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Zinc and zinc nanoparticles: biological role and application in biomedicine

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Summary. Due to nanodimension of functional components of living cells, the application of nanotechnologies in biomedical purposes is an important problem for today. One of the most promising directions is to use zinc nanoparticles for molecular diagnostics, target delivery of drugs, developing new pharmaceutical preparations. The paper presents the data on biological properties of zinc and its compounds, their location in the organism and role in important biological processes, which show the ways of possible practical applications of zinc nanoparticles in biomedicine. Particular attention is paid to the role of ion's zinc in muscle functioning.

Keywords: zinc, zinc nanoparticles, functional properties, biomedical applications.

Introduction. The currently existing nanoparticles are classified by their chemical composition, namely: 1) metallic nanoparticles (Au, Ag, Cu, Fe, Zn (Fig. 1), etc.); 2) nanoparticles of metal and non-metal oxides (FeO, VO, AlO, ZnO (Fig. 2, Tabl. 1), etc.); 3) semiconductor nanoparticles (ZnS, CdSe, ZnSe, CdS, etc.); 4) carbon nanoparticles (fullerenes, nanotubes, graphene [1-5], diamond); 5) nanoparticles of organically modified layered silicates and alumosilicates (nanoclays of different compositions); 6) nanoparticles of organic dendrite polymers (dendrimers of different composition); 7) quantum dots [6, 7]. Zinc and zinc nanoparticles (Figs. 1 and 2) can be classified into 1-3 and 7 groups, respectively.

At present the medicinal preparations based on nanoparticles of metals (silver, gold, iron and others) 5-16 nm in size are considered to be the most promising for practical applications in biomedicine. It has been found that high-disperse powders of nanometals (magnesium, copper, zinc, etc.) as well as their oxides show a pronounced biological activity [8]. They are used both independently and in complexes with organic compounds. These nanoparticles are not only capable of inhibiting aggregation of colloid solutions and increase their stability but also can deliver medical preparations to the target location of pathological process [9]. In particular, nanozinc has been used in non-organic complex-

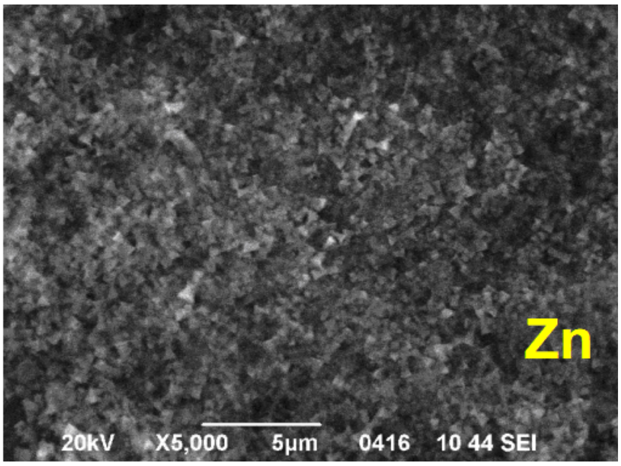

Fig. 1. A typical electron microscopy image of Zn nanoparticles.

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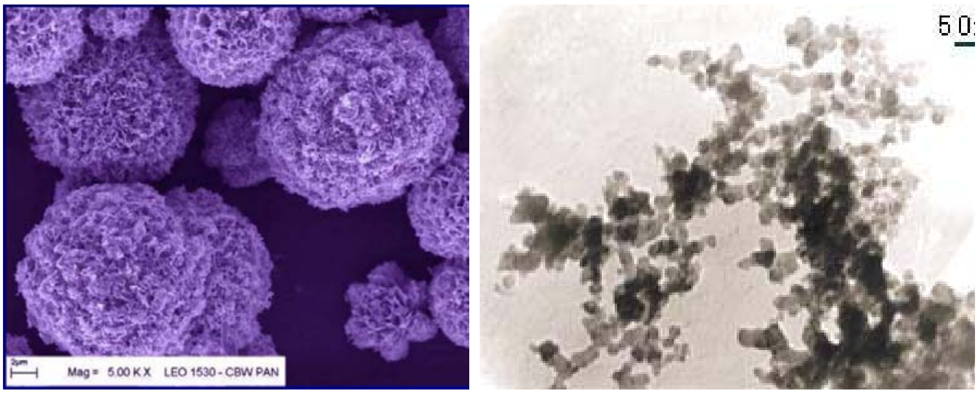


Fig. 2. A typical electron microscopy image of ZnO nanoparticles.

es with different chemical elements such as ZnS, ZnO (Figs. 2 and 3; Table 1), etc.

The applications of nanoparticles are wide and diverse: interactions of nanomaterials with living cells and tissues, researches in polymer nanocoupling, creation of biohybrid systems (artificial muscles), regenerative medicine (protometrocytes and nervous cells, bone tissue), nanomedicine (drug delivery, cell therapy) and others [9, 10]. It has been found that chemical and biological properties of nanoparticles are essentially different from the properties of the initial material from which they are made. When entering the organism, it takes metal nanoparticles certain time to dissolve, bind to bioligands and reach the target. Therefore their action may be prolongated, which is important factor in medical treatment that should be taken into account. Moreover, metal nanoparticles are less toxic in comparison with metal salts and their action on the organism has multifunctional character [6, 9]. Thus, a depot of high-disperse zinc powder created in the body will ensure slow intake of this microelement into the organism in dozes close to physiological, which may prove one of the ways to obtain durable therapeutic action, for example in case of ethanol dependence, since chronic alcohol intoxication is one of the main causes of zinc deficiency development in the organism [11].

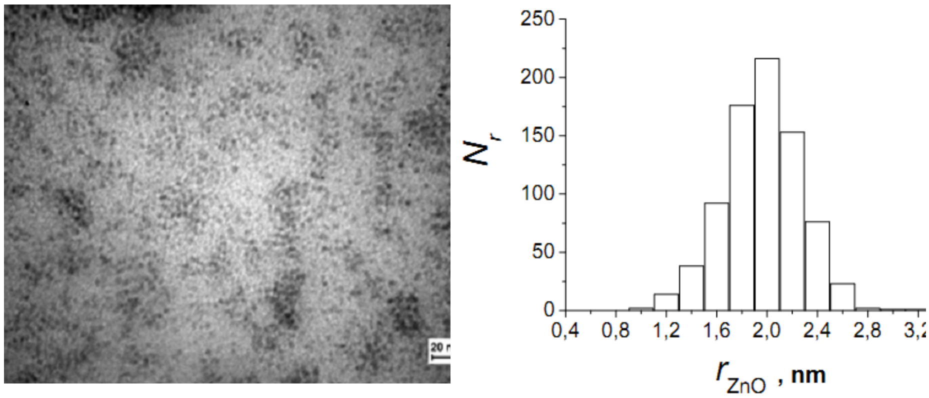
The role of zinc in life activity of organism. Zinc is known to be one of the most essential microelements indispensable for vital functions. Zinc that comes into the organism from food and water is mainly absorbed in small intestine, and then it is transported to blood plasma, where it is bound by albumins and globulins, or to the tissues in which it is deposited in zinc and cadmium accumulating protein. Zinc is included in the structure of metalloenzymes and hormonal complexes. The property of zinc to take part in the processes of forming ligands with organic molecules explains why it is widely available in different biological systems. However, zinc distribution in tissues may change, since zinc can be displaced by other cations accumulated in proteins. The transport and metabolism of zinc in the organism is characterized by its fast assimilation. At the same time its deficiency is often caused by pathological conditions, and decreased concentration of zinc cations may, in turn, influence vital processes in cells [12, 13]. For example, zinc plays important role in such biological processes as growth and division of cells, ceratogenesis, osteogenesis, immune response, wound reparation postsurgical wounds included; it also plays role in reproduction and functioning of pancreas.

As known zinc exists in biological systems in two forms: bound zinc and chemically reactive Zn^{2+} (Table 2). It is a structural constituent of

Table 1

Dependence of mass concentration on the dimension of ZnO particles and their concentration in the unit of volume

Sample	density, kg/m^3	$^*N$, d=20 nm	N, d=50 nm	N, d=100 nm	N, d=200 nm
ZnO	5610	4255480	272351	34044	4255



A **B**

Fig. 3. A typical electron microscopy image of ZnO nanoparticles in colloid solution (A) and their size distribution (B).

many zinc-binding proteins including the molecules of cellular signalling pathways [14, 15]. Over the recent years the researchers have studied zinc, zinc ions and compounds and their effect on organism as biomarkers and antioxidants, as well as intravital and lethal distribution in tissues, activity in certain structures (cell membranes, proteins, etc.), toxicity, and as a promising pharmaceutical target [14-17]. It has been long consiered that zinc is not toxic, but recent studies *in vivo* evidence about its toxic action [11, 18]. However, the mechanism of its harmful effect in the organism has not yet been revealed.

Zinc plays important role in controlling apoptosis. The excess of zinc may cause cell death due to apoptosis or necrosis [19, 20]. Researchers distinguish two main antiapoptotic functions of zinc: (1) direct action on apoptosis regulators especially on enzyme belonging to caspase family, which may prevent oxidation injury, and (2) decrease the damage caused by toxins by inhibiting induction caspase activity aimed at preparation and start of apoptosis. This process is triggered, when the concentration of intracellular zinc decreases. Thus, zinc-deficiency may considerably increase the frequency of apoptosis events in tissues [21].

There are several possible biochemical mechanisms through which zinc reduces oxidative stress in cells. In particular, it has been found that zinc has negative effect on the synthesis of antiinflammatory cytokines (for example, tumour necrosis factor — α and interleukin 1β) that produce active forms of oxygen and therefore this metal can function in the organism as antioxidant [22].

Current and perspective applications of nanozinc compounds in biomedicine. Due to nanodimension, zinc particles acquire unique physical and chemical properties which may be different from those they posses in the known metal compounds. This allows using them in new biomedical applications [8, 9, 23-26]. For example, the ability of ZnO nanoparticles to absorb a wide spectrum of radiation (ultraviolet, microwave, infrared and at radiofrequencies) can be used for manufacturing cosmetic creams, ointments, etc., which protect organism from ultraviolet radiation.

Zinc oxide is a semiconducting material. Producing nanocomposits by immobilizing ZnO nanoparticles on the surface of graphene results in formation of efficient sensor elements [27]. It has been reported that materials based on ZnO nanoparticles can be used in infrared and electrochemical sensors [28, 29]. To produce of bio-

Table 2

Physicochemical characteristics of Zn^{2+} ion

Sample	Ion radius, nm	Enthalpy of hydration ΔH, kJ/mole	z^2/r, eV	E, eV	E-ΔH, eV	W, eV
Zn^{2+}	0,083	2094	4,82	27,35	5,86	10,68

sensor the platinum electrode coated with a film made from ZnO nanoparticles and polypyrrole, on which csantoxidase is immobilised. The enzyme-modified electrode is applied to detect csantin (it generates electric signal during oxidation of hydrogen peroxide formed in processing csantin by csantinoxidase). The biosensor produced in this way is stable in storage at the temperature of 4 °C and endures 200 operations within 100 days [30]. ZnO nanoparticles have found analogous application in electrochemical biosensor for detecting glucose [28].

ZnO nanoparticles of 20-30 nm in size display antibacterial properties [31], which is now used in textile industry for producing fabrics for cloths. When in contact with human body the fabrics serves as a substrate, on which microbes may grow and this growth of microorganisms can be prevented by using ZnO nanoparticles in the production of fabrics [32].

Nanodiagnostics is another field where nanotechnologies are applied. At present they are used in clinical diagnostics to increase sensitivity of investigations and early detection of various diseases. For this purpose the most promising are nanoparticles less than 10 nm in size (quantum dots). They are characterized by large spectral absorption activity and can be used as fluorescent markers of biomolecules [23]. Quantum dots of nanozinc are bright photoresistant fluorophores. Colloidal nanocrystalline quantum dots of CdSe/ZnS possess unique size-dependent optical properties, which makes them an alternative to fluorescent organic dyes. Besides the ability to emit light CdSe/ZnS possess such characteristics as photostability, hydrophobility and biocompatiblity. The binding quantum dot protected by polymer with multifunctional receptor makes it possible to distinguish the detailed structure of cell skeleton under electron microscope. With the help of quantum dots the problem of visualizing the motion of individual molecules in living cells has been solved, which allows real time observations, impossible by using organic dyes. Quantum dots investigations may provide deeper insight into the dynamics of receptors, biomolecule transport and enzyme functioning.

Nanozinc compounds have found application in identifying antigens in malignant tumors. CdSe/ZnS nanocrystals conjugated with polyclonal antibodies are used as immune markers. P-glycoprotein, for example, is detected by the method of immune fluorescence by zinc nanocompounds, which are also used for three-dimensional analysis of one of the main mediators of tumour drug resistance [25, 33]. The immune marking p-glycoprotein by nanocrystals conjugated with antibodies is 4200 and 2600 times more stable to photobleaching than flourescein-isothiocyanate-antibodies and P-phycoerythrin-antibodies respectively. This conjugation is highly specific.

ZnS nanoparticles covered by L-cysteine are used in the method of synchronous fluorescence, when the intensity of fluorescence grows synchronously for all nanoparticles in presence of protein molecules [34]. This method reveals all proteins composing blood serum of human body. This is a very sensitive, simple and stable method that has a wide linear range in comparison with other physical and chemical methods. ZnS nanoparticles have low toxicity and high stability. They are resistant to photobleaching (in contrast to organic phluorophores) and their fluorescence is bright. In contrast to traditionally used organic markers the zinc nanoparticles ensure accuracy in detecting proteins and tracing their biomolecular dynamics: protein coagulation, transduction and enzyme catalysis.

Semiconducting nanoparticles are considered to be a new class of fluorescent probes for molecular and cellular fluorescence microscopy [9, 23]. Because of their size, these nanoparticles posses unique optic properties, that differ from those displayed by organic dyes or fluorescing proteins. For example, CdSe/ZnS particles of about 2 nm emit blue colour, while the same particles of 7 nm in size emit red colour. Fluorescing semiconducting nanoparticles such as ZnS, CdSe, ZnSe or combined structures of CdSe/ZnS and others have larger surface area, where a greater number of different functional groups can be located. This allows creating nanoparticles that could perform diagnostic and therapeutic tasks [9]. In future, the laboratory methods of detecting biomarkers with the help of fluorescent semiconducting nanoparticles may become a real breakthrough of nanobiotechnologies. In such case, that is very important, the toxicity of nanomaterials will not be able to produce any toxic effect on the organism, since biopsy material for diagnostics will be examined in the laboratory *in vitro*.

Nanozinc compounds with insulin and high-molecular substances foster prolongation of hypoglycemic drug action in contrast with duration of insulin effect. Moreover, this kind of nanostructure with amphotericin-B, antifungal drug of systemic action, decreases nephrotoxic effect of this pharmaceutic [35]. Another example demonstrating how available nanozinc changes the properties of complex chemical compounds or gives them new properties is the system of designed peptide with Eudragit s-100 (anionic polymer based on methacrylate; in this structure the surfactant is used as peptide) [36]. Nanozinc increases the elasticity of polymer-peptide compound, which decreases their absorbability [25].

The investigation of toxic effect of ZnO nanoparticles (20-120 nm) in mice has shown that parenteral administration causes damage in liver, heart, spleen, pancreas and bones [37]. When ZnO nanoparticles delivered through thrachea, they cause, depending on doze, the pneumonia, proliferation and thickening of alveolar membranes, loss of weight and anemia in mice [38].

In vitro experiments have shown that ZnO and Zn^{2+} nanoparticles activate complex cytotoxic paths in bronchi epithelial cells and macrophages, which include intercellular flows of calcium, mitochondrial depolarization and leak of plasmolemma [39].

There are also reports about the study of ^{65}Zn activity on bioprobes by using gamma spectrometry equipment, which was performed with the aim to reveal bioavailability of zinc from zinc oxide nanoparticles [40].

The main problem that prevents a fast development of cancer therapy methods is the inability of anticancer drugs to distinguish between healthy and cancerous cells. This is a cause of complications and side effect of chemotherapy. It has been found that oxide zinc nanoparticles can selectively kill cancerous cells [41, 42]. Moreover, the process of interaction between ZnO nanoparticles and cancerous cells can be monitored. For example, the selectivity of nanoparticles may be enhanced if interdependence is found between the proteins attacking cancerous cells (monoclonal antibodies and peptides) and small protein molecules bound to cancerous cells, or if they are used to deliver drugs to the target. The action of ZnO nanoparticles (cytotoxic effects of zinc oxide nanoflakes (ZnO NFs)) has been studies in a model of human muscle carcinoma [43].

In general, the zinc-containing medicinal preparations, vitamin and mineral complexes including, have ummunomodulatory, antibacterial and antifungal effect [23-25]. ZnO nanoparticles have shown pronounced anti-inflammatory and reparation action in treating experimental septic wounds. They are included in the composition of cosmetics, which protect skin from burns and cancerogenic action of ultraviolet radiation [23]. Zinc is also used in radioisotope diagnostics, in particular as a marker for zinc-containing enzymes. Zinc sulfide is applied in testing blood coagulation. In recent years zinc compounds (gluconate, asparaginate, picolinate, etc.) have become widely used in dermatology, endocrinology and in therapy of immune deficiency states.

Zinc and muscles. Human body contains about 1,3-2,3 g of zinc, almost 90 % of total amount of which is in the muscles and bones [12]. High level of zinc content is known to be not only in endocrine glands but also cells of muscles (1,4-7,1 mg per 100 g of tissue). In other reports the content of zinc in the muscles comprises 240 mg/kg [24]. In the heart the mechanism of controlling intercellular distribution of Zn^{2+} and its change during the cycle of functioning has not been revealed so far [44-46]. The research in changes of Zn^{2+} homeostasis have been performed by using specific fluorescent dye FluoZin-3 and mass-spectroscopy, which allows «mapping» the metal in the biological tissue [47]. For example, zinc has been found to be distributed inhomogeneously with the average concentration of 26 mg per gram of tissue [12]. The results show that zinc is accumulated mainly in the muscle fibres of endocardium. Zinc is distributed evenly in sarcoplasma reticulume, while in myocardium fibres it is concentrated mainly in anisotropic disks of myofibrils, that is, in the regions, which consist of myosin. The investigations of microelement content in different regions of the left ventricle in patients with ischemic coronary disease, dilated cardiomyopathy and critical heart failure by X-ray fluorescence analysis with synchronous emission, have revealed disbalance in microelement contents, in particular an increase the content of zinc [47, 48]. In the result of research in cardioprotecting properties of zinc-containing compounds an assumption has been made about the ability of zinc ions to decreased ischemic and postischemic damages of tissues due to antagonism with copper reactivity [49].

The researchers report that Zn^{2+} influences ATPase activity of myosin and superprecipitation of cardiac muscle actomyosin, probably, being able to replace calcium and magnesium ions (although this displacement is less efficient for superprecipitation reaction and ATP-hydrolysis process) and modulate actin-myosin interaction by changing functional characteristics of actomyosin macromolecules of cardiac muscles [50].

Conclusions. Current nanotechnologies make it possible to design nanoparticles with desired physicochemical and biological properties. Zinc and its compounds can open wide possibilities of biomedical applications due to nanosize, optical, chemical, biological and pharmaceutical properties. The researches in this field also have practical importance due to possibility to regulate functional activity of muscles using zinc ions both in normal and pathological states.

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Цинк та наночастинки цинку: біологічна роль і використання в біомедицині

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Резюме. Враховуючи норозмірність функціональних компонентів живих клітин, застосування нанотехнологій у біомедичних цілях наразі є актуальним завданням. Один з таких напрямів — використання наночастинок, зокрема цинку, для молекулярної діагностики, адресної доставки лікарських засобів, розробки нових фармакологічних препаратів. Представлені дані біологічних властивостей цинку та його сполук, знаходження в організмі та участі у біологічно важливих процесах, що уможливлює практичне використання цих наночастинок у біомедицині. Окремо розглянуто роль іонів цинку у функціонуванні м'язів.

Ключові слова: цинк, наночастинки цинку, функціональні властивості, біомедичне застосування.

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