

Chapter 8

Zinc and Neurodegenerative Disorders

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ABSTRACT

Zinc (Zn) is an essential trace element that is abundantly present in humans. Despite its importance in normal brain functions, alterations in zinc homeostasis cause various neurological pathologies such as dementia, Parkinson's disease, Prion's disease, etc. A growing body of evidence has shown that zinc might play a dual role: in which both zinc depletion and excess zinc cause severe damage and hence neurotoxicity develops. Homeostatic controls are put in place to avoid the accumulation of excess zinc or its deficiency. This cellular zinc homeostasis results from the actions of a coordinated regulation effected by different proteins involved in the uptake, excretion, and intracellular storage or trafficking of zinc. Further investigation has also shown the role of endogenous carnosine (beta-alanyl-L-histidine) in binding excess zinc. Hence, it has the ability to prevent neurotoxicity. Also, the role of a zinc-rich diet cannot be overemphasized. The authors of the chapter, however, provide an insight into the link between zinc homeostasis and neurodegenerative disorders (NDs).

INTRODUCTION

One of the most important mineral identified in the human system is zinc, a crucial trace element in the metabolic activities, cell division, immune system and as a co-factor of over 300 well-known enzymes (Hambidge, 2000) in the control of different cellular activities and signaling pathways expedient for both neuro and systemic operation (Takeda, 2000). This divalent metal constitutes a cofactor of a number of enzymes like carbonic anhydrase, alcohol dehydrogenase, alkaline phosphatase, phospholipase, carboxypeptidase, zinc/copper superoxide dismutase (SOD) and other allosteric proteins (McCall *et al.*, 2000). This is the reason why zinc is referred to as antioxidative element in human beings because these enzymes which have zinc as cofactor are involved in combating oxidative stress (Feng *et al.*, 2013). Zinc is used to make the hormone thyrotropin-releasing hormone (TRH) that signals the thyroid to make thyroid hormones. It converts the protein we eat into amino acids, including tyrosine which powers the thyroid hormone production. Finally, it is involved in the making of triiodothyronine (T3) the active form that is used in the muscles (Soh *et al.*, 2012). Furthermore, in the formation of bone, zinc is used by enzymes in the production of collagen and alkaline phosphatase (ALP), which are important for bone formation (Hyun-Ju *et al.*, 2010). It is also used to make calcitonin, a hormone that inhibits the breakdown of bone. Zinc is also a critical component of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) polymerases and has a fundamental role for nucleic acid metabolism and gene activation and repression. 30% of the zinc found in a cell is found in the nucleus (Ali *et al.*, 2012). This makes sense as it is very involved with DNA and the replication of cells and proteins needed by the body. At the transcription level during protein expression, zinc fingers structure enables transcription factors to anchor to DNA helix. Cyclins and cyclin-dependent kinases are directly influenced by this divalent metal and in essence regulate cell cycle. (Chesters and Petrie, 1999). The activities of many growth factors are zinc dependent, hence cell proliferation is regulated by the concentration of zinc ions (Hamza *et al.*, 2012). Zinc functions as a neurotransmitter (Tóth, 2011); in addition, it modulates the function of glutamate and other neurotransmitter receptors. Recent studies have indicated zinc to play important signaling roles in different human biological activities (Hirano *et al.*, 2008). Zinc deficiency in neonates is known to cause dwarfism, the retardation of mental and physical development, immune dysfunction, furthermore, learning incapacities and in grown-up certain neurodegenerative issue, for example, sadness, schizophrenia, Alzheimer's diseases (AD), Parkinson's diseases (PD), maturing, or amyotrophic horizontal sclerosis (AHS) (Prasad, 2009).

The mechanism of action of zinc is that, it modulates certain receptors at the post synaptic cleft. During the neuronal activity, when zinc with glutamate is released from synaptic vesicles into synaptic cleft, zinc interactions with postsynaptic receptors may occur (Morris and Levenson, 2012). The well-known process of zinc inhibition of *N*-Methyl-D-aspartic acid receptors (NMDAr) in synapses is one of such interaction. Excessive influx of zinc into neurons has been found to result in neurotoxicity and damage to post synaptic neurons. Zinc is additionally proposed as a hazard factor for melancholy, AD, maturing and other neurodegenerative issue (Izumi, 2006).

Then again, a developing assemblage of proof proposes that a lack as opposed to an overabundance of zinc prompts an expanded hazard for the improvement of neurological issue (Szewczyk, 2013). Without a doubt, zinc insufficiency has been appeared to influence neurogenesis and increment neuronal apoptosis, which can prompt learning and memory deficiencies. There is need for homeostatic controls to be put in place to avoid the accumulation of excess zinc or its deficiency. Disturbances of zinc homeostasis are considered as important factors in neurodegenerative brain disorders (Konoha *et al.*, 2006). The involve-

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