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Does the Zinc Neuroprotective Effectiveness of Mean Prevention of Intracellular Zinc Accumulation in Water in INDIA

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Abstract

Zinc (Zn) plays an important role in the activity of all cells, including neurons. Both the neurotoxic and neuroprotective effects of zinc have been well established, but the exact mechanism of its dual abilities still remains unclear. The same effect may also be found in other cells, but it should be remembered that lower sensitivity to hypoxia prolongs in time the cytotoxic effect of Zn^{+2} excess.

It seems that the apparent dualism depends primarily on the energetic condition of the cell, and also on the efficacy of ion pumps, genetically conditioned mechanisms regulating Zn cell efflux and Zn sequestration inside the cell and also on the concentration of extracellular free Zn.

Keywords: Neuroprotective effect of zinc; Neurotoxic effect of zinc

Neurotoxicity of zinc ions is currently the issue of numerous research programmes and publications.

Intracellular zinc content is genetically conditioned. It shows a relatively low intrasubject variability compared to intersubject variability and it varies depending on the organ [1-5]. There are two pools of intracellular zinc: slow pool, which is related among other things to protein synthesis or cell membranes (structural zinc), and fast pool (catalytic centre, signal transmitter, so called 'free zinc') [6,7].

Concentration of free zinc (Zn^{+2}) inside the cell is lower than outside the cell, e.g. in serum [4,5], which produces electrochemical gradient conditioned by the presence of transmembrane transport forms that require energy expenditure. Thus, each change leading to a decrease in ATP production will cause an increase in intracellular zinc level.

In physiological conditions, an increased zinc influx to the cell results in an increase in zinc membrane transporter synthesis, both in the cell membrane (ZnT-1) causing zinc efflux from the cell and in lysosomal membranes (ZnT-4, ZnT-6) increasing intracellular sequestration, thus keeping the intracellular cytoplasmic free zinc content on the optimal level.

Neurons are cells that are especially sensitive to hypoxia. Zinc plays an important role in the activity of all cells, including neurons. Both the neurotoxic and neuroprotective effects of zinc have been well established, but the exact mechanism of its dual abilities still remains unclear. The same effect may also be found in other cells, but it should be remembered that lower sensitivity to hypoxia prolongs in time the cytotoxic effect of excessive amount of Zn^{+2}.

It seems that the apparent dualism depends primarily on the energetic condition of the cell, and also on the efficacy of ion pumps, genetically conditioned mechanisms regulating Zn cell efflux and Zn sequestration inside the cell and on the concentration of extracellular free Zn.

If mechanisms regulating energy production, which are subject of negative feedback, and mechanisms regulating cytosolic zinc level work properly, zinc fulfils its important metabolic tasks and cytoprotective functions. In the event of cell energetic dysfunction, zinc influx and accumulation in cytosol intensifies this dysfunction by means of positive feedback, thus leading to cell death. Zinc has been proposed to disrupt calcium homeostasis, inhibit mitochondrial electron transport, disrupt tubulin assembly, and overactivate calcium-mediated enzymes. Furthermore, zinc reacts with the thiol and imidazole moieties of many proteins, and, thus, can disrupt their structure and function [8].

The above considerations may be confirmed by the fact that physiological ZnT-1 distribution within the central nervous system lines up with areas of high intraneuronal zinc content [9]. It has also been found out that transient experimental brain ischemia increases ZnT-1 gene expression [10], which in view of the above considerations may correspond with the pre-conditioning phenomenon.

It seems that all phenomena leading to disorders in the neural energetic condition (oxygen deficit, glucose deficit) due to changes in inflowing blood composition, decreased blood inflow, blood stasis, prolonged route of diffusion and damage to cell membrane–shall lead to changes in neural function, including neural death, at a rate depending on the intensity and progression of processes that result in impairment of intracellular production of energy.

No matter what pathological process or clinical condition within the central nervous system is being considered – microembolism (e.g. with cholesterol crystals), macroembolism, small vessels disease, leukoaraiosis, vascular changes in diabetes or arterial hypertension (microvascular changes), Alzheimer's disease – the target mechanism on the cell level is the same, both for small and large areas–zinc excess causes loosening of the mitochondrial respiratory chain [11].

Regulation of changes in zinc metabolism–lowering the level of dyshomeostasis will be possible to achieve, depending on the primary

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cause, by administration of medicines directly or indirectly influencing zinc metabolism. Taking into account the toxic effect of excessive intracellular Zn^{2+}, an essential condition will be to improve cell membrane function and effectiveness of zinc efflux into the extracellular space. Since excessive intracellular Zn^{2+} loosens the mechanisms of oxygen metabolism, it at the same time diminishes zinc efflux from the cell. The mechanism initiates a vicious circle. Experimental use of agents affecting intracellular oxygen metabolism, such as pyruvates, decreases zinc accumulation and improves cell survival [12].

A similar mechanism may relate to the neuroprotective effect of agents lowering the activity of carbonic anhydrase [13], a zinc-dependent enzyme. Cytosol acidification, unmanageable by negative feedback, is a factor impairing intracellular production of energy, which also increases intracellular zinc accumulation. Moreover, Zn^{2+} ions affect regulation of H^+ ion influx into the cell [14,15]. It may be assumed that a higher level of Zn^{2+} ions in the extracellular environment reduces the influx of H^+ ions into the cell, i.e. it prevents excessive acidification, whereas a lower level of Zn^{2+} ions in the extracellular environment increases the influx of H^+ ions into the cell, i.e. it increases cytosol acidification [16].

Reception of antiplatelet drugs may also be treated as an important issue in the context of zinc neuroprotective effect – in the process of aggregation, platelets release large amounts of zinc increasing its local concentration 30–40-fold, which is an independent cytotoxic effect accompanying changes caused by hypoxia [17].

A similar situation occurs with drugs affecting RAAS or blocking calcium channel, since the RAAS is involved in zinc metabolism [18] and calcium channels are functionally related to ZnT-1 [19].

Neuroprotective effect in relation to zinc toxicity may also be revealed by estrogens [20]. Such effect has also been revealed for carnosine, a substance occurring in the CNS and meeting the criteria for a neurotransmitter [8].

It seems that the discovery of substances blocking zinc channels directly influencing membrane proteins transporting zinc will be essential for the aspect of zinc neuroprotection, due to the influence on zinc flow through cell membranes and zinc content in cytosol. Substances inhibiting zinc influx to the cell (blocking influx complying with the electrochemical gradient– "zinc entry/channels blockers") seem to be more promising than substances enhancing its efflux (against the electrochemical gradient), since this form of neuroprotection requires a relatively efficient energetic condition of the cell. In theory, an expedient and short-term neuroprotective effect could be achieved by zinc-chelating substances (reduction of extracellular free zinc level leading to a decrease in its influx to energetically insufficient cells).

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