Biochemical Pharmacology 91 (2014) 426–435

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Commentary

Zinc: An underappreciated modulatory factor of brain function

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ARTICLE INFO

Article history:
Received 20 June 2014
Accepted 8 August 2014
Available online 15 August 2014

Keywords:
Zinc
Ion channels
Transporters
Brain function
Neurotransmission

ABSTRACT

The divalent cation, zinc is the second most abundant metal in the human body and is indispensable for life. Zinc concentrations must however, be tightly regulated as deficiencies are associated with multiple pathological conditions while an excess can be toxic.

Zinc plays an important role as a cofactor in protein folding and function, e.g. catalytic interactions, DNA recognition by zinc finger proteins and modulation ion channel activity. There are 24 mammalian proteins specific for zinc transport that are subdivided in two groups with opposing functions: *ZnT proteins* reduce cytosolic zinc concentration while *ZIP proteins* increase it. The mammalian brain contains a significant amount of zinc, with 5–15% concentrated in synaptic vesicles of glutamatergic neurons alone. Accumulated in these vesicles by the ZnT3 transporter, zinc is released into the synaptic cleft at concentrations from nanomolar at rest to high micromolar during active neurotransmission.

Low concentrations of zinc modulate the activity of a multitude of voltage- or ligand-gated ion channels, indicating that this divalent cation must be taken into account in the analysis of the pathophysiology of CNS disorders including epilepsy, schizophrenia and Alzheimer's disease.

In the context of the latest findings, we review the role of zinc in the central nervous system and discuss the relevance of the most recent association between the zinc transporter, ZIP8 and schizophrenia. An enhanced understanding of zinc transporters in the context of ion channel modulation may offer new avenues in identifying novel therapeutic entities that target neurological disorders.

1. Introduction

The sky was dark blue without a single cloud, and in the light of the early morning, the man viewed the profile of the Jungfraujoch and the Alps around him. As the first rays of sunlight shone on the white snow he removed a tube of ointment from his backpack and used it to cover his lips with a white paste to protect them from the ultraviolet light. Elsewhere a mother was treating the infected skin of her son with a medication while an old man was painting clouds on his canvas using a white color paint. What can be the common denominator of these three situations, and why could this be relevant in understanding the biology and function of the brain? Many compounds in common use were discovered to have beneficial medical applications long before our understanding of biology was sufficient to identify their active ingredient. The discovery that zinc chloride forms an excellent screen for ultraviolet light, acts as a powerful bactericide and irreplaceable paint pigment is a perfect illustration of the serendipity encountered in scientific discovery.

One particularity of zinc is its high toxicity that underlies its bactericidal activity. It was therefore surprising to discover that this cation, the second (after calcium) most abundant divalent cations in organisms, plays a determinant role in regulating cellular processes, including stabilizing the three-dimensional structure of the zinc finger (ZNF) proteins that recognize specific regions of DNA or RNA (reviewed in [1]).

Zinc is an essential trace element required by all living organisms. It plays critical roles as a cofactor both to stabilize proteins structurally, as well as facilitate enzymatic catalysis. It is thus not surprising that zinc is associated with various genetic traits, rare and common, that affect a multitude of physiological functions. The importance of zinc in human physiology and metabolism was identified by the consequences of zinc deficiency or metabolic disorders affecting zinc uptake [2]. Zinc insufficiency can be manifest in a diminished immune response, reduced tissue regeneration and healing after traumatic insults, as well as the occurrence of select neurological disorders. While commonly

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http://dx.doi.org/10.1016/j.bcp.2014.08.002
0006-2952/

the result of dietary factors, several inherited disorders of zinc deficiency have been identified to date, including *acrodermatitis enteropathica* (*AE*), also known as Brandt syndrome, and Danbolt-Closs syndrome or congenital zinc deficiency (reviewed in [3]). Physiologically, tight regulation of zinc homeostasis is necessary and its concentration can be steadily maintained even if the dietary content varies by as much as 15-fold ranging from 22 μmole per day up to 306 μmole per day [4]. In healthy subjects, normal blood values of zinc are between 9 and 17 μM. Zinc deficiencies have multiple effects, including infertility [5] and a correlation between zinc concentrations of approximately 1.8 μM and depression has been observed [6]. Zinc is not distributed homogenously (Fig. 1) being present in higher concentrations in muscle and bone. Despite lower concentration of zinc in the nervous system, it plays a key role in multiple brain functions as discussed below.

While a progressive reduction of zinc concentration has been observed in the elderly, and most specifically in patients suffering from Alzheimer's disease, cohort studies concluded that zinc is not a major determinant for AD neurodegeneration [7]. Zinc concentration is primarily maintained by intestinal intake, which balances the losses caused by fecal and urinary excretion. Cloning of ZnT1, a protein that transport zinc ions with high affinity and specificity in kidney tissue, constituted a major advance in understanding zinc homeostasis [8]. Since this initial study, 24 genes encoding zinc transporters have been identified. These proteins are divided in two groups: *the ZnT zinc transporter family*, which is composed of 10 members and can reduce intracellular zinc to the nanomolar range [9], and the *ZIP* (*Zrt-*, *Irt-like protein*) *transporter family*, [10] which is composed of 14 members, and is responsible for increasing intracellular zinc levels by transporting the metal from the extracellular space into the cytoplasm or from intracellular organelles back into the cytoplasm. Genes encoding for ZnT proteins are designated *SLC30A* (*1-10*) while those encoding ZIP proteins are designated *SLC39A* (*1-14*). ZnT proteins have six transmembrane domains with both the N- and C-termini facing the cytoplasm. ZIP proteins have eight transmembrane domains with both the N- and C-termini facing the cytosolic or intracellular organelle lumen [10].

ZnT transporters can decrease intracellular zinc concentration, whereas ZIP transporters regulate zinc homeostasis by actively transporting the cation into the cytoplasm. While ZnT proteins appear to selectively transport zinc, some ZIP transporters can also transport, cadmium, cobalt or manganese [10]. The efficiency of zinc transport depends upon the density of zinc transporters, ZnT and ZIP, expressed in different subcellular compartments. Their pattern of expression and localization is a function of the zinc present in the cellular milieu [11].

Zinc is critical for oocyte maturation and its ability to exit from meiosis [12] and also contributes to growth, fertility, and metabolism by interacting with vitamin D and peptide and steroid hormones like insulin, osteocalcin, somatomedin-c, thyroid hormone and testosterone [13]. After absorption from the digestive tract, zinc is transported by the blood to all tissues including the brain where its concentration can reach approximately 200 μM. The majority of the zinc is sequestered intracellularly, with extracellular levels being estimated to be in the nanomolar range [14,15]. It is important however, to note that zinc can be actively released in synapses during neurotransmission where its concentration can increase to the micromolar range, at which level it can physiologically regulate many synaptic processes [16]. As in other organs, in brain zinc is maintained at low levels by active transporters such that its levels are tightly and consistently regulated.

2. Zinc in the CNS

2.1. Physiological relevance in synaptic and extrasynaptic neurotransmission

Advances in the understanding of central nervous system (CNS) function have highlighted the selective expression of receptors and ion channels in neuronal subdomains, e.g., the postsynaptic, perisynaptic, extrasynaptic or axonal domains. Ligand-gated ion channels (LGICs) of particular subtypes are expressed postsynaptically, while other subtypes in the same family are expressed extrasynaptically as illustrated for the $GABA_A$ receptors [17] or for

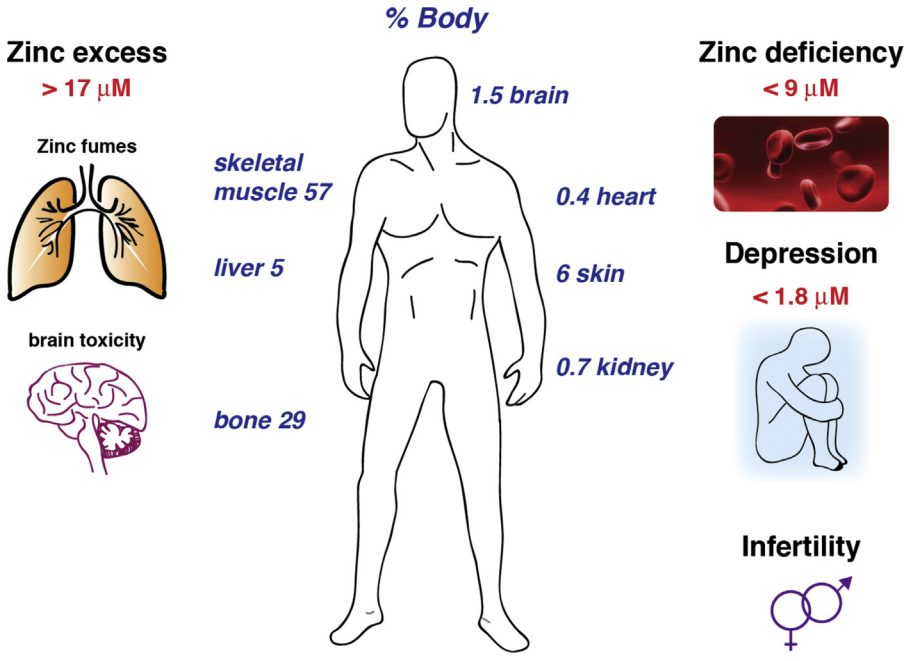

Fig. 1. Zinc distribution in the human body. Schematic representation of zinc distribution in the human body and its concentration (measured in the circulation under normal conditions). Abnormally low concentrations of zinc are known to cause infertility and other illnesses and are associated with depression. Inhalation of zinc-containing smoke causes adult respiratory distress syndrome (ARDS). Excess zinc is also known to be toxic to the brain, causing lethargy and inducing neuronal loss.