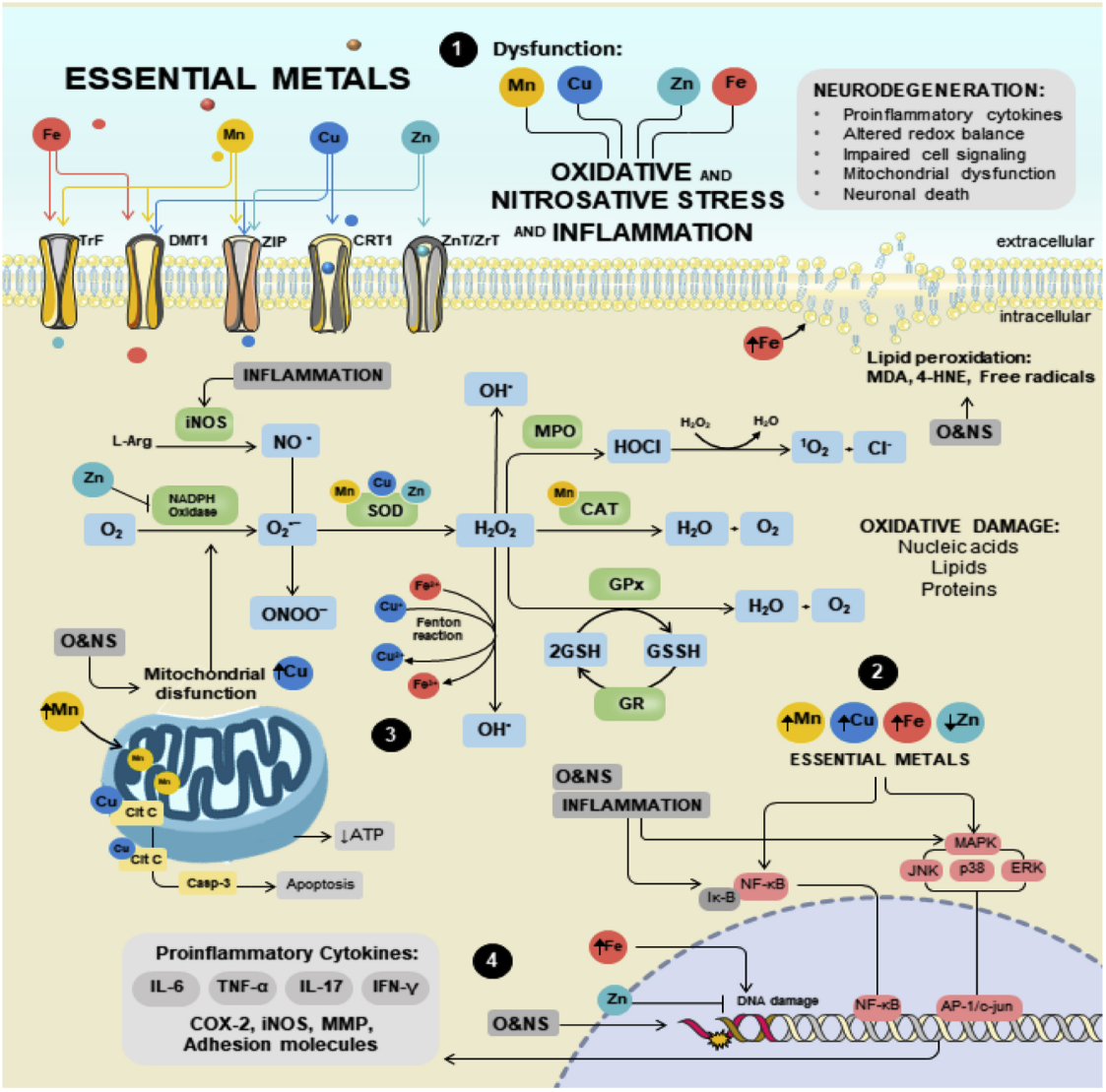

Fig. 1. The role of zinc (Zn), copper (Cu), manganese (Mn), and iron (Fe) in the mechanisms of inflammation, oxidative and nitrosative stress (IO&NS) in the central nervous system (CNS). The role of Zn, Cu, Mn and Fe in the mechanisms of IO&NS in the CNS is visualized in the following sequence: 1) the essential metals interact with different cell membrane receptors, such as the divalent metal transporter-1 (DMT-1), transferrin receptor (TrF), Zn transporter (ZnT) and Zrt/Irt-related proteins (ZIP), Cu transport protein 1 (CRT-1), to participate in a wide array of physiological and cellular functions; 2) changes in the essential metal levels, including low levels of Zn, as well as high levels of Mn, Cu and Fe participate in the activation of signaling pathways involved in the IO&NS, including the nuclear factor Kappa B (NF-kB) and activator protein-1 (AP-1). With the activation of the NF-kB and AP-1/c-jun transcriptional factors, the deleterious effects of these metals are through the induction of proinflammatory cytokines interleukin (IL)-6, tumor necrosis factor (TNF)-α, IL-17, and interferon (IFN)-γ, as well as cyclooxygenase 2 (COX-2), inducible nitric oxide synthase (iNOS), matrix metalloproteinases (MMP), and adhesion molecules that are key molecules in the brain damage; 3) Fe and Cu participate in the Fenton reaction to generate free radicals for the innate immune response; on the other hand, high levels of Fe contribute to the blood-brain-barrier (BBB) breakdown and deoxyribonucleic acid (DNA) damage; 4) Zn participates in the modulation of the deleterious effects of these molecular and cellular events on CNS, inhibits the DNA damage, inhibits the nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase, as well as Mn is for the catalase (CAT), Mn, Cu and Zn for the superoxide dismutase (SOD), important enzymes of the antioxidant enzymatic system defense against toxic effects of metal-induced free radicals.

Thus, Zn transport proteins are indispensable for the physiology of Zn. In particular, Zn transporter (ZnT) and Zrt/Irt-related proteins (ZIP) contribute to a wide array of physiological and cellular functions (e.g., immune, endocrine, reproductive, skeletal, and neuronal) by tightly controlling Zn homeostasis. The mobilization of Zn into or out of the cytosol, therefore, is directed though ZIP and ZnT and in the cytosol, MT bind Zn to reserve, buffer, and chelate. The physiological importance of Zn homeostasis in humans, as well as ZIP and ZnT transporters mutation in human genetic are demonstrated by the deleterious consequences of NDDs (Szewczyk et al., 2013). Excess levels of Zn, for example, suppresses Cu and Fe absorption, promoting ROS production in the mitochondria, disrupting activities of metabolic enzymes, and activating apoptotic processes (Chen et al., 2016).

Zn can influence the production and signaling of numerous inflammatory cytokines in a variety of cell types. Plasma Zn concentrations rapidly decline during acute phase response to different stimuli, such as stress, infection and trauma. Consequently, Zn is shuttled into cellular compartments, where it is utilized for protein synthesis, neutralization of free radicals and to prevent microbial invasion. The Zn redistribution during inflammatory events seems to be mediated by cytokines. Therefore, patients with acute illnesses show hypozincemia along with elevated cytokine production (Gammoh and Rink, 2017). On the other hand, patients with chronic inflammation, which is characterized by increased levels of inflammatory cytokine production, the Zn intake may influence the cytokine production. Patients with lower Zn dietary intake present with lower plasma and intracellular Zn

concentrations along with upregulated gene expression of inflammatory cytokines, including interleukin (IL)-1α, IL-1β, and IL-6, compared to patients with higher Zn intake (Costarelli et al., 2010).

Zn has been well known to be essential for the normal function of both innate and adaptive immunity responding to pathogen or tissue damage and exerting anti-inflammatory and antioxidant functions (Lee, 2018). Zn exerts its antioxidant function through four different mechanisms. First, by competition with Fe and Cu ions for binding to cell membranes and proteins, displacing these redox active metals, which catalyze the production of hydroxila (·OH) from H_2O_2; second, Zn binds to sulfhydryl (SH) groups of biomolecules protecting them from oxidation; third, by increasing the activation of antioxidant enzymes, such as GSH, CAT, and SOD and also for reducing the activities of oxidant-promoting enzymes, including inducible nitric oxide synthetase (iNOS) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, as well as inhibiting the generation of lipid peroxidation products; and fourth, Zn induces the expression of metallothioneins, which are very rich in cysteine and an excellent scavenger of ·OH ions (Bao et al., 2013).

Moreover, Zn acts as anti-inflammatory element influencing major pro-inflammatory signaling pathways. Zn prevents the dissociation of nuclear factor k B (NF-kB) from its corresponding inhibitory protein, thus preventing the nuclear translocation of NF-kB and inhibiting subsequent inflammation. Zn also inhibits IL-6-mediated activation of STAT3 (Gammoh and Rink, 2017).

Homeostasis of Zn is essential for proper brain function (Zn and Fe are prevalent cerebral metals) and changes in its levels are associated with AD, PD, and MS (Grabrucker et al., 2011). In these diseases, Zn deficiency decreases the activity of serum thymulin (a thymic hormone), which is required for maturation and differentiation of T helper (Th) cells. Th1 cytokine profile is decreased but Th2 cytokine profile is not affected by Zn deficiency in humans. This shift of Th1 to Th2 function results in cell-mediated immune dysfunction and, because IL-2 production (a Th1 cytokine) is decreased, this leads to decreased activities of natural killer (NK) cells and T cytotoxic cells, which are involved in host defense mechanisms. Zn deficiency may also decrease the generation of new $CD41^+$ T cells from the thymus. On the other hand, Zn supplementation to patients with AD, PD, and MS decreased the gene expression and production of pro-inflammatory cytokines and decreased oxidative stress biomarkers (Bredholt and Frederiksen, 2016).

AD and PD are the primary NDDs and, particularly, are two NDD that occur in an age-related manner. For example, serum Zn levels were found to be significantly decreased in older AD patients compared to control subjects. AD is characterized by the abnormal intracellular accumulation of the amyloid beta (Aβ) protein and/or its assembly into paired helical filaments and extracellular accumulation in plaques. Possible causes of AD include increased levels of oxidative stress in the brain, as well as the sequestration of Zn ions within amyloid plaques. Zn can induce Aβ monomers to aggregate in different forms and is known to bind Aβ via its histidine imidazole rings and accumulate within senile plaques. So, at low concentrations (a few micromolar), Zn suppresses β-amyloid-induced neurotoxicity by selectively precipitating aggregation intermediates. However, at high levels, the binding of Zn to β-amyloid may enhance formation of fibrillar β-amyloid aggregation, leading to neurodegeneration (Cristóvão et al., 2016).

The incidence of AD is increasing and major risk factors for AD are advancing age, family history, heredity, besides modifiable factors as type 2 diabetes mellitus and obesity (Alzheimer's Association, 2017). These factors, in turn, have been associated with an increased risk of dementia. In the brain, Zn co-localizes with glutamate in synaptic vesicles, and modulates N-methyl-D-aspartate receptor (NMDA) receptor activity (Mlyniec, 2015). Intracellular Zn is involved in apoptosis and fluctuations in cytoplasmic Zn affect modulation of intracellular signaling (Olesen et al., 2016).

Both increased and reduced levels of cytoplasmatic Zn have been implicated in AD pathophysiology. Intracellular Zn depletion destabilizes microtubules, herby starting a cascade of tau release, hyperphosphorylation and formation of neurofibrillary tangles. Intracellular Zn excess, occurring as consequence of Aβ aggregation and ROS generation, releases Zn from metallothioneins and may affect mitochondrial function and induce apoptosis. One way to reconcile these seemingly contradictory findings is to suggest that intracellular Zn must be tightly regulated to avoid adverse molecular consequences reducing the amount of Zn available for crucial intracellular processes (Olesen et al., 2016).

Experimental and clinical data support Zn as a plausible therapeutic intervention to ameliorate cognitive impairment in disorders characterized by alterations in Zn and Cu, such as AD (Sandusky-Beltran et al., 2017; Brewer, 2012). Six months of Zn therapy in patients age 70 and over stabilized cognition loss in and also reduced serum free Cu in AD patients, suggesting that the efficacy may come from restoring normal Zn levels, or from lowering serum free Cu, or from both (Brewer, 2012). However, at this point, the author can't be certain that Zn deficiency could be is a risk factor in AD, because Zn supplementation may be acting through lowering serum free Cu (Brewer, 2014). On the other hand, an experimental study in a Tau mouse model showed that Zn supplementation intensified the deficits in behavior and biochemistry caused by Tau (Craven et al., 2018). These authors suggested that individuals at risk for tauopathies should be cautioned against excessive Zn supplementation. Moreover, a systematic review found no conclusive evidence to recommend a modification of Zn diet in order to lower the risk of AD. Neither the small number of interventional studies that supplemented or translocated Zn nor the prospective studies provide consistent evidence, although a subclinical deficiency appears common in the elderly and subjects with AD. Actually, the authors suggested that, in dietary studies with animals, the impact of dietary Zn on cognitive performance depend on additional nutrients (Loef et al., 2012).

It has been suggested that carnosine (β-alanyl histidine) may well play neuroprotective roles against AD (Corona et al., 2011; Kawahara et al., 2018). Carnosine is a Zn chelator, acts as a neuroprotector in these diseases owing to its numerous beneficial characteristics including anti-endoplasmic reticulum stress, antioxidant, and anti-cross-link activities. Orally administered carnosine inhibits the accumulation of AβP, and prevents learning deficits in a murine model of AD (Corona et al., 2011). Considering the beneficial characteristics of carnosine, dietary supplementation with carnosine or its component may become useful for health, as carnosine in food plays a critical role in the regulation of Zn homeostasis and the prevention of NDD (Kawahara et al., 2018).

In PD, in turn, α-synuclein aggregates in intracellular inclusions called Lewy Bodies, which are associated with the degeneration of dopaminergic neurons in the substantia nigra pars compacta. Patients with PD show significant decrease in Zn levels compared to control subjects and oxidative stress is also implicated as a major causative factor for this NDDs (Du et al., 2017).

In both AD and PD, disorders in Zn^{2+} and Cu^{2+} homeostasis play a pivotal role in the mechanisms of their pathogenesis. The interactions of Zn^{2+} and Cu^{2+} with amyloid precursor protein (APP), β-amyloid and Tau proteins are considered, as well as the role of these interactions in the generation of free radicals in AD and PD. The main factors of AD and PD pathogenesis, such as oxidative stress, structural disorders and aggregation of proteins, mitochondrial dysfunction, energy deficiency that initiate a cascade of events resulting finally in the dysfunction of neuronal networks, are mediated by the disbalance of Zn^{2+} and Cu^{2+} (Stelmashook et al., 2014).

In its turn, MS is a prototypic chronic inflammatory immune-mediated disease of the CNS, which is characterized by inflammation, oligodendrocyte depletion, reactive astrogliosis and demyelination in the brain, optic nerve and spinal cord. Usually, occurs in adults and is more common in women than men (Mirshafiey et al., 2014). A

disrupted Zn homeostasis affects the immune cells, leading to impaired activation and maturation of lymphocytes, disturbed intercellular communication via cytokines, and weakens innate host defense via phagocytosis and oxidative burst (Maares and Haase, 2016; Sheykhansari et al., 2018). Low levels of Zn have been also reported to be associated with T cell-mediated autoimmunity (Pawlitzki et al., 2018). Indeed, Zn deficiency is reported to induce an imbalance between Th1 and Th2 cell functions and between T regulatory (Treg) and pro-inflammatory T cells, as well as a failure of the Th17 down-regulation, the major mechanisms that contribute to the pathogenesis of MS autoimmunity (Pawlitzki et al., 2018; Li et al., 2017).

The association between Zn deficiency and the development of MS has been supported by numerous studies, especially in the relapsing-remitting MS (RRMS) clinical form (Choi et al., 2018; Pan et al., 2017). Other studies showed lower levels of Zn in the plasma of MS patients compared to controls (Bredholt and Frederiksen, 2016; Socha et al., 2017; Popescu et al., 2017; Sanna et al., 2018).

The imbalanced immune response associated with Zn deficiency could be restored by Zn integration. It was shown that Zn supplementation suppresses Th17 development via inhibition of STAT3 activation (Kitabayashi et al., 2010). With this possible effect on Th17, the Zn supplementation was evaluated in EAE and MS. An approach with redistributing Zn in the body with Clioquinol, a Cu or Zn chelator, has shown promising results in the EAE. The study showed suppression of demyelination, reduced infiltration of encephalitogenic immune cells, inhibited BBB disruption, reduced MMP-9 activation and reduced clinical score of EAE after treatment with Clioquinol (Salari et al., 2015). However, a clinical study showed no improvements of neurological signs in patients with MS compared with the placebo group after 12 weeks of Zn supplementation (Choi et al., 2013).

In summary, Zn is a multipurpose metal that is vital for the growth and function of the cells. The immune system is especially affected by the modification of Zn homeostasis, specially the pathways associated with AD, PD and MS pathogenesis. Achieving an optimal immune response to different stimuli and avoiding damage of tissues and organs is a delicate balance that relies, amongst other factors, on the regulation of Zn in extracellular and intracellular compartments (Gammoh and Rink, 2017).

2.2. Mechanisms of copper neurotoxicity

The balance between beneficial and harmful effects of free radicals is a very important aspect of living organisms and is achieved by mechanisms called “redox regulation”. Redox regulation protects living organisms from various oxidative stress processes and maintains “redox homeostasis” by controlling the redox status. In fact, the neurotoxic effects are attributed to increased ROS production in CNS due to inherent redox properties of Cu ions (Rana et al., 2018). Because of its high metabolic rate and relatively capacity for cellular regulation compared with other organs, brain is believed to be particularly susceptible to the damaging effects of ROS. Manifestation of ROS damages and neurodegeneration has been related to essential metals, including Cu. The excess of Cu is neurotoxic and has been implicated in the pathogenesis of AD and PD as well as prion disease and other NDDs. Moreover, altered Zn and Cu homeostasis is implicated in several conditions, such as high Cu/Zn ratio was observed in the elderly, particularly those with NDD (Hane et al., 2016).

Cu is an essential element and an integral component of various enzymes, including Cu/Zn-superoxide dismutase (Cu/Zn-SOD or SOD1), cytochrome c oxidase, dopamine β hydroxylase and monoamine oxidase, playing an important role in electron and oxygen transport, protein modification, and neurotransmitter synthesis (Kawamata and Manfredi, 2010). On the other hand, excess amounts of Cu are toxic as it is a potential generator of free radicals via Fenton chemistry. Thus, Cu homeostasis must also be strictly regulated in the systemic, cellular, and subcellular levels as dysregulation causes severe consequences (Nishito and Kambe, 2018).

Dietary cupric Cu (Cu^{2+}) needs to be reduced to cuprous Cu (Cu^{1+}) before uptake across the apical membrane by Cu transporter 1 (CTR1), a high affinity Cu uptake transporter. The reduction is thought to be mediated by several reductases such as ferrireductase, duodenal cytochrome or cytochrome b reductase 1 (DCYB) and six-transmembrane epithelial antigen of the prostate-2 (STEAP2) metalloreductase. Cu^{1+} is taken up by CTR1, which localizes to the apical membrane, and early endosomes in the intestinal epithelial cells. Cu exported from the intestinal epithelial cells binds to albumin or α_2-macroglobulin in the blood and is transported to the liver, where Cu loading onto ceruloplasmin occurs for systemic circulation. The former is functional for loading Cu to the SOD1, while the latter is necessary for Cu mobilization into the mitochondria. Excess Cu in the cytosol binds to the metallothioneins, thereby reducing free Cu ions, which is thought to be important for avoiding the toxicity caused by free Cu ions (Nishito and Kambe, 2018).

Since Cu is loosely bound to albumin, it is possible that Cu ions may be released from albumin-bound moiety at the BBB and that these free Cu ions may subsequently be transported into the brain (Nishito and Kambe, 2018). Two intracellular proteins, i.e., Cu-transporting P-type ATPases (ATP7A and ATP7B) belonging to a subclass of ATPases, are responsible for ATP-dependent transport of Cu across the BBB, but the distribution pattern of ATP7A and ATP7B in the BBB are unknown. Under normal physiological conditions, the BBB is impermeable to Cu. Movement of Cu across the BBB between two fluid compartments requires specific Cu transport systems. Only under certain pathological conditions, in which BBB permeability is compromised, Cu may enter the cerebrospinal fluid (CSF) through passive diffusion (Zheng and Monnot, 2012).

Regarding SOD1, this enzyme acts as a first line of defense against toxicity of superoxide anion ($O_2^{\bullet -}$) radicals. The enzyme may also participate in cell signaling where ROS have been invoked. Although largely cytosolic, SOD1 also resides in the mitochondrial intermembrane space, where the enzyme can directly remove superoxide ($O_2^{\bullet -}$) generated from the mitochondrial respiratory chain (Wang et al., 2015).

AD is one of the biggest healthcare challenges in developed countries, which Cu and Fe toxicity is implicated in the metal hypothesis of its pathogenesis. Aaseth and coworkers (Aaseth et al., 2016) suggested that Fe and Cu promote Aβ formation/accumulation in AD plaques, and this deposition in the CNS appears to promote the progression of the Aβ cascade. Inside of neurons, Fe and Cu binding to hyperphosphorylated Tau protein precedes the formation of intracellular tangles. The presence of free Fe^{2+} or Cu^{1+} species will induce deleterious Fenton reactions with ROS generation and microinflammation (Ward et al., 2015).

The neurotoxic mechanism of action of Cu was classically viewed as its strong affinity to Aβ to help its aggregation and increase oxidative stress via Fenton reaction. Thus, it has been thought that accumulation of Cu mediates neurotoxicity and removing it from the brain prevents or reverse Aβ plaque burden. However, recent evidence suggests that dyshomeostasis of Cu and its valency in the body, instead of the accumulation and interaction with Aβ, are major determinants of its beneficial effects as an essential metal or its neurotoxic counterpart. This notion is also supported by the fact that genetic loss-of-function mutations on Cu transporters lead to severe neurological symptoms. Along with its altered distribution, it was proposed novel mechanisms of Cu neurotoxicity mediated by non-neuronal cell lineages in the brain, such as capillary endothelial cells, leading to development of AD neuropathology (Hsu et al., 2018).

In its turn, Cu plays a dual role in PD. On one hand, free Cu is associated with increased oxidative stress, oligomerization of α-synuclein protein, and formation of Lewy bodies via Fenton and Haber–Weiss reactions. On the other hand, Cu acts as a cofactor of important antioxidant enzymes, such as Cu/Zn-SOD, which reduces

oxidative stress. Studies of PD patients have reported total serum or plasma Cu levels, rather than individual levels of the different pools of Cu. Theoretically, as the concentration of non-ceruloplasmin bound Cu is very low relative to total serum Cu concentrations, a clinically significant change in the highly reactive pool of non-ceruloplasmin-bound Cu may not be apparent. Taken together, these findings suggest that Cu and ceruloplasmin levels in the blood are unaltered in PD and, therefore, unlikely to represent a valid diagnostic marker or prediction tool in PD (Davies et al., 2016).

The role of Cu in MS pathology is proposed to be via excessive Cu and subsequent oxidative damage. The injury of mitochondrial electron transport system, cytochrome oxidase, and activated glia increase Cu contents. However, according to Sheykhansari et al (Sheykhansari et al., 2018), conflicting findings have also been reported. Previous results show that the elevated Cu levels found in CSF and serum of MS patients could be due to serum ceruloplasmin reduction of ferroxidase function. The latter could be the consequence, but also the triggering factor of the higher oxidative environment found in MS subjects (De Riccardis et al., 2018).

2.3. Mechanisms of manganese neurotoxicity

Mn is an essential ubiquitous trace element required for normal growth, development and cellular homeostasis (Erikson et al., 2005). Daily intake of Mn through dietary sources provides the necessary amount required for several key physiological processes, including blood sugar regulation, bone formation, reproduction, metabolism of lipids, proteins and carbohydrates, antioxidant defense, and immune response. In humans and animals, Mn functions as a cofactor for maintaining the function and regulation of many biochemical and cellular reactions, including multiple enzymes, such as glutamine synthetase (GS), pyruvate decarboxylase, serine/threonine protein phosphatase I, Mn-SOD and arginase, which are required for neurotransmitter synthesis and metabolism, as well as for neuronal and glial function (Erikson and Aschner, 2003; Horning et al., 2015).

The routes of Mn exposure are mainly through dietary intake, dermal absorption, and inhalation. Moreover, Mn in the diet is found mostly in whole grains, nuts, and seeds, tea, legumes, pineapple, and beans. Ingested Mn is absorbed in the intestine; however, molecular mechanisms of Mn uptake are not well characterized. It is thought that Mn can enter cells either through passive diffusion or active transport via divalent metal transporter 1 (DMT-1) (Aschner et al., 2007). The gastrointestinal tract responds to dietary Mn levels to regulate Mn uptake. High Mn intake, either through dietary or environmental exposure, leads the gastrointestinal tract to absorb less Mn while the liver increases metabolism and biliary and pancreatic increases excretion, respectively. While uncommon, Mn deficiency can contribute to birth defects, impaired fertility, bone malformation, weakness, and enhanced susceptibility to seizures (Aschner et al., 2002).

Mn exists in various chemical forms including oxidation states (Mn^{2+}, Mn^{3+}, Mn^{4+} Mn^{6+}, Mn^{7+}), salts (sulfate and gluconate), and chelates (aspartate, fumarate, succinate). However, Mn^{2+} and Mn^{3+} are the two common species found in human body. Since Mn^{2+} is chemically more stable than Mn^{3+} in the body, Mn is mainly incorporated into metalloenzymes in the form of Mn^{2+} (Horning et al., 2015). Ceruloplasmin effectively oxidizes Mn^{2+} to Mn^{3+} and this trivalent oxidation state, though a minor form of Mn in the circulation, has been shown to access the CNS via a transferrin receptor (TfR)-mediated mechanism. In contrast to the Mn^{3+}, Mn^{2+} is readily transported into the brain, either as a free ion species or as a nonspecific protein-bound species (Aschner and Dc, 2006).

The abundant manganoprotein glutamine synthetase (GS) is predominantly expressed in astrocytes and synthesizes glutamine via the conversion of glutamate to glutamine. As Mn has been suggested to regulate GS activity, low levels of Mn reduce GS activity in the brain. As consequence, increased glutamate trafficking and glutamatergic signaling results in excitotoxicity through an excessive amount of glutamate at the synapse (Lewerenz and Maher, 2015).

Mn^{2+} is a central component of some metalloenzymes and an activator of many metal-enzyme complexes and activates these enzymes by binding the protein directly or by acting through an intermediate interaction with a substrate, like ATP, to initiate a conformational change and activate enzymatic activity. Mn^{3+} is found in the essential enzymes like CAT and Mn superoxide dismutase (MnSOD), both of which break down oxidants using the Mn^{3+} in their reactive catalytic centers. Mn serves as a cofactor for MnSOD that catalyzes superoxide to hydrogen peroxide through the Mn^{2+}/Mn^{3+} cycle and thereby detoxifies free radicals in the mitochondria to prevent oxidative stress. On the other hand, the Mn^{2+}/Mn^{3+} cycle can trigger dopamine auto-oxidation, which is one of proposed mechanisms for Mn-induced neurotoxicity (Peres et al., 2016). CAT converts hydrogen peroxide into oxygen and water, aiding in reducing oxidative stress. MnSOD is involved in the dismutation of superoxide in mitochondria to decrease oxidative stress, which is also significant in Mn-induced dopaminergic (DAergic) neurodegeneration (Martinez-Finley et al., 2013; Karki et al., 2013). Therefore, the Mn redox cycle contributes to both nutritional metabolism and toxic effects on biological function (Ye et al., 2017).

A growing body of literature indicates the role of Mn in NDDs (Bowman et al., 2011). Despite its essentiality, Mn is toxic to the CNS at excessive levels. Overexposure from environmental sources can result in a condition known as manganism that features symptomatology similar to PD. Manganism is an extrapyramidal, Parkinson-type movement disorder that presents with debilitating motor and cognitive deficits that arise from a neurodegenerative process (Chen et al., 2015a).

Despite its essential role in multiple metabolic functions, excessive Mn exposure can accumulate in the brain and has been associated with dysfunction of the basal ganglia system that causes a severe neurological disorder similar to PD. Although Mn-induced parkinsonism and PD are pathologic and clinical distinct, both disorders share generalized bradykinesia and widespread rigidity, as well as broadly similar pathophysiological mechanisms such as oxidative stress, protein aggregation, impaired proteasomal and autophagy functions, excitotoxicity, aberrant signal transduction, mitochondrial dysfunction and cell death pathways (Ye et al., 2017). Mn overload affects two vital organs, the brain and lungs; the latter results from inhalation (Aschner and Aschner, 1991). The dystonic high-stepping gait disturbance associated with Mn poisoning is easily distinguishable from the shuffling gait of PD (Ratner and Fitzgerald, 2016).

In PD, Mn toxicity is characterized by motor and sensory disturbances, as well as neuropsychiatric and cognitive deficits. The motor impairments include hypertonia with cogwheel rigidity, bradykinesia, “cock-gait”, rapid postural tremor, and tendency to fall when walking backwards. In human patients and animal models, neurons of the globus pallidus appear to be most sensitive to Mn-induced degeneration while the striatum is less severely affected. Other brain areas that may be affected in Mn toxicity include the cerebellum, red nucleus, pons, cortex, thalamus, and anterior horn of the spinal cord. So, this pathologic phenotype is distinct from idiopathic PD, where dopaminergic neurons of the substantia nigra pars compacta are specifically degraded (Kwakye et al., 2015).

Increasing evidence has shown that Mn is potentially involved in the progression of AD. It has been reported that AD patients have a deregulated metabolism of Mn, and a dysfunction of the Mn-SOD scavenger system, associated with the formation of senile plaques. Reduced mitochondrial MnSOD activities have been found in the brain of neuropathology confirmed AD patients. Moreover, it has been reported that the transport of Mn across the BBB is regulated by Fe, and perturbed Fe distribution has been implicated in the pathogenesis of AD (Du et al., 2017).

In order to maintain a balance between its essentiality and neurotoxicity, several mechanisms exist to properly buffer cellular Mn levels. These include transporters involved in Mn uptake, and newly

discovered Mn efflux mechanisms (Chen et al., 2015b). Mn is transported to the CNS either as a free ion or as a non-specific protein-bound species. Transport of Mn^{2+} is mediated, at least in part, by the family of natural resistance-associated macrophage proteins, the DMT-1. In the Mn^{3+} oxidation state, Mn complexes with transferrin and, in a similar manner to Fe, is transported by a Tf receptor-mediated mechanism. Genetics factors influence Mn toxicity, for example, mutations in one of Mn exporters (*SLC30A10*) result in liver impairments and neurological disfunction (Chen et al., 2015b).

Mn accumulates primarily in the globus pallidus, γ aminobutyric-acid (GABAergic) neurons of the basal ganglia, but the effects of Mn on GABAergic neurotransmission are controversial. Kuakye and coworkers (Kwakye et al., 2015) included a variety of results such no statistical difference in the GABA levels in Mn-exposed groups. It's possible that the conflicting effects of Mn on GABA homeostasis are due to diverse experimental techniques used to examine the effect of extracellular GABA homeostasis and transport dynamics, but more research is necessary to establish the effect of Mn exposure on GABA neurotransmission. Actually, the basal ganglia have been more studied because Mn intoxication patients often show symptoms that resemble those of PD; therefore, the basal ganglia have been targeted as a putative location for studies on Mn toxicity (Lao et al., 2017). Among different sub-cortical structures, the basal ganglia have been investigated as a putative anatomical biomarker in magnetic resonance imaging-based studies of Mn toxicity. The striatum and the globus pallidus, structures of the basal ganglia, are thought to be the primary targets of Mn accumulation in the brain. However, other brain areas that may be affected in Mn toxicity include the cerebellum, red nucleus, pons, cortex, thalamus, and anterior horn of the spinal cord (Kwakye et al., 2015).

Astrocytes accumulate higher levels of Mn than neurons and are therefore considered an important target cell for transport of Mn into the brain as well as for initiating inflammatory signaling during neuronal stress and injury. Astrocytes serve as the major homeostatic regulator and storage site for Mn in the brain and are a prominent contributor to Mn-stimulated nitric oxide (NO) production through inducible nitric oxide synthetase (iNOS). Results of an experimental study with immunopurified cultures of primary microglia and astrocytes demonstrate that microglia directly accumulate Mn and develop a mixed inflammatory phenotype characterized by release of IL-6, TNF-α, and the CC chemokines CCL2 and CCL5. The results show that products from Mn-activated microglia are essential for neuroinflammatory activation of Mn-exposed astrocytes and that NF-κB-dependent release of TNF-α from microglia is a key signaling event in microglia regulating these glial-glial interactions (Kirkley et al., 2017; Tjalkens et al., 2017).

Compared with neurons, astrocytes have a greater tendency to accumulate Mn and its neuroimmunotoxicity is associated with altered glial function and secondary impairment of astrocyte-dependent neuronal functions (Karki et al., 2013). Glial cells are an important target of Mn in the brain, both for sequestration of the metal, as well as for activating inflammatory signaling pathways that damage neurons through overproduction of numerous ROS and RNS, as well as inflammatory cytokines (Tjalkens et al., 2017).

Mitochondria is the primary storage site for intracellular Mn and the elevation of Mn levels in this organelle can directly interfere with oxidative phosphorylation for inhibiting the function of F1-ATPase and consequently with cellular ATP synthesis (Martinez-Finley et al., 2013). In turn, elevated intra-mitochondrial Mn levels trigger oxidative stress generating the excessive ROS, causing mitochondrial dysfunction. The transition of Mn^{+2} to Mn^{+3} increases its pro-oxidant capacity. Mn-induced oxidative stress leads to the opening of mitochondrial transition pore, resulting in increased solubility to protons, ions and solutes, loss of the mitochondrial inner membrane potential, impairment of oxidative phosphorylation and ATP synthesis and mitochondrial swelling (Milatovic et al., 2011). Furthermore, Mn exposure has also been linked to the activation of signaling pathways involved in response to oxidative stress, including activator protein-1 (AP-1) and NF-kB (Reuter et al., 2010).

The transcription factor NF-κB is a family of transcription factors regulating the expression of an extensive number of genes involved in cell survival, cell death, inflammation, proliferation, and cell differentiation. The NF-κB family of transcription factors is activated by canonical and non-canonical signaling pathways, which differ in both signaling components and biological functions. Some studies have shown either a protective or a detrimental role of NF-κB depending on the insult (Mc Guire et al., 2013).

Within the CNS, NF-κB has diverse functions. One the one hand, NF-κB signaling pathway in glia cells induces an inflammatory response that propagates demyelination and inhibits remyelination in the CNS and has been implicated in several CNS diseases, including AD, PD and MS. On the other hand, the activation of NF-κB in neurons promotes survival and plasticity, regulates the neuronal morphology and plays important roles in brain tolerance, nerve cell survival, neuronal plasticity, influencing learning, memory, and behavior (Mc Guire et al., 2013; Mattson and Meffert, 2006; Blondeau et al., 2001). Moreover, neuronal NF-κB has been implicated in suppressing local inflammation and enhancing neuronal survival, protecting against excitotoxic or oxidative stress and ischemia-induced neurodegeneration, as well as can prevent the death of neurons by inducing the production of anti-apoptotic proteins such cellular inhibitors of apoptosis (cIAP), Bcl-2, and MnSOD (Mattson and Meffert, 2006). Additionally, several cytokines and chemokines NF-κB-induced, such as TNF-α and IL-1, that were initially considered detrimental have also been demonstrated to be involved in CNS repair mechanisms for myelin repair following toxic demyelination of the corpus callosum (Mc Guire et al., 2013).

Besides, Mn has been shown to trigger apoptosis in dopaminergic neurons in a caspase-3-dependent manner by activation of protein kinase C delta (PKC-*δ*) and to cause apoptotic cell death in astrocytes by mitochondrial pathways involving cytochrome c release and caspase activation (Gonzalez et al., 2011). Mechanism of Mn toxicity also involves a proinflammatory role with the activation of glial cells that is characterized by the release of non-neuronal derived ROS, such as nitric oxide (NO), prostaglandins and hydrogen peroxide. Mn also cause increased release of several cytokines, including tumor necrosis factor (TNF-α), IL-6, IL-1β from the activated glial cells, so activating various transcription factors including NF-kB (Karki et al., 2013).

In MS, the activation of microglia precedes astrogliosis and overt neuronal loss. Although microgliosis is implicated in Mn neurotoxicity, the role of microglia and glial crosstalk in Mn-induced neurodegeneration is poorly understood. Recent results provide evidence that NF-κB signaling in microglia plays an essential role in inflammatory responses in Mn neurotoxicity by regulating cytokines and chemokines that amplify the activation of astrocytes (Kirkley et al., 2017).

Taken together, Mn has an important role in neurological homeostasis but in excess has been associated with a neurological syndrome comprising cognitive deficit, neuropsychological abnormalities and parkinsonism. For this reason, in the last decade there has been significant progress using state-of-the-art neuroimaging and behavioral methodologies that have opened up a new understanding of Mn neurotoxicology.

2.4. Mechanisms of iron neurotoxicity

In normal human plasma, Fe exists primarily in the Fe^{3+} form and is complexed with the high affinity iron binding protein transferrin in a 2:1 ratio. Inside the cell, free Fe in its reduced form (Fe^{2+}) constitutes the Fe pool, which supplies Fe^{2+} molecules as cofactors for many Fe^{2+}-dependent enzymes in the cytosol, mitochondria, and nucleus (Mills et al., 2010). Fe 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 (Paul et al., 2017). Hemoglobin, cytochromes,

catalases and peroxidases are examples of proteins that consist of heme Fe (Pantopoulos et al., 2012). Their main function includes oxygen transport, activation and storage, electron transport and cellular respiration (Pantopoulos et al., 2012; Papanikolaou and Pantopoulos, 2005). CAT, one of the foremost antioxidant enzymes in oligodendrocytes contains four heme groups; its production and maintenance is therefore dependent on a constant supply of Fe. If the CAT antioxidant system fails, oligodendroglial cell death may follow (Paul et al., 2017).

The absorption of metals from dietary sources occurs by a number of metal transporters to provide specific needs for individual nutrient metals. In particular, the DMT-1 is a major Fe transporter essential for its absorption from diet. Fe bioavailability is affected by valence state, form, solubility, particle size, and complexation which in turn may be affected by the food matrix. DMT-1 also plays an important role in the uptake of several other divalent metals, including Mn. Since the expression levels of DMT-1 are regulated by several factors, such as body Fe status, gene polymorphism and inflammation changes in DMT-1 could also alter the transport and neurotoxicity of metals. For example, Fe deficiency up-regulates intestinal DMT-1 levels and increases the absorption of Mn and neurotoxicity (Kim and Kim, 1991).

Fe is likely an integral part of metabolism because it can gain (ferric to ferrous, or Fe^{3+} to Fe^{2+}) or lose (Fe^{2+} to Fe^{3+}) electrons relatively easy. Fe has a functional split personality in the CNS where it is essential for life yet toxic if levels are perturbed. At the cellular level, Fe is required for the cell growth; however, excessive Fe (Fe overload) causes oxidative stress and cell death. Fe levels are tightly regulated in a process referred to as Fe homeostasis. The main protective strategy to avoid Fe overload in the brain is the BBB, which limits Fe via highly regulated, selective transport systems (Mills et al., 2010).

Within the brain, multiple feedback loops form an elaborate control system for cellular Fe levels to ensure that a precisely balanced Fe level exists for normal function of the CNS. Fe-induced oxidative stress is particularly dangerous because it can cause further Fe release from Fe-containing proteins such as ferritin, heme proteins, and Fe-sulfur clusters, forming a destructive intracellular positive-feedback loop that exacerbates the toxic effects of brain Fe overload. In the brain, Fe uptake is through the BBB. Fe is taken up by the capillary endothelial cell TfR, in the form of transferrin-Fe^{3+} (Mills et al., 2010).

Fe is transported to cerebral compartment from the basolateral membrane of endothelial cells and is then made available to neurons and glia. Of note, oligodendrocytes stained for most of the detectable Fe in the brain. Transferrin is also found predominantly in these cells, which is important for myelination formation. Although ependymal cells can mediate Fe absorption into the brain from the blood, their contribution is thought to be rather small (Liu et al., 2017).

During aging, different Fe complexes accumulate in specific brain regions, which are associated with motor and cognitive dysfunction, although the etiology of the deposits differs. In AD, PD and MS changes in local Fe homoeostasis result in altered cellular Fe distribution and accumulation, ultimately inducing neurotoxicity (Lewerenz and Maher, 2015).

Bound Fe is considered safe, but free Fe is more likely to exchange electrons with nearby molecules and produce free radicals. Normal metabolic processes in the mitochondria form hydrogen peroxide as the result of molecular reduction of oxygen. Hydrogen peroxide alone is not particularly toxic, but in the presence of free Fe a hydroxyl (˙OH) is formed when free Fe donates an electron to hydrogen peroxide via the Fenton reaction. This free radical can interact with oxygen and other molecules in the brain to form more free radicals propagating a deleterious positive feedback loop. Hydroxyl radicals can attack proteins, DNA, and lipid membranes. This process can disrupt cellular integrity and function eventually leading to oxidative stress and cell apoptosis (Menon et al., 2016).

Fe deficiency can also enhance absorption of divalent metals, such as lead (Pb), cadmium (Cd), aluminum (Al), and Mn. Fe deficiency can enhance brain Mn accumulation even in the absence of excess Mn in the environment or the diet. For this event, the effects of Fe deficiency on Mn transport have been documented. Previous studies have shown that Fe deficiency increases blood levels of Mn in adults (Menon et al., 2016). Fe and Mn, as well as other essential metals, are regulated within the CNS by influx into the brain via transferrin and TfRs, as well as via DMT-1; as such, there is an inverse relationship between Mn and Fe. Fe deficiency increases transferrin and DMT-1, facilitating Mn uptake. Consequently, Fe deficiency can lead to increased Mn accumulation in the brain and vice versa. Fe and Mn compete for the same carrier transport system; both TfR and DMT-1 regulate their influx into the brain (Stankiewicz et al., 2014). Likewise, other essential metals sharing the transporters may be altered by imbalances in Fe and/or Mn (Aschner, 2000). Neonatal rats exposed to either a low-Fe diet (ID) or a low-Fe diet supplemented with Mn (IDMn) via maternal milk during the lactation period had decreased Fe and increased Cu brain levels; IDMn pups also had increased brain levels of several other essential metals including Mn, chromium (Cr), Zn, cobalt (Co), Al, molybdenum (Mo), and vanadium (V), as well as DMT-1 and TfR. The results of this study confirmed that there is homeostatic relationship among several essential metals in the brain and not simply between Fe and Mn. Indeed, Fe deficiency is a known risk factor for metal toxicity, resulting in enhanced absorption and accumulation of divalent metals (Beard, 2001).

Fe deficiency is associated with increased accumulation of Mn in the brain in a region-specific manner; elevated Mn levels observed with Fe deficiency are more pronounced in the caudate putamen and globus pallidus. A clinical study evaluated the Mn level in the brain of Fe deficient/anemic patients and the results showed that Fe deficiency was correlated with increased Mn deposition in the basal ganglia. In contrast, Mn levels in the globus pallidus were minimally affected in anemic humans. Moreover, dietary Fe deficiency up-regulated the expression of DMT-1 in the intestine, resulting in increased basal levels of Mn in various tissues, including brain, heart, kidney, testis, femoral muscle and tibia (Ye et al., 2017).

Fe and its deregulated homeostasis have been proposed to have a role in the pathogenesis of PD because of its pro-oxidant characteristics that may lead to ROS generation via Fenton and Haber-Weiss reactions. However, epidemiological evidence concerning the possible association between Fe and PD remains still controversial. In meta-analysis of available case-control studies, Mostile and coworkers (Garcia et al., 2007) state there are still not sufficient evidence supporting higher or lower serum levels of Fe in PD patients as compared to controls, assuming this may be related to metal exposure or pathological processes in such subjects.

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. Fe accumulation has been identified in the substantia nigra of PD patients. It acts as a co-factor for tyrosine hydroxylase, enzyme that limits the dopamine synthesis, as well as free Fe is toxic to the cell (Mostile et al., 2017). In AD, a diffuse accumulation of Fe occurs in various regions, for example, cortex and hippocampus, with Fe marginally increased in the senile plaques. In MS, elevated levels of Fe occur in certain brain regions, such as the thalamus and striatum, which may be due to inflammatory processes disrupting the BBB and attracting Fe-rich macrophages. Moreover, reduced axonal clearance of Fe has been postulated to promote disease activity by amplifying the activated microglia, promoting mitochondrial dysfunction and catalyzing the production of ROS (Ward et al., 2015).

Oligodendrocytes need Fe for the extremely high energy requirements of producing and maintaining the complex myelin sheath which is many times larger than the cell body, indicating that Fe deficiency could seriously compromise the viability of these cells. Fe is essential for many of biochemical reactions, such as cholesterol synthesis, which occurs at a higher rate in oligodendrocytes than any other cell type in the brain. Fe is also a prerequisite for the maturation of oligodendrocyte precursor cells into oligodendrocytes (Gangania et al., 2017).

The death of oligodendrocyte in MS is associated with the

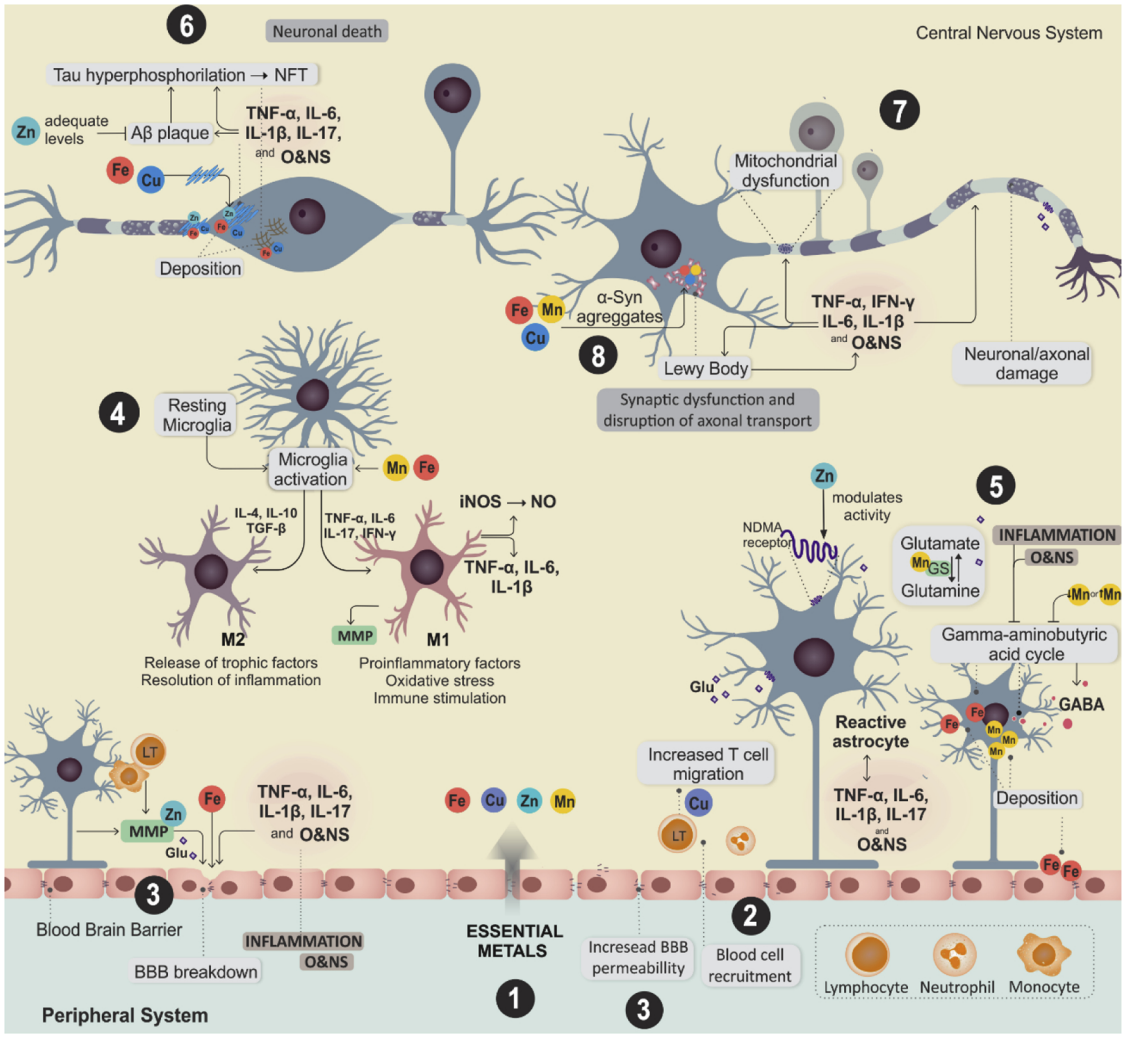

Fig. 2. Related events with the interaction of the essential metals zinc, copper, manganese and iron with the central nervous system through the breakdown of the blood-brain barrier. 1) The interaction of the essential metals zinc (Zn), copper (Cu), manganese (Mn), and iron (Fe) with the Central Nervous system (CNS) through the breakdown of the blood-brain-barrier (BBB). 2) The inflammatory immune response, as well as the oxidative nitrosative stress, lead to neurodegeneration through different mechanisms, such as those mediated by blood cells recruitment; 3) matrix metalloproteinases (MMP), a family of proteolytic zinc-containing enzymes involved in physiological as well as in pathological conditions; 4) proinflammatory cytokines interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α, IL-17, and interferon (IFN)-γ released by microglia activated (M1); on the other hand, microglia M2 participates with the release of trophic factors and anti-inflammatory cytokines IL-4, IL-10 and transforming growth factor (TGF)-β in order to mediate the inflammation; 5) Moreover, the essential metals are involved in different injurious mechanisms in CNS. High or low levels of Mn inhibit the gamma-aminobutyric acid (GABA) cycle, high levels of Mn and Fe activate the microglia, high levels of Fe result in iron storage in the brain cells, Zn and Fe participate of the BBB breakdown; 6) the immune-inflammatory through the proinflammatory cytokines and oxidative and nitrosative stress (O&NS) molecules exert deleterious effect on the brain cells, such as Tau hyperphosphorylation with the formation of neurofibrillary tangles, aggregates of hyperphosphorylated Tau protein are most commonly known as a primary marker of Alzheimer disease (AD); 7) Demyelination and axonal injury; oligodendrocyte death; and mitochondrial dysfunction; 8) Zn inhibits the formation of Aβ plaque, high levels of Fe, Mn and Cu participate in the formation α-synuclein aggregates in intracellular inclusions, called Lewy Body, another marker of PD, that result in synaptic dysfunction and interruption of axonal transport. All these metal-mediated events contribute to the enhancement of the inflammatory and O&NS damage mechanisms.

demyelination, the content of the extracellular milieu (the interstitial fluid) being increased, thereby amplifying oxidative stress in axons has been postulated to promote disease activity by amplifying the activated microglia, promoting mitochondrial dysfunction and catalyzing the production of ROS (van Rensburg et al., 2012).

In MS, data is emerging indicating that this Fe could participate in pathogenesis by various mechanisms, for example, promoting the production of ROS, increasing the production of proinflammatory cytokines and accumulation with white matter injury (Stankiewicz et al., 2014). Duck and Conor (Barnhamabc and Bush, 2014) demonstrated that Fe across BBB both a transcytotic and an endocytic mechanism primarily transferrin-dependent by which Fe is released from transferrin in the endosome for export into intercellular Fe pool.

Increased Fe deposition in cerebral deep gray matter has been considered a global marker for neurodegeneration in MS. Cerebral Fe levels are highest in deep gray matter and are associated with age, and disease duration and disability in MS (Duck and Connor, 2016). Elevated levels of Fe accumulation in deep gray matter nuclei in MS have been reported using different Fe-sensitive magnetic resonance imaging measures, with studies focusing particularly on the large basal ganglia nuclei (caudate, putamen, globus pallidus, and the thalamus). A study revealed that increased Fe in the globus pallidus, measured using quantitative susceptibility mapping, was moderately associated with a lower cognitive composite score in MS patients and suggested a specific role of globus pallidus Fe accumulation in global cognitive functions, irrespective of globus pallidus atrophy, implying that Fe accumulation in this structure may have a unique role in globally affecting cognitive processes in MS (Ropele et al., 2017).

Increased Fe^{3+} in the vicinity of lesions in MS suggests the presence of proinflammatory nonphagocytizing M1 macrophages. Conversely, actively demyelinating lesions contain a high number of myelin-laden M2 anti-inflammatory macrophages, which contain small amounts of Fe^{3+} (Fujiwara et al., 2017). One obvious source of immune uptake of free Fe in the vicinity of lesions is oligodendrocyte destruction in MS, which contain profound amounts of Fe because of their role in myelin production (Mehta et al., 2013). Elevated Fe in MS deep gray matter may occur as a compensation mechanism for enhanced oxidative stress, and may be taken in neurons via astrocyte end-feet processes, passage through voltage-gated calcium channels, and/or ferritin uptake through heavy chain subunit (H)-ferritin receptors. TfR upregulation could also account for elevated Fe levels in patients with secondary progressive SPMS (Bagnato et al., 2011).

Some studies suggest that Fe insufficiency may play a role in MS disease progression as MS patients display clinical improvement upon Fe supplementation. However, other studies indicate improved disease outcome in Fe-limited MS patients. It is possible that inadequate Fe levels (both low and high) may be harmful in MS since Fe excess might elevate oxidative stress, while Fe reduction could decrease immune system function and cause an energy deficit due to loss of mitochondria membrane potential (van Rensburg et al., 2012).

So, although Fe is vital for normal neuronal metabolism and in excessive levels may be harmful for life. It's indisputable that the transport and metabolism of brain Fe and where it normally accumulates with aging and that the hypothesis that excessive brain Fe can lead to free radical damage, lipid peroxidation, and cellular death. In conclusion, it is essential that the brain remains in a homeostasis with low inflammation and low Fe content in order to sustain health and longevity (Ward et al., 2015).

The Fig. 2 shows the interaction of the essential metals Mn, Zn, Cu and Fe with the CNS through the breakdown of the BBB, with emphasis on microglia activation, MMP cofactor metals, Fe deposition in the brain, increased production of IO&NS, and neurodegeneration.

3. Conclusions

As many of the NDDs are associated with aging, immunological causes, as well as environmental factors and epigenetic modifications, the scientific community observes an increased number of disabling patients; however, this fact is not being matched by advances in understanding and treatment of these diseases. As we show, essential metals, such as Zn, Cu, Mn and Fe probably exert critical roles in the pathophysiology of AD, PD and MS. These metals accumulate in different brain regions at different levels. Therefore, it is difficult to isolate their specific toxicity. So, the maintenance of homeostasis of these metals is critical as any substantial change can lead to neurotoxic outcomes. A better comprehension of the possible mechanisms associated with the disrupted homeostasis of these metals may improve the acceptance of essential and heavy metals as key point in brain and NDDs.

Delineating the specific mechanisms by which metals alter redox homeostasis is essential to understand the pathological processes of some NDDs and may provide possible new targets for the prevention of AD, PD, and MS, as well as for the treatment of the patients affected by these NDDs.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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