Copper Toxicosis

Subjects: Rheumatology

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Copper, manganese, and iron are vital elements required for the appropriate development and the general preservation of good health. Additionally, these essential metals play key roles in ensuring proper brain development and function.

Keywords: copper ; iron ; manganese ; neurodegeneration

1. Introduction

Copper (Cu), iron (Fe), and manganese (Mn) play important roles in brain biology. They are present in some regions of the brain in very small millimolar concentrations. Cu and Fe are involved in the production of oxygen radicals; therefore, they are major causes of oxidative stress. The above-mentioned metals may also have an impact on protein misfolding and the progression of the neurodegenerative processes. Metals are essential for their integral roles in many enzymes that catalyse metabolic or biochemical processes common to all life forms.

The crossing of metals through the blood–brain barrier (BBB) is very strictly regulated. Enzymes, transporters, and chaperones regulate the metal ion content within the brain. In healthy people, the concentration of free metal ions is very low. Metal ions are selectively delivered where their action is needed. Metal dyshomeostasis is widely documented as a cause of several neurodegenerative diseases, including prion disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD), among others [1][2][3][4][5]. Metal ions play a key role as necessary elements for biological processes and act as cofactors for many enzymes, but they can also be potentially dangerous to a cell involved in redox reactions that lead to the formation of reactive oxygen species. Under normal conditions, reactive oxygen species (ROS) are detoxified by the cell, but in pathological states, ROS production exceeds the capabilities of intracellular antioxidant defense, and an increase of ROS production is observed.

This is a condition known as oxidative stress. Various studies have expanded on conceivable molecular mechanisms and signaling pathways through which metals cause neurotoxicity and degeneration of the central nervous system [6]. A number of explanations of cell death due to metal neurotoxicity have been proposed. These include malfunction of the mitochondria and interruption of cell energy metabolism, oxidative stress, as well as modification in levels of neurotransmitters and excitotoxic cell death [6].

Oxidative stress, described as the creation of ROS, is a focus point of many other mechanisms of metal toxicity. Furthermore, the occurrence of metal toxicity gives rise to neuronal damage. Mitochondria are intracellular objects for metals toxicity. The resulting oxidation of membranal polyunsaturated fatty acid creates lipid peroxides (LPO), thus affecting mitochondrial permeability and inducing cell apoptosis [6][7][8].

Additionally, proteins associated with neurodegenerative diseases, such as amyloid-β (Aβ), α-synuclein (αS), and prion protein (PrP), bind several metal ions that can affect the process of aggregation of Aβ and αS, for example, in Parkinson's disease or Alzheimer's disease. In those cases, Cu and Fe generate reactive oxygen species (ROS) through Fenton reactions "($Cu^{1+} + H_2O_2 \rightarrow Cu^{2+} + OH\cdot + OH^-$ or $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH\cdot + OH^-$)". This process may lead to oxidative stress because of the formation of the highly reactive hydroxyl radical (OH·) in the substantia nigra [9].

2. Copper Toxicosis

Copper is a heavy metal that plays an essential role in many physiological processes, such as skin pigmentation, myelination, Fe homeostasis, oxygen metabolism, and the synthesis of neurotransmitters. Copper is essential in a variety of biological processes and plays an important role as a cofactor or as a structural component in numerous cuproproteins. The oxidative state of copper may change from Cu(I) to Cu(II). Copper can also interact with ceruloplasmin (Cp) and takes part in Fe homeostasis, exhibiting Cu-dependent oxidase activity, with Fe(II) into Fe(III) transformation taking part in Fe transport in the plasma [10]. Copper accumulates mostly in the liver and brain, which is the main organ responsible for its

metabolism, and it enters the bloodstream via the protein adenosine triphosphatase 7A (ATP7A). Adenosine triphosphatase (ATPase) 7B (ATP7B) is also responsible for balancing Cu levels in tissues; ATP7B is involved in Cu incorporation into apoceruloplasmin and for the synthesis of functional ceruloplasmin, and this enzyme also facilitates the excretion of biliary Cu [11]. Copper is incorporated into the blood of ceruloplasmin molecules, and physiologically, Cu is not present in the free form. As mentioned before, Cu is also stored in the brain, especially in the *substantia nigra*, hippocampus, cerebellum, olfactory bulbs, hypothalamus, and cortex [12]. Excess copper may cause neurodegeneration [12]. Wilson's disease (WD) is a good example of this process.

2.1. Neuropsychiatric Diseases Associated with Copper Toxicosis

Wilson's Disease

Wilson disease is an inherited Cu metabolism disorder with Cu accumulation in many organs, particularly the liver and brain. The disease is caused by mutations in the ATP7B gene, which encodes a transmembrane Cu-transporting ATPase. The pathological highly toxic excess of Cu ("free" copper) released from hepatocytes into the bloodstream and then to the brain causes a wide range of neuropsychiatric symptoms. After crossing the BBB, copper is stored by astroglia, causing oedema and degeneration; it is believed that neurons are affected by the functional insufficiency of astroglia [13]. In vitro studies have shown that the administration of Cu significantly reduces the survival of neurons [14]. This ion damages the regulation of glutamate by triggering NMDA receptors and activating the excitotoxic cascade that produces nitric oxide (NO) by stimulating the expression of nitric oxide synthase (NOS1-3). Ceruloplasmin deficiency with excess free Cu and Fe deposits can lead to excitotoxicity, enhanced nitrosative/oxidative stress, and damage to mitochondria [12]. There are also hypotheses that ceruloplasmin can play a protective role in neurodegenerative diseases [15]. Wilson's disease mostly presents with hepatic disturbances; the disease is manifested by neurological signs in 40–50% of cases and by psychiatric signs in 10–25% [16]. The most common psychiatric disturbances are personality disorders, including abnormalities, antisocial behaviour, disinhibition, and irritability. Mood disorders such as bipolar disorders or depression with suicidal attempts are also commonly diagnosed [17]. Psychosis and other psychiatric alterations, such as anorexia and sleep disturbances, can be seen [17]. When psychotic symptoms occur as the first manifestation of WD, they can result in diagnostic and therapeutic challenges, but such manifestations must be taken into consideration [17]. The neurological presentation is associated with dysarthria (extrapyramidal, dystonic, cerebellar, mixed, or unclassified origin) or other speech disorders, dysphagia, salivation, involuntary movements such as tremor ("wing beating"), dystonia, athetosis, chorea, parkinsonism, cerebellar ataxia (gait ataxia), gait and balance disturbances, and cognitive decline [18].

The diagnosis of WD is based on the presence of Kayser–Fleischer rings (brown discoloration of the cornea), which is the pathognomonic sign of this disease. In WD, the concentration of Cu in the brain in the liver is high, but in blood, low levels are diagnosed. Levels of urinary Cu are typically increased and are used as a biomarker of the disease, and ceruloplasmin is also decreased Cu deposits in the brain (appearing as hypointense lesions in T2-weighted MRI imaging and hyperintense in T1-weighted imaging) occur as a result of the paramagnetic qualities of copper and are mainly visible in the globus pallidus, putamen, caudate nuclei, and substantia nigra. Other changes appearing as hyperintense lesions in T2-weighted MR imaging are associated with cellular oedema, necrosis, cystic degeneration, and glial proliferation; these are mostly visible in the putamen, caudate, thalami, pons, midbrain, white matter, and cerebellum [16].The disease is mostly successfully treated with medications (chelators, zinc (Zn) sulfate). It is currently recommended by international societies that chelators should be the first-line treatment of WD [16]. The most prominent goal for new treatment strategies is to prevent neurological deterioration during treatment. From the current new therapeutic strategies for WD treatment, bis-choline tetrathiomolybdate and once-daily trientine are the most advanced and promising methanobactin bis-choline in animal models [19]. The gene therapy will also be an option for the treatment of WD in the coming years. Selective serotonin reuptake inhibitors can be chosen as a first-line treatment for depression in these patients. For manic or hypomanic syndromes in the treatment of Parkinson's disease with psychotic symptoms, clozapine or quetiapine monotherapy is recommended due to the relatively low risk of exacerbating parkinsonism [20]; olanzapine could be another therapeutic option. Behavioral disturbances can also be treated with quetiapine and tiapride [20].

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