УДК 577.118:546.47:612.015.31(048.8) doi: 10.20998/2220-4784.2025.01.02

G. SYROVA, N. CHALENKO, S. KOZUB

BIOLOGICAL ROLE OF ZINC AND ITS COMPOUNDS

The presented data indicate that the biological role of zinc in the body is largely mediated through its involvement in the synthesis and stabilization of nucleic acids and proteins, energy metabolism, cellular proliferation and differentiation, and the maintenance of antioxidant status. Numerous studies have demonstrated that zinc is essential for preserving cellular integrity and maintaining the structural and functional integrity of cell membranes. Zinc also plays a protective role under the influence of various pathogenic factors. The article provides a review of the physiological role of zinc at various stages of human life and development, as well as the pharmacological properties of zinc-containing compounds used in the treatment of certain diseases. Zinc-based preparations exhibit immunomodulatory, antibacterial, antifungal, and anti-inflammatory effects. The article also analyzes recent scientific studies concerning zinc metabolism and its biological significance in the human and animal body.

Keywords: zinc, zinc-containing enzymes, physiological role, pharmacological activity, zinc deficiency, pharmaceutical preparations.

Г. СИРОВА, Н. ЧАЛЕНКО, С. КОЗУБ

БІОЛОГІЧНА РОЛЬ ЦИНКУ ТА ЙОГО СПОЛУК

Представлені дані свідчать про те, що біологічна роль цинку в організмі значною мірою опосередковується його участю в синтезі та стабілізації нуклеїнових кислот і білків, енергетичному обміні, клітинній проліферації та диференціації, а також підтримці антиоксидантного статусу. Численні дослідження показали, що цинк необхідний для збереження цілісності клітин та підтримки структурної та функціональної цілісності клітинних мембран. Цинк також відіграє захисну роль під впливом різних патогенних факторів. У статті наведено огляд фізіологічної ролі цинку на різних етапах життя та розвитку людини, а також фармакологічних властивостей цинквмісних сполук, що використовуються для лікування певних захворювань. Препарати на основі цинку мають імуномодулюючу, антибактеріальну, протигрибкову та протизапальну дію. У статті також аналізуються останні наукові дослідження щодо метаболізму цинку та його біологічного значення в організмі людини та тварин.

Ключові слова: цинк, цинквмісні ферменти, фізіологічна роль, фармакологічна активність, дефіцит цинку, фармацевтичні препарати.

Introduction.

Zinc is a well-known d-block chemical element belonging to group II of the periodic table and one of the most widespread trace elements, ranking second after iron in terms of prevalence in the human and animal body as well as involvement in metabolic processes. Zinc-based preparations have been used in medicine since ancient times. More than 3,000 years ago, zinc oxide—known as calamine—was used by humans for wound treatment. Later, various zinc salts were employed in treating epilepsy and chorea, as an emetic in cases of poisoning, and for topical use. The discovery of zinc deficiency in the 1960s sparked interest in its clinical applications and led to numerous studies in this field. Zinc is classified as an essential trace element that is present in all cells of the human body and participates in numerous biological processes, including the synthesis and stabilization of nucleic acids and proteins, energy metabolism, cell proliferation and differentiation, and the maintenance of antioxidant status. Zinc enters the human body primarily through dietary sources, and to a much lesser extent through water. Zinc deficiency in humans most commonly develops as a result of inadequate nutrition but may also be associated with malabsorption syndromes, excessive loss of the element (e.g., diarrhea, severe burns), or increased physiological demands. The prevalence of zinc deficiency varies widely depending on geographical location, socioeconomic status, and dietary traditions. According to the World Health Organization (WHO), the prevalence of zinc deficiency in the population ranges from 10% to 80%. In particular, in Eastern European countries, the prevalence of zinc deficiency is approximately 10%.

The main purposes of this paper are:

Zinc deficiency is associated with a complex array of disorders due to the element's diverse physiological functions. Nearly all zinc (99.9%) in the human body is localized in tissues (particularly concentrated in the pancreas), while only 0.1% is found in blood plasma. Zinc exhibits a high affinity for forming chelate complexes.

The main part. Within cells, zinc predominantly exists as part of stable biocomplexes, in which it is tightly bound to endogenous organic ligands.

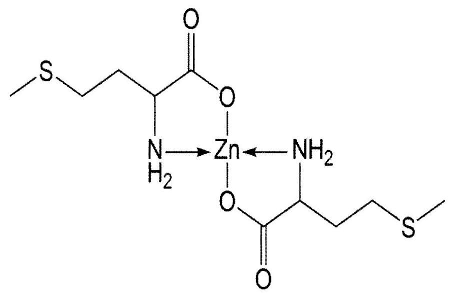

Fig. 1. Zinc–methionine chelate

Zinc is characterized by the ability to form coordination compounds with nitrogen- and oxygen-containing ligands, most commonly exhibiting coordination numbers of 4 and 6.

Zinc is involved in gene regulation. A well-known example is the family of site-specific DNA-binding proteins known as "zinc fingers.

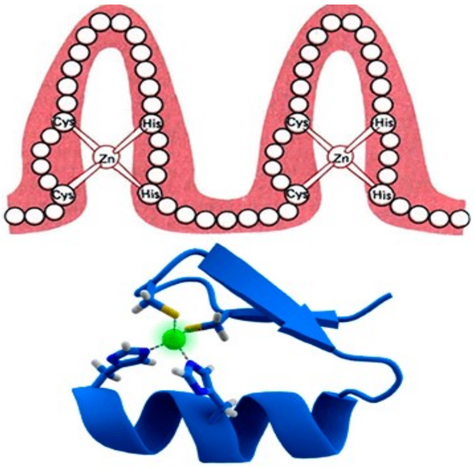

Fig. 2. Zinc finger

These proteins contain domains composed of repeating units of approximately 30 α-amino acids. Each domain folds into a distinct structural unit around a zinc ion, which is coordinated by two cysteine and two histidine residues. "Zinc fingers" recognize and bind to specific DNA sequences through conformational complementarity with the major grooves of the DNA helix.

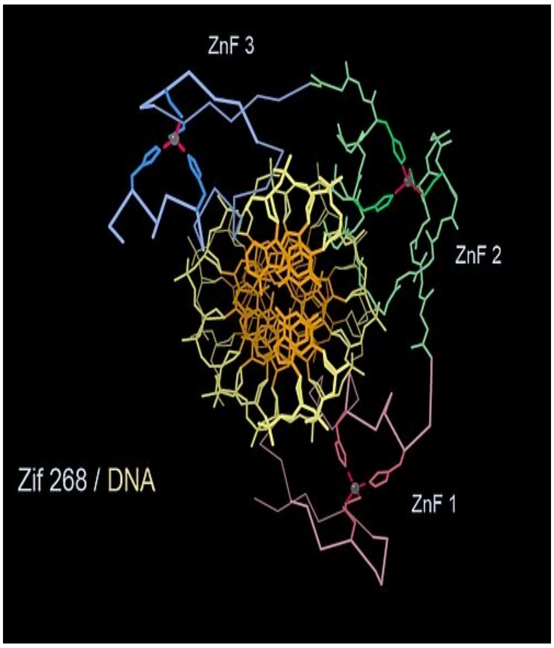

Fig. 3. Transcription factor Zif268 containing three zinc finger domains in complex with DNA

Adequate zinc levels are essential for the following physiological functions:

- normal blood circulation and metabolic processes, as zinc serves as a cofactor for numerous enzymes;

- maintenance of normal blood glucose levels, as zinc ions form labile biocomplexes with insulin molecules and reduce steric hindrance during insulin-carbohydrate interactions;

- support of a healthy intestinal microbiota;

- functioning of the reproductive system in both males and females, including the maturation of oocytes and spermatozoa;

- synthesis of hormones, such as somatotropin (growth hormone), insulin (pancreatic hormone), and testosterone (sex hormone);

- activation and metabolism of tocopherol (vitamin E), one of the body's most important antioxidants.

There is evidence supporting the involvement of zinc, in particular, in processes of free radical oxidation. It acts as a cofactor for superoxide dismutase, an enzyme that catalyzes the conversion of superoxide radicals into molecular oxygen and hydrogen peroxide. Additionally, zinc inhibits nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, an enzyme responsible for the production of reactive oxygen species. This trace element also stimulates the synthesis of metallothioneins, which, due to their high cysteine content, effectively scavenge reactive oxygen species. Moreover, zinc competes with copper and iron, thereby reducing the ability of these metals to interact with hydrogen peroxide and generate reactive radicals.

Zinc is known to be essential for maintaining the barrier function of cellular membranes. Research findings indicate that zinc deficiency increases the permeability of epithelial intercellular junctions in the intestine, particularly at the sites of tight and adherens junctions. This, in turn, is associated with enhanced neutrophil migration, elevated production of pro-inflammatory cytokines, and excessive progression of the inflammatory response. Such conditions contribute to the development of complications and the prolonged or chronic course of intestinal inflammation. Similarly, zinc deficiency disrupts skin homeostasis. A lack of this trace element increases permeability, especially within the stratum corneum and tight junctions. One possible consequence of such an imbalance is the development of atopic dermatitis.

Zinc contributes to maintaining oncotic pressure in the blood through its association with albumins and other plasma proteins. In addition, zinc mitigates the harmful effects of alcohol on the liver and brain and helps alleviate hangover symptoms. This is due to the fact that zinc is a structural component of the enzyme alcoholdehydrogenase, which is active in the liver and is responsible for the oxidation and breakdown of ethanol. Overall, zinc possesses a significant detoxifying function, as it forms active complexes with albumin and other blood proteins that bind and eliminate toxic exogenous proteins from the body.

Zinc is a component of the hydrolytic enzyme carboxypeptidase, which catalyzes the breakdown of proteins into amino acids. A notable example of a metalloenzyme containing a single zinc ion is carbonic anhydrase, whose physiological function is associated with respiration: the enzyme catalyzes the hydration of carbon dioxide (carbon (IV) oxide), a metabolic product. In vitro, carbonic anhydrase exhibits considerable versatility, catalyzing several reactions involving both OH^- and H^+ ions, such as the hydrolysis of esters and the hydration of aldehydes. [6].

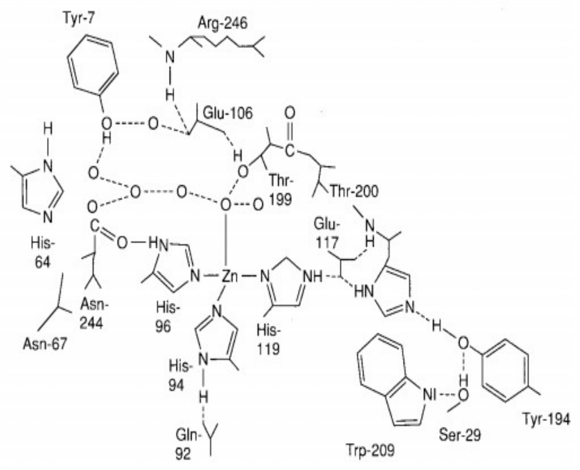

Fig. 4. Schematic representation of the active site of human carbonic anhydrase II

Zinc synthesizes approximately 300 different enzymes essential for normal brain function, cell growth, metabolism, and digestion. Zinc activates enzymes such as peroxidase, enolase, carbonic anhydrase, and aminopeptidase, while inhibiting alkaline phosphatase, protease, and succinate oxidase. It also plays a role in regulating brain activity and strengthens nerve fibers. The proper synthesis of serotonin, the so-called "happiness hormone", is also impossible in the context of zinc deficiency. For this reason, zinc-containing supplements are often prescribed by physicians for individuals experiencing depressive tendencies, chronic stress, anxiety, and sometimes chronic fatigue syndrome.

In metalloprotein molecules, zinc can be incorporated into the active site. In addition, zinc is a component of a large group of non-enzymatic metalloproteins, in which the microelement's cations contribute to stabilizing secondary and tertiary protein structures. The formation of such zinc-ion complexes is essential for executing specific functions of numerous proteins. In human cells, zinc-dependent proteins are accumulated in the cytoplasm, nucleus, endoplasmic reticulum, Golgi-derived secretory vesicles and mitochondria. In the nucleus, metalloproteins play a critical role in the transmission of genetic information, mediating both DNA transcription and replication processes. Nearly 20% of the total zinc in human cells is accumulated in the form of specific cysteine-rich proteins known as metallothioneins. These proteins form complexes capable of binding up to seven zinc ions. Metallothioneins are essential for maintaining zinc homeostasis, regulating its intracellular concentration and protecting cells from the toxic effects of elevated zinc ion levels. In blood plasma, approximately 80% of zinc is bound to serum albumins. The albumin molecule possesses multiple metal-binding sites, with site A exhibiting high affinity specifically for zinc ions.

Various zinc-containing pharmaceutical agents are used in medical practice. Zinc sulfate heptahydrate ($ZnSO_4 \cdot 7H_2O$) is applied in the form of 0.1–0.25% solutions for the treatment of eye diseases. $ZnSO_4$ is also an active component of dental cements and dermatological preparations. Zinc oxide (ZnO) is widely used in dermatology as pastes, powders and ointments. A zinc-insulin suspension, which contains zinc chloride and insulin, is used to manage diabetes mellitus. Zinc is also included in many vitamin and mineral complexes to support eye health. This mineral enhances the absorption of retinol (vitamin A), one of the key nutrients essential for vision. Additionally, zinc improves night vision, helps protect the macula from degeneration, and reduces the risk of cataract development.

Zinc plays a crucial role in the functioning of the immune system. During infectious diseases, it is essential not only for the proper function of the host organism but also for meeting the metabolic needs of pathogenic microorganisms. Current evidence indicates that this trace element is involved in immune responses at various stages and is critical for the functioning of both the innate and adaptive branches of the immune system.

The invasion of a pathogen triggers the activation of the immune response. One of the key signaling pathways involved in initiating this response is mediated by nuclear factor kappa B (NF-κB). NF-κB is a protein complex present in nearly all cell types and is known to play a central role in transmitting inflammatory signals in both innate and adaptive immune responses. The influence of zinc on this activation pathway of the inflammatory mechanism has been investigated in several studies. Activation of NF-κB requires the phosphorylation and subsequent degradation of its specific inhibitor, IκB. Most studies indicate that zinc exerts an inhibitory effect on NF-κB activity; however, some findings also suggest that the activity of this nuclear factor may be impossible in the absence of this trace element. A negative feedback mechanism during the development of the inflammatory response has also been identified. It operates as follows: activation of NF-κB enhances the activity of the membrane transporter ZIP8, leading to increased zinc influx into the cell and contributing to the regulation of the pro-inflammatory response. In the presence of adequate zinc levels, the replication of rhinoviruses is inhibited, resulting in a milder course of illness. Moreover, updated protocols for the prevention and treatment of COVID-19 include recommendations for zinc supplementation: for prevention – 30-50 mg of zinc per day; for treatment –

75-100 mg (limited to patients with mild forms of the disease and only under medical supervision).

The spectrum of infectious diseases for which the efficacy of zinc-based preparations has been studied is broad. Compelling evidence has been obtained regarding its effectiveness in certain conditions, such as skin infections, acute respiratory illnesses, and intestinal infections. Moreover, the beneficial effects of zinc have been demonstrated not only in treatment but also in the prevention of specific diseases.

Zinc is absolutely essential for male health. It is highly concentrated in the prostate, and approximately 10 mg of zinc are present in every 50 mL of semen. In the male body, zinc plays several roles: it is involved in testosterone production; together with tocopherol (vitamin E), it contributes to the formation and development of sex cells and the initiation of erection; it also helps prevent inflammation and tumor development in the prostate. This is why many prostate-protective formulations contain zinc (Prostatilen-Zinc suppositories, Prostata Plus capsules and others). Zinc deficiency may lead to erectile dysfunction – a condition that can significantly affect a man's psychological well-being and may contribute to the development of alcoholism and other serious mental health issues.

Zinc deficiency may lead to reduced testosterone levels, elevated blood glucose, and the formation of microplaques in the blood vessels of the genital organs – all of which ultimately contribute to erectile dysfunction. If a man turns to alcohol for comfort, the remaining zinc reserves in the body are redirected to protect brain and liver cells from the toxic effects of ethanol, further exacerbating zinc deficiency. Therefore, it is recommended that all men over the age of 40 not only maintain a healthy diet and lifestyle but also periodically take zinc-containing supplements.

In the female body, zinc directly influences the function of the reproductive system. It plays a role in initiating puberty and ensuring its normal progression, as well as supporting the proper development of the reproductive organs. Zinc deficiency in adolescent girls may result in delayed puberty and can contribute to ovarian or uterine dysfunction. In some cases, zinc deficiency may lead to infertility, underscoring the element’s importance in female reproductive health. Special attention should be paid to zinc intake during the first trimester of pregnancy, when the fetus's reproductive organs are being formed.

Throughout pregnancy, zinc supplementation is recommended to reduce the risk of preterm birth, support proper fetal development – particularly of the skeletal system – and help maintain the mother's physical appearance, dental and joint health, and immune function. Zinc intake is advisable even during the preconception period, as it promotes the maturation of oocytes and follicles, and significantly reduces the risk of miscarriage. Zinc deficiency in women tends to peak during the climacteric (menopausal) period. Zinc supplementation at this stage can help alleviate many of the unpleasant symptoms of menopause, such as hot flashes, mood swings, irritability, skin problems, weight gain, and hair loss. After reviewing a patient’s medical history and test results, gynecologists often prescribe zinc-containing supplements. Although such treatment may not completely eliminate menopausal symptoms, it can significantly reduce their severity. After menopause, a woman's zinc requirements increase, as older women are more susceptible to musculoskeletal disorders than men of the same age group. It is well established that calcium and zinc supplementation is essential for the prevention of osteoporosis.

Zinc is absolutely essential for the developing body of a child, as it: participates in hormone synthesis; exhibits antioxidant properties; regulates growth; and supports the normal formation and development of two of the most critical systems in the body—the reproductive and immune systems. Official WHO materials include publications dedicated to the use of zinc supplements in children with respiratory infections, as well as the role of zinc in normal growth and development. It is also worth noting that acne in adolescents is often associated with zinc deficiency and can be effectively treated with zinc-containing supplements and topical zinc-based preparations.

The primary dietary sources of zinc include: pumpkin seeds – which are commonly used in formulations for the treatment of prostatitis and are also considered a traditional remedy for helminth infections; lean pork and other red meats such as beef and lamb, with lean pork being particularly rich in zinc; sprouted oats and wheat; flaxseeds and sesame seeds; dark chocolate (75–85%) and cocoa; cheese and yogurt; lentils and other legumes; leafy green vegetables; nuts such as cashews, almonds and hazelnuts; and certain seafood – particularly oysters, lobsters, crab meat, and mussels. It is advisable to regularly include at least some of these zinc-rich foods in the daily diet.

Phytic acid salts (phytates), present in staple plant-based foods such as grains, rice, and legumes, exert a strong inhibitory effect on zinc absorption from dietary sources. This is particularly true for specific forms such as inositol hexaphosphate and inositol pentaphosphate. The phosphate groups of these compounds bind to zinc cations, forming stable, insoluble complexes that hinder the absorption of the trace element. Phytates can also form complexes with zinc endogenously secreted into the small intestinal lumen by the pancreas, thereby inhibiting its reabsorption. It is believed that this mechanism contributes to the development of zinc deficiency in individuals adhering to long-term plant-based diets. Additionally, dietary plant fibers negatively affect zinc absorption, which is primarily attributed to the fact that such fibers often contain phytates. It is known that among rural populations, approximately 60–70% of dietary zinc intake comes from plant-based foods with a high phytate content. As a result, the zinc absorption rate in these populations is lower, and the molar ratio of phytate to zinc is higher compared to urban populations. The average daily zinc intake in rural areas is approximately 5.2 mg for women and 7.3 mg for men.

Conclusions and ideas for further investigation

A decrease in plasma zinc levels has been observed during episodes of hyperthermia. Similar phenomena have been reported in patients with rheumatoid arthritis, alcoholic liver cirrhosis, decompensated heart failure, and in cases of tissue injury involving the brain, kidneys, lungs, or heart. It is believed that the reduction in plasma zinc concentration results from the rapid redistribution of the microelement into damaged tissues. This effect is associated with the activation of metallothionein synthesis and increased expression and activity of Cu/Zn-superoxide dismutase in the affected organ's cells.

Disruption of zinc metabolism or deficiency of this essential microelement in the human body leads to deterioration of health and, in some cases, the development of serious diseases. This is due to zinc's critical role in maintaining the proper structure and function of numerous essential proteins for the functioning of various organs and systems. The wide range of consequences associated with zinc deficiency underscores this element's important role in fundamental biological processes.

It is known that various factors cause the lack of this essential microelement in the human body and is not only a medical and biological, but also a socio-economic problem. Dietary habits also play a role in the development of zinc deficiency conditions 12–.

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Надійшла (received) 20.03.2025

Відомості про авторів / About the Authors

Сирова Ганна Олегівна (Syrova Ganna) – доктор фарм. наук, професор кафедри медичної та біоорганічної хімії, Харківський національний медичний університет, м. Харків, Україна; ORCID: https://orcid.org/0000-0001-8849-9755 e-mail: ho.syrova@knmu.edu.ua

Чаленко Наталія Миколаївна (Chalenko Nataliia) - кандидат фарм. наук, старший викладач кафедри медичної та біоорганічної хімії, Харківський національний медичний університет, м. Харків, Україна; ORCID: https://orcid.org/0000-0002-6087-2201 e-mail: nm.chalenko@knmu.edu.ua

Козуб Світлана Миколаївна (Kozub Svitlana) – кандидат технічних наук, доцент кафедри медичної та біоорганічної хімії, Харківський національний медичний університет, м. Харків, Україна; ORCID: https://orcid.org/0000-0002-7162-027X e-mail: smkozub@knmu.edu.