

REVIEWS

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Is the Zinc Neuroprotective Effect Caused by Prevention of Intracellular Zinc Accumulation?

Czy neuroprotekcyjne działanie cynku polega na zapobieganiu wewnątrzkomórkowej kumulacji cynku?

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Abstract

Zinc plays an important role in the functioning of all cells, including neurons. The precise mechanisms responsible for its neurotoxic and neuroprotective effects remain unclear despite extensive investigations. Similar Zn⁺² effects can also be observed in cells outside the nervous system, and their lower sensitivity to hypoxia prolongs the cytotoxic effect of excess zinc. The evident dualism of zinc's effects depends primarily on the energetic state of the particular cell and the efficacy of ion pumps; on genetically conditioned mechanisms regulating Zn efflux from cells and Zn sequestration inside the cell; and on the concentration of extracellular free Zn (*Adv Clin Exp Med* 2012, 21, 2, 245–248).

Key words: zinc, neuroprotection, neurotoxicity.

Streszczenie

Cynk odgrywa ważną rolę w funkcjonowaniu wszystkich komórek, w tym neuronów. Zarówno neurotoksyczne, jak i neuroprotekcyjne działanie cynku było przedmiotem licznych badań, niemniej jednak mechanizm jego podwójnego oddziaływania nadal pozostaje niewyjaśniony. Podobne rezultaty działania jonów cynku można także obserwować w komórkach poza układem nerwowym, a ich mniejsza wrażliwość na niedotlenienie przedłuża w czasie cytotoksyczne działanie nadmiaru cynku. Ten oczywisty dualizm działania cynku zależy głównie od stanu energetycznego komórki i wydajności pomp jonowych, jak również od uwarunkowanych genetycznie mechanizmów regulujących wpływ cynku z komórki i jego nagromadzenie wewnątrz komórki, a także od stężenia wolnego cynku w przestrzeni pozakomórkowej (*Adv Clin Exp Med*. 2012, 21, 2, 245–248).

Słowa kluczowe: cynk, neuroprotekcja, neurotoksyczność.

The neurotoxicity of zinc ions (Zn²⁺) has been the subject of numerous investigations. Intracellular zinc content is genetically conditioned. Interestingly, it shows a relatively low intraindividual variability, but varies from organ to organ [1–3]. There are two pools of intracellular zinc: a slow pool, which is related to (among other things) protein synthesis and cell membranes (so-called structural zinc), and a fast pool, which serves as a catalytic center and signal transmitter (so-called “free zinc”) [4, 5].

The concentration of free zinc inside cells is lower than the concentration outside cells, for example in serum [2, 3], which yields an electro-

chemical gradient conditioned by the presence of transmembrane transport that requires energy expenditure. Thus, each change leading to a decrease in adenosine-5'-triphosphate (ATP) production will cause an increase in intracellular zinc concentration.

In physiological conditions, increased zinc influx to the cell enhances 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 an optimal level.

The dual neurotoxic and neuroprotective effects of zinc are widely known, but the precise mechanisms responsible for its neurotoxic and neuroprotective effects remain unclear [6].

Zinc plays an important role in the activity of all cells, including neurons, which are extremely sensitive to hypoxia. Similar effects of zinc activity can also be observed in cells outside the central nervous system (CNS), and it should be emphasized that their lower sensitivity to hypoxia prolongs the cytotoxic effect of excessive amounts of Zn^{2+} ions [7].

It seems that the apparent dualism of zinc's functioning depends primarily on the energetic state of the cell and the efficacy of the transmembrane ion pumps, but also on genetically conditioned mechanisms regulating Zn cell efflux and ion sequestration inside the cell, and on the extracellular free zinc concentration [7, 8].

If mechanisms regulating energy production, controlled by the negative feedback loop, and mechanisms regulating the cytosolic zinc level work properly, zinc fulfills its important metabolic tasks and cytoprotective functions. In cases of cellular energy imbalance, subsequent zinc influx and accumulation in cytosol enhances the dysfunction through positive feedback, finally leading to cell apoptosis [9].

As Trombley et al. wrote: "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" [10].

It has also been shown that expression of zinc homeostatic proteins in the CNS is, as Karol et al. phrased it, "regulated by crosstalk between synaptic and intracellular pools of $Zn(2+)$ " [11].

It is of interest that physiological distribution of ZnT-1 (the cell membrane transporter) within the CNS corresponds to areas of high intraneuronal zinc content [12]. Moreover, it has also been found that transient experimental brain ischemia coincides with stronger ZnT-1 gene expression [13]. Both of these facts might reflect a pre-conditioning phenomenon.

It seems that all neural energy-state disorders (i.e., oxygen and glucose deficit) caused by alterations in the composition of inflowing blood, decreased blood inflow, blood stasis, prolonged route of diffusion and damage to cell membranes can disturb neural function, due to impairment of intracellular energy production [14].

In numerous conditions affecting the central nervous system, such as microembolism (e.g. with cholesterol crystals), macroembolism, small vessel

disease, leukoaraiosis, diabetic vascular changes, arterial hypertension (microvascular changes) or Alzheimer's disease, the causative mechanism on the cell level is the same, i.e. excess zinc causing a loosening of the mitochondrial respiratory chain [15, 16].

An increase in vesicular zinc release from pre-synaptic terminals, leading to inhibition of reactive oxygen species (ROS) production and microglia activation, appears to alleviate brain neuronal injury caused by insulin-induced hypoglycemia [17].

Regulation of zinc metabolism, decreasing the level of its dyshomeostasis, could be possible by administering medicines that would directly or indirectly influence the zinc turnover. Taking into account the toxic effect of excessive loads of intracellular Zn^{2+} , an essential goal appears to be improving cell membrane function and the effectiveness of zinc efflux to the extracellular space. Since an excess of intracellular Zn^{2+} disturbs the mechanisms of oxygen metabolism, it simultaneously diminishes zinc efflux from the cell, initiating a vicious circle. The experimental use of agents affecting intracellular oxygen metabolism, such as pyruvates, results in reducing zinc accumulation and improving cell survival [18, 19].

A similar mechanism may be associated with the neuroprotective effect of agents lowering the activity of carbonic anhydrase, which is a zinc-dependent enzyme [20]. Cytosol acidification, which cannot be managed by negative feedback, is a factor impairing intracellular energy production, which also increases intracellular zinc accumulation. Moreover, zinc affects the regulation of H^+ ion influx into the cell [21].

It can be assumed that a higher level of Zn^{2+} in the extracellular environment reduces the influx of H^+ into the cell and therefore prevents excessive acidification, whereas a lower level of extracellular Zn^{2+} increases the intracellular influx of H^+ , i.e. cytosol acidification [22].

It is supposed that the use of antiplatelet drugs could be effective in neuroprotection, because during 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 [23].

A similar situation occurs with drugs affecting the renin-angiotensin-aldosterone system (RAAS) or blocking calcium channels, since the RAAS is involved in zinc metabolism [24] and calcium channels are functionally related to ZnT-1 activity [25].

Neuroprotection from zinc toxicity may also be provided by estrogens [25]. Such an effect has also been shown for carnosine, a substance that occurs in the CNS and shows features of a neurotransmitter [10].

The authors suppose that some substances blocking Zn^{2+} channels, directly affecting membrane protein zinc transporters, could be essential for neuroprotection, because of their probable reduction of the zinc flow through cell membranes and its content in cytosol. Substances inhibiting Zn^{2+} influx to the cell (flowing with the electrochemical gradient) seem to be more promising than substances enhancing its efflux (flowing against the electrochemical gradient) [2, 3].

Because the first mentioned neuroprotective agents require an efficient energetic state of the cells, the current authors hypothesize that a short-term expedient neuroprotective effect could be achieved by using zinc-chelating agents to reduce the extracellular load of zinc, which would decrease its influx to energetically inefficient cells.

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