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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.

KEYWORDS: Alzheimer disease; Essentials metals; Multiple sclerosis; Oxidative stress; Parkinson disease

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