Zn(II) FOR HUMAN ORGANISM

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There are more than 25 inorganic compounds, which are used for treatment in medical therapy and veterinary science in the form of antibacterial, antiviral, antifungal, antitumoral means. The cations of these compounds were widely used in the synthesis of complexes and chelates of organic compounds, which resulted in the synthesis of completely novel antibacterial, antiviral, antifungal and antitumoral compounds. This work examines Zn(II) containing organic chelates and their fields of their probable biological activity.

INTRODUCTION

Zinc has great importance for human organism. Zinc is needed for human organism as much as cations of sodium, potassium, magnesia, calcium, iron, zinc, vanadium, chromium and manganese [4]. As much as amino acids, fatty acids, vitamins are needed, so metalloelements are needed for normal metabolic process of the organism and the organism can't synthesize them. Lack of zinc in the human is expressed by loss of appetite, disorders in skeleton and hair distribution, skin damage, delay in pubescence. In several cases, the lack of zinc led to high abnormalities in sensory apparatus expressed in taste and smell perversion. The symptoms of anorexia and disorders of physiological functions in these patients may be relieved by adding zinc in the diet. The lack of zinc causes growth impairment in animals. According to the recent data, zinc has significant influence on the synthesis of nucleic acids and actively takes part in the preservation and transfer of genetic information playing the role of original biological switch. Zinc affects on the secretion of thyroid stimulating hormone, which may be one of the causes for hypothyroidism. Zinc is the component of more than 300 metaloproteins, including receptors of triiodothyronine [5] and a whole class of transcriptional factors, inhibitors of apoptosis and mitochondrial breathing. Zn (II) also inhibits iNOS expression, and consequently, formation of NO [6-14]. Change in zinc level in daily urine is an indicator to assess dysfunction of thyroid gland. Hypoplasia of thymus and development of immunodeficiency are observed in case of experimental lack of zinc, mainly T-cell [15]. Lack of zinc may lead to the intense accumulation of cadmium, lead and copper in the organism (functional antagonists of zinc), particularly on the background of protein lack in the diet. Carcinogenic properties of cadmium, lead and other toxic metals are connected with their ability to substitute zinc ions in "finger" protein karyoplasts, transcriptional factors and hormone-binding proteins that disturb the intracellular transduction of signals and gene expression [5]; it also takes part in such processes as mitosis: synthesis of DNA and protein, expression and activation of genes. That conditions the exceptionally important role that zinc plays in the physiological period of fetus growth and gestation.

The first signal about the significance of zinc for the growth of live organisms appeared in 1869. In 1922, Bertrand and Benson showed that diets poor in zinc reduced the lifetime of rats [16]. There is constant balance between the content of zinc in the blood and organs, suction and extraction from organism. The highest concentration of zinc in detected in hypophysis, pancreas, particularly in α- and β-cells from pancreatic islets, sex glands and liver. Underwood gave data about the content of zinc in human organs (in mg %): adrenal glands – 12, brain – 14, heart – 33, kidneys – 55, liver – 55, lungs -15, muscles – 54, pancreas – 29, prostate gland – 102, spleen – 21, testicles – 17 [17].

The total amount of zinc in human organism makes up from 1.36 to 2.32г [18]. In case of normal digestion of zinc in human organism, its amount is twice as low as iron as and 10 times as high as copper.

Zinc in organs and tissues is easily combined with amino acids, nucleic acids, purine bases and proteins. Among zinc proteins dominant majority are ferments. Thus, one atom of zinc is included in the composition of molecules of carbonic anhydrase catalyzing the reversible process of hydration of dioxide carbon. Zinc carbonic anhydrase is tightly connected with protein and when it is removed, the ferment loses its specificity.

In 1934, the enzyme of carbonic anhydrase was extracted, cleaned, and proved it contains 0.32% zinc. Later it was found out that zinc is a necessary part of molecules in many enzymes: alcohol dehydrogenases, milk dehydrogenases, carbonic anhydrases, metallothionein, glutamine dehydrogenases, carboxypeptidases A and B etc [19-23].

Insufficient content of zinc leads to the disturbances in the synthesis of nucleic acids and proteins in microorganisms and plants [24,25]. In case of zinc deficiency in animals and people, the synthesis of protein and RDA reduces, and consequently growth inhibition is observed.

Zinc together with other metals (chromium, manganese, nickel) forms part of RNA and stabilizes its structure. Zinc is able to hamper ribonuclease, while in the liver of animals the rate of RNA decomposition increases with zinc deficiency. The rate of protein synthesis determines regeneration process as well: it was established that introduction of zinc sulfate promotes quicker wound repair.

Humans have only one demonstration of zinc deficiency - dwarfism. There are indications that zinc also affects on atherosclerosis [26]. Adequate diet increases growth and accelerates sexual development: quick growth acceleration and in case of additionally introducing 20 mg of zinc sulfate into organism per day quick growth and weight acceleration, as well as development of secondary sexual symptoms is observed [27].

Zinc and Atherosclerosis

As the analysis of results on studying the content of zinc in tissues and organism of health people showed, the maximum concentration of zinc was in the liver, as well as in the tissue of thyroid gland, then in kidneys, pancreas, heart and aorta, the lowest content was in the tissues of adrenal glands.

The results of determining zinc content in the organs people ill with atherosclerosis and healthy people essentially differ. The highest decrease of zinc content was detected in the tissues of aorta. It was

established that decrease in zinc content in people ill with atherosclerosis is parallel with increase in cholesterol [21]. When studying zinc content in several organs of the people died from heavy atherosclerosis, it was established that the level of this element was reduced in most studied organs, particularly in aorta, heart, liver and thyroid gland. The introduction of zinc salts to experimental animals improves metabolic processes, hampers development of atherosclerosis in vessels. Valeric-acidic zinc was also used for the treatment of atherosclerosis. Studies of copper, zinc, cobalt and iron balance conducted before and after the treatment with valeric-acidic zinc showed that this preparation promotes improvement of metabolic processes, mainly people ill with atherosclerosis of stage III. The most common and the most threatening complication for cardiovascular diseases is formation of trombus. In fact, it was established in experimental studies that zinc, additionally introduced into animal organisms against the background of atherosclerosis caused by cholesterol, does not affect negatively on blood clotting [28,29].

Zn as Antitumor Mean

In 1931Koller and Kraus first carried out systematic studies of ties between biological activity and toxicity in case of metal containing compounds, when studying metal-containing complexes as inhibitors of tumor formation [30]. One of metal-containing compounds used in medicine was $ZnSO_4$ for the treatment of conjunctivitis, laryngitis, and vagina and at the same time, ZnO was used as anti-inflammatory mean for skin diseases. Falke used $ZnSO_4$ as antiviral active compound for treating HSV [31].

Studies examining the interrelation of zinc with malignant diseases are numerous. There are many reports about low concentration of zinc in leukemic cells. It was detected that zinc level in leukocytes was decreased in people ill with carcinoma [32], while low content of zinc in blood serum was observed in case of neoplasm [33]. The content of zinc in the serum was also decreased in case of such diseases as Hodgkin’s disease and other diseases of lymphoma apparatus [34].

Zinc is needed for DNA replication – during zinc binding DNA synthesis was hampered. In cancer cells, zinc is in tighter binding with protein than in normal cells. There is opinion that change of zinc binding with protein disturbs the inclusion of zinc into mitotic process, while this can become a reason for malignant regeneration of cells. Besides, zinc is necessary for inclusion of glycine into glutathione [35]. These changes of protein exchange are quickly reduced when introducing additional quantities of zinc [36, 37].

In vivo studies of Zn(II) chelates of amino acids, peptides and nucleic acids, as well as several medicinal preparations revealed their antitumor activities [38-40] and catalytic function of zinc as a carcinostatic or baceriostatic agent in various ferments [41,42].

It was proved that $Zn(aspartate)_2$ suppresses the growth of tumors more expressively than cysteamine, mercaptoethyl-amine (MEA) and WR-2721 [43]. A number of authors carried out the synthesis of Zn(II)-containing Schiff base complexes of secondary 2-carbonylpyridines possessing medium anti-leukemic activities [41-46]. On the example of Zn(II) chelates of Schiff-2-aminothiazoles derivatives it’s shown that chelates as antitumor means are more active than initial Schiff base derivatives

[47,48], as Zn(II) may promote the transport of oxygen, play the role of DNA inhibitors, as well as to influence on the enzymatic activities of appropriate enzymes [49-51]. On one hand, it's shown that substituted phenylglyoxal-bis-4-methyl-3-(thiosemicarbazone)zinc chelates are potential cellulotoxic compounds in regard with Ehrlich ascites. Comparative quantitative analysis enables to suppose this selective action on tumor cells may be explained by improvement of binding due to electro-repellent properties or lipophile nature of cells [52]. Besides, it's known that Zn(II) containing antitumor means possess lower toxicity than corresponding initial ligands [53].

Recently data about the antitumor activities of ZnO particles have been published [54], as well as about Zn(II) dacarbazine [55], about increase in antitumor activities of curcurmine and antibiotics of in the form of Zn(II) complexes [56,57] and mithramythicin, increase in antitumor activities of ZnO nanocomposites with Cu(II) chelates of salicylidene amino acids [58,59].

Zn(II) for Organs of Genitourinary System and Diabetes

Zinc forms part of many proteins regulating the level of transcription and biosynthesis of nucleic acids and proteins. Respectively, this microelement ensures the control of gene expression in the process of proliferation and cell differentiation. It also takes part in the formation of sensitivity to various hormones and growth factors. This important biological role is conditioned by deflections arising in organism in case of zinc deficiency. Early stages of cell cycle are particularly sensitive to zinc deficiency [60]. Zinc deficiency is, in varying degrees, detected in case of all immunodeficiency conditions. Decrease in zinc content level is accompanied with depression of metalloprotease activity that leads to disorders in phagocytosis, persistence of infections in case of inadequate immune response. Against background of zinc deficiency, arrest of sexual development may occur in men and decrease in fertility in women. It's characteristic that zinc is selectively accumulated in the prostate gland and is a specific component of its secretion. It takes part in the regulation spermoplasma and ferment activities playing a role both as an activator and as an inhibitor. It promotes processes of coagulation and attenuation of the ejaculate. Zinc concentration in spermoplasma makes up 131-719 mg/l [61]. The content of this microelement in spermatozoids is the highest in the organism and makes up 1900mkg/kg [62]. In case of chronic prostatitis and cancer of prostatitis the zinc concentration in the secretion of prostatitis reduces [63].

Symptoms of hypogenitalism are developed in the presence of zinc deficiency; all stages of sex cycle are disturbed.

The experiment on animals proves that zinc deficiency leads to retarded development of sex glands and to hypogalactia for bitches. Zinc deficiency prenatally negatively affects on the gland function of inner secretion, including hypohysis, endocrine apparatus of pancreas.

The high content of zinc was proven in case of prostate and epididymis of several animals and humans. Zinc deficiency for animals leads to degeneration and atrophy of sex glands, this phenomenon is reversible, if the deficiency is expressed not very drastically and continually. Development of hypogenitalism is a characteristic syndrome of zinc deficiency for humans. Zinc in human tissues is mainly contained in the form of carbonic anhydrase or alkaline phosphatase [64]. Autodegradation of

prostate tissues enables to suppose that zinc concentrates mainly in the cells of mucous membrane of glands, but chemical analysis showed that quantity of zinc in the cells of mucous membrane was not higher than in the rest of prostate tissue, though acidic phosphatase was concentrated there [65].

In fact, the quantity of zinc in the prostate tissues [66,67] plays a determining role in the process of forming destructive nidus in the prostate and its further conversion into prostatic sarcoma.

It's known that in case of acute zinc intoxication the content of sugar in blood goes up, meanwhile the content of glycogen in muscles decreases and the quantity of lactose increases [68]. It was found out that insulin during crystallization, depending on conditions, binds various amount of zinc [69]. Three dimmers of insulin, tightly binding two atoms of zinc, form hexamer with molecular mass of 36.000 [70]. As insulin secreted from pancreas is always bound with zinc, while the latter is apparently a natural component of insulin, responsible for maintaining complex polymer structure of insulin [71,72].

Zn(II) in Blood, Antiseptic, Anti-inflammatory and Anticonvulsive Actions

The main part of zinc in blood, 85%, is contained in erythrocytes, 12% in deficiency, the rest is in leukocytes [73]. Approximately one third of plasma zinc is connected with serum albumen, while the rest of zinc is more strongly bound with globulin [74]. In erythrocytes zinc is mainly found in carbonic anhydrase [75]. The level of zinc in blood depends on its intake with food. In case of alimentary deficiency of zinc, its level decreases both in the serum and in erythrocytes. Increased amount of zinc and carbonic anhydrase in erythrocytes is observed in case of anemia pernicitosa, atherosclerosis, and leukemia [76]. Increase in zinc level in the serum is observed for hypertensive diseases and hyperthyroidism, while decrease is observed for chronic diseases of liver, kidney and tumors. Proved fluctuation in zinc level in whole blood is observed with people ill with myocardial infarction. Decrease in zinc level in leucocytes is observed in case of various malignant cancers that may have diagnostic significance [77]. When measuring the content of zinc in marrow and peripheral granulocyte it was detected that in marrow zinc is found in metamyelocyte, while zinc amount increases with aging [34]. High activity of zinc is observed in the process of tissue generation after wounds and burns. Zinc in the form of zinc oxide is applied in medicine in the form of powders, ointments, pastes as binding, drying and disinfecting-antiseptic mean for skin diseases. Zinc (II) salicylate and zinc (II)(DL-aspartate)$_2$ are also applied as antiseptic and anti-inflammatory mean [78]. Much information has appeared about anticonvulsive, anti-inflammatory activities of Zn(II) chelate 3,5-diisopropylsalicylic acid [Zn(II)(3,5-DIPS)$_2$(H_2O)$_2$], Zn(II) (DL-aspartate)$_2$ and Zn(II)(salycilate)$_2$ [79]. The unique role of zinc for the development of central nerve system and behavior is proven [80]. The experiment shows that zinc deficiency causes slow generation of acquired reflexes and the ability to learn decreases. In case of zinc deficiency nuclear-cytoplasm ratio is supposed to be changed, brain development and structural maturing of cerebellum are hampered [81].

Zn(II) Containing Antioxidants and Radioprotectors

Many publications discuss the antioxidant activity of zinc cation, and zinc-containing metallothioneins play a decisive role even in ionizing radiation [82]. Metallothioneins are low molecular (mB 6000-7000 kilodalton) metal-binding proteins, which contain 60-68 amino-acid residues out of which 25-30% is cysteine. They don't contain residues of aromatic amino acids or disulphide bonds and may bind 5-7g of zinc (mol/protein) [83-85]. Metalloproteins show antioxidant effect in cases of intoxication with antitumor preparations, such as doxorubicin [86,87] and other antitumor preparations [88,89], while in case of ethanolic intoxication [90], oxidative mutation [91], and oxidative stress [92] eventually happens decomposition of zinc through zinc-thiol-disulphide transformation [93,94].

It should be mentioned that free aggressive radicals are formed in the organism as O^{*}_{2}(superoxide-onion), hydroxy-radical HO^{*}, peroxy-radical HO^{*}_{2}, alkyl-radical R^{*}, alkoxy-radical LO^{*}(lipid), peroxy-radical LO^{*}_{2} (lipid) in such experimental cases, as chemical, industrial, food and ecological poisoning, any oxidative stress, ionizing radiation [95].

If the action of H_2O_2, O^{*}_{2} was studied parallel with ionizing radiation, hydroxy-radical HO^{*} has recently turned into an object for studies [93]. This radical, interacting with nucleic acids, leads to the damage of genome and that causes bond breaking between DNA and RNA. Thereby, HO^{*} can cause mutation and death of cells [96].

It was shown that in experimental situations metalloprotein Cu(II) *и* Zn(II) containing ferment Cu(II)Zn(II)СОД act in the organism as antioxidant, which first plays the role of interceptor and damper of free radicals, and secondly this prevents break of DNA chain and apoptosis [97,98]. The radioprotective effect is also observed when this ferment was intravenously injected into mice [99]. Radioprotective action of $Zn(II)SO_4$ also presents interest in the form of diluted water solution for experimental mice to drink [100]. The same experiment was carried out in case of applying 100mM of water solution $Zn(II)Cl_2$ [101]. Antioxidant and radioprotective activities have also $Zn(II)(aspartate)_2$ [102], $Zn(II)(diethyldithiourethane)_2$ [103], $Zn(II)(histidinate)_2$, $Zn(II)(orotate)_2$, where quantitative changes of erythrocytes, leukocytes and platelets of blood of experimental animals were studied in detail [104]. In case of Zn(II) chelate 3,5-diisopropylsalicylic acid $[Zn(II)(3,5\text{-}DIPS)_2(H_2O)_2]$, the authors also studies the action of this substance on the central nervous system as sedative-hypnotic compound in a dose of 123 mmol/kg, though the toxic dose of preparation is 381 ± 75 mmol/kg [105]. Radioprotective activity of mentioned Zn(II) chelates are tested both *in vitro*, and *in vivo* conditions on rats before and after the radiation.

Zn(II) and Antibacterial Activity

Still in 1949, the antibacterial effect of zinc on staphylococcic and streptococcic microorganism [106]. Then zinc oxide dressing began introducing into medical practice for the fixation of different bone fractures [107]. Then it was found out that growth of microorganisms is observed in case of

concentrations of zinc 10^{-5} – 10^{-7} mM *in vitro* [108], nevertheless, it was detected that increase in zinc concentration in the studied bacterial medium resulted in opposite – antibacterial nature of this cation [109]. This effect was used to detect antibacterial activity of zinc acetate $(CH_3COO)_2Zn$ in regard with S. Aureus, S. Epidermids, P aeruginosa bacteria using it 2; 8; 5,5; 11; 16 and 22mmol/l diluted water solution and it was shown that $Zn(CH_3COO)_2$ is more active as antibacterial mean in regards with S. Aureus and S. epidermidis bacteria than P. aeruginosa ($p<0,05$) under conditions of solution [110]. Later Zn(II) carboxylate $Zn(R\text{-}COO)_2.nH_2O$ was synthesized, where (R=H-, CH_3-, $CH_3CH_2CH_2$-, $(CH_3)_2CH$-, XCH_2-, X=Cl, B, J, n=O or 2), $[ZnX_2(NiaCH_2COO_2)]$ where (Nia= nicotinamide, X=Cl, B, J) and $[Zn(XCH_2COO)_2(Caf)_2].2H_2O$ where (Caf=caffeine, X=Cl, Br) which were tested in regard with Staphylococcus aureus, Escherichia coli и Candida albicans bacteria [111]. Besides antibacterial activity, the antiviral effect of zinc cation is very important also in pharmacological aspect [112,113]. Zn(II) inorganic compounds, particularly $Zn(CH_3COO)_2.2H_2O$ together with organic compounds – erythromycin, is used for the treatment of acne [114]. Vet researchers came to the conclusion that in most cases it's better to use Zn(II) organic complexes as antibacterial mean than well-known antibiotics, which eventually show tolerance to bacteria [115]. In this regard, Zn(II) amino acids and peptides are largely applied [116] both for gram-positive and gram—negative bacteria [117-120]. Besides, it was shown that organic Zn(II) containing compounds have more antibacterial activity than inorganic derivatives [120-122]. These data stimulated the synthesis and studies of antibacterial properties of a number of Zn(II) containing organic complexes – particularly, pyrazinedicarboxamide [123], Zn(II) Schiff base chelates [124-126], Schiff base Zn(II) chelate aminoacids [127-128], Zn(II) complexes of benzimidazole derivatives [129], Zn(II) complex of cefixime antibiotic [130] in regard with gram-negative and gram-positive Staphylococcus aureus, E. Coli, Klebsiella и Proteus microorganism. Due to antibacterial activity of Zn(II) cation, some of its derivatives were largely applied when producing OKCEL Zn-M, OKCEL ZnNa-L, OKCEL ZnNa-M designed to take care of wounds or as components for making pharmaceutical preparations. These cotton or micro-granulated means have wide antibacterial activities against Escherichia coli, Pseudomonas aeruginosa, Stafylococcus epidermidis, Bacillus licheniformis, Aspergillus niger, Penicillium chrysogenum, Rhizopus oryzae,, Scopulariopsis brevicaulis, Candida albicans and Candida tropicalis [131-133]. In perspective, ZnO nanoparticles can be applied for making food packaging to prevent formation of such bacteria as Campylobacter jejuni, only in bactericidal respect and not in bacteriostatic respect [134-136]. ZnO nanoparticles are also used in textile industry [137,138].

Thus, analyzing the submitted material it's possible to say that necessary amount of Zn(II) cation must definitely be present in human organism, as:

1) Its lack causes diabetes mellitus,

2) It takes part in the synthesis of RNA, while zinc lack brings to disorders in the synthesis. Zinc is also a component of most cell proteins [139].

3) Much quantity of zinc promotes developing anaemia caused by iron deficiency, which shows connection between these two elements [140].

4) Excessive zinc reduces copper content in the liver, which, in its turn, leads to decrease in iron in liver [141].

5) It can affect on the activity of other necessary microelements, meanwhile promoting to formation of metalloenzymes of 3d group(Ni(II), Cu(II), Cd(II), Fe(II), Fe(III), Mn(II)) [142].

6) It regulates comprehensive producing ferments of SOD, NO-synthase (NOS) numerous other immunobiological ferments and metalloenzymes [3].

7) It takes part in the transfer and formation of genetic information [3]. In case of zinc deficiency children have significant development lagging in growth and sexual development [143].

8) Increased content of Zn(II) in thyroid gland promotes formation of goiter, usually in this case the amount zinc in the gland tissues increases.

9) Zn(II) is necessary for atherosclerosis, it leads to inhibition of atherosclerosis development in vessels.

10) The content of Zn(II) in blood may be used as an indicator of healthy organism.

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Zn(II) ԿԱՏԻՈՆԻ ԴԵՐԸ ՄԱՐԴՈՒ ՕՐԳԱՆԻԶՄԻ ՀԱՄԱՐ

Ս.Հ. Ղազարյան

Հ.Հ. ԳԱԱ օրգանական և դեղագործական քիմիայի գիտատեխնոլոգիական կենտրոնի նուրբ օրգանական քիմիայի ինստիտուտ

Աշխատանքում քննարկվում է Zn(II) կատիոնի դերը օրգանիզմում կատալիտիկ ֆերմենտների ստեղծման և դրանց անհրաժեշնության խնդրում: Ամփոփված է Zn(II) կատիոն պարունակող կոմպլեքսային միացությունների անհրաժեշտությունը այնպիսի միացությունների ստեղծման խնդրում, որոնք ցուցաբերում են արտահայտված հակաաթերոսկլերոտիկ, հակաուռուցքային, հակաշաքարախտային, հակաբորբոքային, հակացնցումային, հակաօքսիդիչ, հակաճառագայթային և հակամանրէային հատկություններ և նման միացությունների հեռանկարայնությունը նոր դեղամիջոցների ստեղծման հարցում:

RESUME

ROLE OF Zn(II) CATION AF CRATION OF NEW PERSRECTIVE MEDICINES

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The presented material shows essentially important qualities of Zn(II) containing compounds in biological aspect and has an interest for chemists, biochemists and pharmacologists

The role of Zn(II) cation in an organism at creation of catalytic enzymes and problem of their necessity for an organism is discussed in the present publication.

Necessity of synthesis Zn(II) cation containing complexes in synthesis of such compounds which possess expressed antiotheroscleros, antiulcer, antidiabet, anticonvulsant, antiinflamatory, antioxidant, radioprotective, antibacterial activities, and also perspectivity of similar compounds in creation of new medical products is generalized.

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