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Brain, aging and neurodegeneration: Role of zinc ion availability

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Abstract

Actual fields of research in neurobiology are not only aimed at understanding the different aspects of brain aging but also at developing strategies useful to preserve brain compensatory capacity and to prevent the onset of neurodegenerative diseases. Consistent with this trend much attention has been addressed to zinc metabolism. In fact, zinc acts as a neuromodulator at excitatory synapses and has a considerable role in the stress response and in the functionality of zinc-dependent enzymes contributing to maintaining brain compensatory capacity. In particular, the mechanisms that modulate the free zinc pool are pivotal for safeguarding brain health and performance. Alterations in zinc homeostasis have been reported in Parkinson's and Alzheimer's disease as well as in transient forebrain ischemia, seizures and traumatic brain injury, but little is known regarding aged brain. There is much evidence that that age-related changes, frequently associated to a decline in brain functions and impaired cognitive performances, could be related to dysfunctions affecting the intracellular zinc ion availability. A general agreement emerges from studies of humans' and rodents' old brains about an increased expression of metallothionein (MT) isoforms I and II, but dyshomogenous results are reported for MT-III, and it is still uncertain whether these proteins maintain in aging the protective role, as it occurs in adult/young age. At the same time, there is considerable evidence that amyloid-β deposition in Alzheimer's disease is induced by zinc, but the pathological significance and the causes of this phenomenon are still an open question. The scientific debate on the role of zinc and of some zinc-binding proteins in aging and neurodegenerative disorders, as well as on the beneficial effect of zinc supplementation in aged brain and neurodegeneration, is extensively discussed in this review.

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Abbreviations: $[Ca^{++}]_i$, intracellular Ca^{++} concentration; $[Zn^{++}]_b$, zinc concentration in the blood; $[Zn^{++}]_e$, extracellular free zinc ion concentration; $[Zn^{++}]_i$, intracellular free zinc ion concentration; $[Zn^{++}]_s$, synaptic zinc; Aβ, amyloid beta-peptide; AD, Alzheimer disease; α2M, alpha2-macroglobulin; ALS, amyotrophic lateral sclerosis; ALS-SODtransgenic mice, transgenic mice which express ALS-linked SOD1 mutant; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic; AP1, activator protein 1; ATP, adenosine triphosphate; Ca-A/K receptors/channels, calcium-permeable AMPA/kainate receptors/channels; cNOS, constitutive nitric oxide synthase; CNS, central nervous system; CuZnSOD, copper/zinc superoxide dismutase; DS, Down's syndrome; GABA, γ-aminobutyric acid; GAD, glutamate decarboxylase; GDH, glutamate dehydrogenase; GSSG, glutathione disulphide; His, L-histidine; ICE, interleukin-1beta converting enzyme; ICP-MS, inductively coupled plasma-mass spectrometry; IL-1, interleukin 1; IL-6, interleukin 6; iNOS, inducible nitric oxide synthase; IP3, inositol 1,4,5-trisphosphate; KA, kainate; LRP, low density lipoprotein receptor-related protein; LTP, long-term potentiation; mGluRs, G-protein linked glutamate receptors receptors; MMPs, matrix metalloproteases; MT, metallothioneins; MTF-1, metal-response element-binding transcription factor-1; NAD^+, nicotinamide; NFκB, nuclear factor κB; NGF, nerve growth factor; NMDA, *N*-methyl-D-aspartate; nNOS, neuronal NO synthase; NO, nitric oxide; PARP-1, poly(ADP-ribose) polymerase-1; PD, Parkinson's disease; PKC, protein kinase C; ROS, reactive oxygen species; SN, substantia nigra; Sp1, specificity protein 1; TNF, tumor necrosis factor; ZnT, zinc transporter proteins

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1. Introduction

Aging is characterized by a gradual and progressive loss of function over time, which decreases health and well-being. Many aged people show a slow decline in cognitive status presenting brain deficits in memory and other cerebral capacities (Hof and Morrison, 2004), but it is still uncertain if this process is a simple consequence of normal aging. The borderline between pathological and normal aging is so thin that, in the opinion of some investigators, age-related memory impairments occur even in persons without neurological diseases (McEntee and Crook, 1990). There is, conversely, unconfutable evidence that all these age-related alterations are coupled to physical changes. The number of nerve cells within the brain and cerebral blood flow decrease with advancing aging (Morrison and Hof, 1997), whereas the pigment lipofuscin, advanced glycation end-products, free radical production and oxidative stress markers increase in neuronal and glial cells (Mrak et al., 1997).

However, compensatory phenomena, such as lengthening and production of dendrites in the remaining nerve cells, may allow maintenance of brain performances in old people. On the contrary, the progressive loss of specific neuronal cells and the accumulation of intra-neuronal inclusions in neurodegenerative disorders come along with dysfunctions in the remaining neurons (Jellinger, 2003), shrinking the compensatory capacity of the brain. Therefore, actual fields of research are not only aimed at understanding the different aspects of brain aging but also at developing strategies useful to preserve brain compensatory capacity and to prevent the onset of neurodegenerative diseases.

Consistent with this trend, much attention has been addressed to metal metabolism during the last decade. In particular, zinc metabolism and homeostasis have been suggested to play a major role in many processes related to brain aging and in the onset and development of age-related neurodegenerative diseases (Doraiswamy and Finefrock, 2004; Mocchegiani et al., 2001; Huang et al., 1997). In fact, zinc acts as neuromodulator at excitatory synapses and has a considerable role in the response to stress, in the process of myelination and in the functionality of zinc-related proteins contributing, as such, to maintain brain compensatory capacity (Takeda, 2000). This review will be particularly focused on the role of ''intracellular zinc ion availability'' (referred to as the free zinc pool plus chelatable or loosely bound zinc that influence numerous intracellular crucial processes) (Haase and Beyersmann, 2002; Liuzzi and Cousins, 2004) and zinc-related proteins, such as metallothioneins (MT) and amyloid-beta (Aβ), in neuronal excitability and stress response during physiological aging and in some age-related neurodegenerative disorders. The possible beneficial effects and risks of zinc supplementation for brain health and function in aging and neurodegeneration are reported and discussed.

2. Zinc distribution into the brain

The brain has the highest zinc content with respect to other organs. The average of total brain zinc concentration was estimated to be approximately 150 μmol/L (about 10-fold serum zinc levels) (Takeda, 2000). However, free zinc ion concentration estimated in the cytosol ($[Zn^{++}]_i$) from cultured neurons is sub-nanomolar, and it is approximately 500 nM in brain extracellular fluids ($[Zn^{++}]_e$) (Weiss et al., 2000). On the contrary, the zinc content in the synaptic vesicles ($[Zn^{++}]_s$) of some neurons in the forebrain was