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ROLE OF COPPER FOR HUMAN ORGANISM

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ABSTRACT

The review focuses on a very peculiar aspect of the application of copper containing biologically active compounds of different chemical classes as have shown at the last scientific researches in the field of Cu (II) chelates, chelates possess have a higher activity of the same sort, than their mother compounds.

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

UDC CODE & KEYWORDS

■ UDC: 547.1 ■ Copper ■ Biological Aspect ■ Biologically Active Compounds ■ Human Organism.

INTRODUCTION

Copper was first shown to be an essential biological element in the 1920s when anemia was found to result from Cu-deficient diets in animals (Hart, Steenbock, Waddell, Elvehjem, 1928) and addition of Cu salts corrected this affliction (Hart et al, 1928; Elvehjem, 1935). It is now recognized as an essential trace element for many biological functions (Howell & Gawthorne, 1987, vol.1; vol.2, 1987). It serves as a catalytic component in many enzymes, e.g. it is an important constituent of metalloproteins (exhibiting oxidative reductase activity, e.g. oxidases or hydroxylases) (Hathaway, 1987), and in such enzymes as lysyl oxidases (required for connective tissue) and cytochrome oxidase (electron transport protein) (Cox, 1999)[6].

Copper also influences specific gene expression in mammalian cells (Uauy, Olivares, Gonzales, 1998; Rucker et al, 1998), nerve myelination and endorphin action (Linder, 1991), with Cu deficiency impairing immunity (Cerone, Sansinanea, Streitenberger, Garcia, Auza, 2000; Percival, 1998; Odell, 1993). The role of trace metallic elements, such as Cu in inflammation, is of great interest given their function as co-factors in metabolic processes involving articular/connective tissue and the immune system (Rosenstein & Caldwell, 1999) and their effect on PG syntheses (Fujita, Ohtani, Aihara, Nishioka, Fujimoto, 1987; Forder, 1974, Fujimoto et al, 1933; Maddox, 1973; Peplow & Hurst, 1986).

Additionally numerous authors have demonstrated that compounds showing anti-inflammatory, analgesic, antiulcer, antihistaminic, antineoplastic, antimutagenic, anticarcinogenic, anticonvulsant, radioprotectant/radiorecovery, and antimicrobial activities are less effective than activities of their Cu(II) chelates.

In fact, questions of probable application of micro-concentrations of copper and its compounds in case of different pathologies in organism are indicated, the presented material may provide a useful information and may serve as an interesting literature data for developing research in that arean.

The significance of copper in more important physiological processes has been studied more thoroughly than that of other microelements, while information about its content in human tissues and organs in various physiological and pathological situations is so huge that the indicators for copper content in the tissues and biological fluids are already in use of clinical practice in the form of physiological tests.

Though the presence of copper in the human tissues and organs was proved still in the first half of the 19th century, copper as biotic drew the attention of physicists – experimenters and practitioners only in the 20-30's of the last century. There were certain publications that say copper micro concentrations that enter the organism have direct connection with blood formation process, as additional introduction of this microelement into organism has therapeutic effect in case of anemias of alimentary origin (Hart et al, 1928; Keil, 1934). Copper is necessary for the organisms like cations of natrium, potassium, calcium, iron, zinc, chromium, vanadium and manganese (Underwood, 1977). Like amino acids, fatty acids, and vitamins, metal elements are needed for normal metabolic processes of the organism and they can't be synthesized by human organism. The organism of an adult person contains from 1.4 to 2.1 mg of copper per one kilogram of weight. The need of copper for grown-up people makes up 0.035 mg per 1 kg.

Daily introduction of copper into human organism mainly depends on its content in the food products that person uses. Under the condition of optimal nourishment a person receives on average 65 mkg copper per one kilogram of body weight. Meanwhile the balance of copper, as a rule, is positive and 28-88% of alimentary/nutritional copper remain in the organism. Table 1 brings information about different authors in regard with copper need with children - from newborn children to 12-year-old children.

At present it is acknowledged that copper is an irreplaceable microelement for people.

Copper enters human organism together with water in the form of easily soluble salts, while the significant amount of copper in vegetable and animal products is in the form of various heavily dissociated complexes.

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Thus, for example, the copper contained in the yolk of egg is not absorbed at all. Copper in organic complexes is also badly absorbed. According to observations receieved from angiostomated dogs (Добротина, Рутницкий, Кузьмина, 1998), the copper in blood of portal vein is capable of dialysis, meanwhile the copper flowing off the liver is linked with proteins and is incapable of dialysis. Through liver wall copper penetrates probably not in the ionic form, but in the form of complex compounds with aminoacids, fatty acids of Krebs cycle, bile acids and with other complexing substances, each of which possesses elective affinities to certain tissues of organism and, due to this, copper may penetrate into almost all organs and tissues.

Table 1: Children's need in copper

Age	Daily Need, mkg/kg	Literature Source
Newborn children	15	Wilson, Lahey, 1960
Infants	100	Войнар, 1960
Up to 6 months	40-80	Lahey, 1957
6-12 months	80	Lahey, 1957
3-6 years old	53-85	Scoular, 1938
8 years old	100	Macy, 1944
3-12 years old	50-100	Lahey, 1957, p. 2.
3-13 years old	100	Toshiaki, 1959

Source: Author

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Tables 2 and 3 show data about the quantitave content of copper in human tissues and organs in different stages of its onthogenesis.

Table 2: Content of copper in tissues of adult person (in mg%)

	Content of copper		
Organ or tissue	In damp substance	In dry substance	In ash
Brain	0,51-0,83	1,81	7,9
Liver	0,4-13,0	4,02	56
Kidney	0,2-2,8	1,42	28
Spleen	0,02-0,2	0,72	12
Lungs	0	0,89	16
Heart	0,5-1,2	1,34	0
Muscles	0,06-0,1	0,64	18
Bones	0	0	0
Grey matter of cortex	0,38-0,44	0	15
White matter of cortex	0,35-0,47	0	0
Thalamus	0	0	13,5
Striate body	0	0	0
Adrenal	0	1,07	23
Pancreas	0	0	13,2
Thyroid gland	0	0	20

Source: Author

Table 3: Content of copper in the ash of foetus organs (in mg%)

Organ	Age of Foetus, weeks			
	14	36	40	42
Liver	99,6	1800	3677,4	3412,7
Spleen	4105	1635,4	246,8	806
Testicles	27,5	36	91,6	12,2

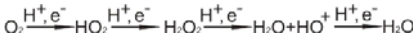
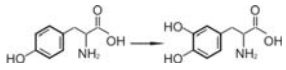
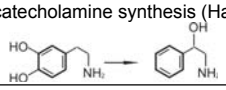
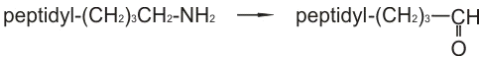
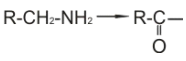
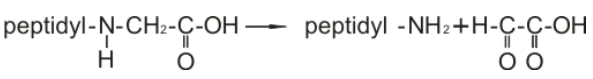
Source: Author

When analyzing these data, it's easy to notice that the dependence of copper content on foetus age in different tissues and organs are not the same. For example, copper content in liver and testicles of the foetus increases paralell with its

prenatal development, while it decreases in the spleen. The copper content in the liver and testicles of the foetus, on the contrary, is many times higher than that of grown-ups (Table 2). As a matter of fact, copper content in the tissues changes not only quantitatively in the course of time, but its form of condition also modifies. Thus, copper after penetrating through intestine wall copper stays in the liver where such protein complexes join it as hepatocupreine and ceruloplasmin. All copper-containing biopolymers play an important role in biochemical processes. Copper insufficiency in blood serum unfavourably affects on the processes of immunogenesis and peritoneal reparation. Copper deficit negatively affects on the function of ceruloplasmin, particularly it decreases the ability of ceruloplasmin to the inactivation of serotonin and histamine (Добротина et al, 1998), which under certain data, (Langer, Liebman, Monk, Pelletier, 1995; Yao, Ishihara, Takai, 2000) plays an important role in the pathogeny of commissure formation. Decrease in copper content causes depression/suppression of phagocytic activities of neutrophils and proliferative cellular response, and decrease in interleukin concentration (Добротина et al, 1998; Percival, 1998). In case of copper deficit, decrease in the activities of superoxide dismutase is observed responsible for the inhibition of lipid peroxidation processes in the cell membrane, as well as the inhibition of copper-dependant ferment, lysyl oxidases, which take part in the formation of cross linkages of collagen and elastic fibers. High elective concentrations of iodine, copper, cobalt and zinc in the immunocompetent organs show the participation of bioelements in the regulation of immunobiological reactions, as well as direct observations about activating or inhibiting impact of their biotic doses on the synthesis of antibodies and reactions of cellular immunity (Окминян, Самсонова, Пыков, 2003). The combination of copper and protein insufficiency in case of kwashiorkor and heavy emaciation is also described (Gopalan, Raddy, Mohan, 1963), as well as for heavy forms of asiderotic [iron-deficiency] anemia (Sturgeon & Brubaker, 1966). The treatment effectiveness for this disease significantly increases when copper is added to iron medicines (Сакфельд, Бабенко, 1959). The significance of copper in the processes of blood formation is important, and it is proved that none of animal-tested microelements – tin, mercury, zinc, cobalt, antimony, manganese, lead, arsenic, germanium, nickel etc, is not capable of substituting copper in hemoglobin synthesis (Whipple, 1930).

Mammals have enzymes, and their activities have essential significance for the organism, but they don't proceed without copper cations. Table 4 shows the essence of these enzymes.

Table 4: Copper-dependent enzymes of mammals and their chemical functions in the organism

Cytochrome-c-oxidase	Oxygen reducing agent (Boyadzhyan, 1985) 
Superoxide dismutase	Catalyses the dismutation of superoxide in oxygen and hydrogen peroxide. It plays the most important role in the antioxidant protection of almost all cells which are in contact with oxygen to any extent (McCord and Fridovich, 1969; Fridovich,1986) 
Tyrosinase	Hydroxylation of tyrosine with melanin synthesis (Sorenson, Oberley, Kensler, 1984) 
Dopamine-β- hydroxylase and other extremely acidic copper-dependent proteins	Hydroxylase of dopamine for catecholamine synthesis (Harris, DiSilvestro, 1982) 
Lysyl oxidase	Oxidation of N-terminal amides of lysine residue of collagen and proelastin into aldehyde group (Frieden, 1986) 
Amine Oxydase	Oxidation of amides into aldehydes in case of the metabolism of catecholamines and other primary amines of oxidation of amides into aldehyde ones (Frieden,1986) 
Factor V	Blood coagulation (Mann, Lawier, Vehar, Church, 1984)
Ceruloplasmin	Accumulation and preservation of iron reserve, iron oxydase, copper transport, SOD-mimetic activity (Frieden, 1986)
Peptidyl -α- amidated mono-oxydases	Synthesis of neuroendocrinal peptides (hypothalamic thyrotropin-releasing hormone, α- melanocyte stimulating hormone, oxytocin and vasopressin-synthisizing hormone) (Gibson & Glembotski, 1987) 

Source: Sorenson (1984)

As a matter of fact, copper plays a significant role in vital functions, and it is a specific and irreplaceable metal component for oxidative enzymatic systems, for example, for such terminal oxidase as ceruloplasmin (copper oxidase), cytochrome c (oxidase), tyrosinase (Грин, Гриффитс, Дур, Уортон, 1961; Фриден, 1964), lysyl oxidase (Frieden,1986). Copper is a mandatory carrier of electrons in respiratory chain, that's why its decrease in tissues below the level needed for this function breaks normal flow of biochemical processes, which is demonstrated in different types of functional illnesses (Fridovich, 1986).

Complex Compounds of Copper as Antidiabetic Substances

Modern clinic medicine possesses information about the correlation between copper exchange and functions of certain endocrine glands. The interaction between copper exchange and the activity of insulin apparatus of pancreas is studied (Бабенко, Гарбарец, Карплюк, Соловцова, 1962). Depending on the extent of decrease in organism tolerance to carbohydrates copper content in the blood of patients with pancreatic [insular] diabetes reduces by 30-50%, while its egestion from the organsim increases from two to four times. Table 5 shows data obtained when studying balance of copper for patients with pancreatic [insular] diabetes.

Table 5: Content and egesting of copper in case of pancreatic [insular] diabetes

Subject of study	Number of examines patients	Blood in mkg%	Egestion per 24 days, mkg	
			urine	faeces
Healthy	10	131±12	475±15	1950±145
III	15	97±8	858±67	4071±129

Source: Author

Experiments on dogs with removed pancreas and experiments with ligation of its excretory ducts confirmed the fact established under clinic conditions about the dependence of copper exchange in the organism on the insulin apparatus of pancreas. It turned out that ligation of excretory ducts of pancreas which, as known, is accompanied with the hyperfunction of insulin apparatus promotes copper retention in the organism, while depancreatization always led to the decrease in copper content in the tissues (blood and liver) by 40-60%.

The use of biotic doses of copper is especially effective for the treatment of diabetes accompanied with atherosclerosis,as in this case it's possible to reduce the dose or to completely exclude the use of isnulin, which, as it is known, increases the tonus of coronary vessels and may provoke attacks of stenocardia.

The mechanism for copper effect on carbohydrate exchange can be presented in the following manner: first of all, copper can deactivate insulinase, a ferment catalyzing insulin destruction: thus the reduced amount of insulin which is till capable of producing the insulin apparatus of pancreas in the organism ill with diebetes, is preserved and manifests more prolonged action. Secondly, copper ions can themsleves activate processes of glycolysis (Войнар, 1960). At last, the effect of copper through the central nervous system is not excluded, as copper is not manifested when transecting the spinal cord of hypoglycemic action (Школьник, 1959). The supplementing of copper deficit is of particular favourable effect on the course of diabetic [glycemic] gangrene. Under the effect of copper microconcentrations curative effect is observed in the gangrene of extremities conditioned by different forms of endarteritis (Соловцова, Сулима, 1963).

First Dunn & McLetchie (1943), then N. Rakieten, M.L. Rakieten, Nadkarni (1963) together with its co-workers studied the diabetes with alloxan or streptozotocin induced by experimental animals. Then it was revealed that introduction of Cu-Zn SOD mimetic comples leads to the suppression of streptozotocin induced dieabetes (Gandy III, Buse, Crouch 1982). Cu(II) salicylate was also used for experimental diabetes with the simultaneous use of Cu-Zn SOD mimetic copper complex (Robbins, Sharp, A.E. Sionim and I.M. Burr 1980).

Copper Compounds with Anti-inflammatory Activity

The significance of copper in exchange processes of animal organism started to be revealed by Viskonsin researchers group who showed that copper deficit is the cause of so-called milk anemia for rats (Elvehjem, Steenbock, Hart, 1929).

A number of articles prove that the uncontrollable inflammatory process irrepressibly develop because of copper deficit in the organism, while the active stage of this process can be suppressed, including the therapy of copper-containing medicine (Sorenson, 1978; Sorenson, 1989).

Then articles were published about anti-inflammatory activities of sodium salt 3-(N- allyltioureido)-1- benzoic acid in the form of Cu(II) chelate (Vykydal, Klabusay, Truavsky, 1956) and copper iodide (Schubert, 1966). Only in 1974 J.R.J Sorenson (1974) was the first to show that Cu(II) complex compounds possessing anti-inflammatory properties simultaneously is used *in vivo* in case of polyarthritis.

There is much information about the anti-inflammatory acitivities of inorganic Cu(I), Cu(II) compounds (Sorenson, 1976; Walker&Whitehouse,1978), such as $(Cu(OH)_2CuCO_3)$, $CuCl_2$, CuO, Cu(I)Cl, Cu_2O, $Na_2Cu_2(S_2O_2)_2$, Cu(II) chelates of acetic acid, lauric acid, oleic acid, caprylic acid, sebacic acid (Beveridge, Whitehouse, Walker, 1982), as well as Cu(II) chelates of D-penicillamine, and such aminoacids as L-tryptophan, D- and L- aspartic acids, L- lysine, glycine, L- histidine, D- and L-cysteine, phenylalanine (Sorenson, 1976; Ruenitz, Sorenson, West 1980), which are themselves deprived of this activity, substituted derivates of benzoic acid (Walker & Whitehouse, 1980), ethylene diamines (Brown, Smith, Teape, Lewis, 1980), different substituted derivates of salicylic acid (Beveridge et al, 1982; Deushle & Weser, 1984), different sulfonamides (Brown et al, 1980), tetrazole (Schubert, 1966; Whitehouse, Field, Denko, Ryall, 1976), thiols (Vykydal, Klabusay, Truavsky, 1956).

Sorenson (1974) and Hirschelmann, Bekemeier, Stelzner (1977) also showed that such ligands as anthranilic acid and 3,5-diisopropylsalicylic acid (3,5-DIPS), that don't manifest anti-inflammatory activity in the form of Cu(II)(anthranilate)$_2$ and Cu(II)(3,5-DIPS)$_2$ chelates demonstrate high anti-inflammatory activity in all the models *in vivo*.

Thus, diflunisal or 5-(2,4- difluorophenyl) salicylic acid, which is a anti-inflammatory compound of non-steroid character, which also possesses analgetic and antipyretic effect and is four times as active as aspirin, moreover, is capable of long-lasting (during 9 hours) effect on people. Based on these qualities, authors have synthesized Cu(II) $(diflunisal)_2$ which turns out to be a more active compound than diflunisal, and its toxic effect is studied more in detail (Razi, Ahmad, Rabbani, Saeed 2003). The same approach wa selected by authors who were studying Cu(II) chelate of enoxacin antibiotics (Arayne, Sultana, Haroon, Mesaik, 2009) and $Cu(II)(nap)_4$, which is Cu(II) chelate naproxen, an anti-inflammatory compound of non-steroid character (Abuhijich & Khalaf 2010), as well as Cu(II) chelate fenoprofen (Agotegaray, Boeris, Quinzani, 2010). The given data show that as a matter of fact, almost all Cu(II) complexes which are anti-inflammatory substances of non-steroid character, show higher anti-inflammatory activity than their precursers (Sorenson, 1978; 1989).

Role of Copper (II) as Antitumoral Substance

The collected material about copper balance and redistribution of this microelement between organism tissue affected with carcinomatosis is of significate interest for clinic. Zondek was the first (1933) to pay attention to copper content in the cells of malignant tumor, nevertheless, according to different authors, who have studied copper content in malignant tumors, as well as in the tissues and organs affected with carcinomatosis (tissues of people died from cancer), copper content turns out to be increased (Квирикадзе, 1964; Willingham & Sorenson, 1986), and in most cases there is decrease in Cu-Zn SOD activity in the cancer itself, as compared with tissues of normal cells (Oberley & Buettner, 1979).

As a matter of fact, this shows that copper compexes should manifest cytostatic effect, thus, reversely inhibiting DNA (Barton, 1986; Friedman, Chambron, Sauvage, Turro, Barton, 1992; Liu, Cheung, Che, 1996; Liu et al, 2002; Miesel & Weser, 2006; Novak-Hofer, Zimmermann, Schubiger, 2001; John, Kuttan, Krishnankutty, 2002; Shrivastav et al, 2006; Mackay et al, 2007; Angeles-Boza et al, 2006; Patra, Gupta, Roy, Chakravarty, 2008).

At first, Sharples (1946) detected antitumoral effect of Cu(II) complex 4-dimethylaminoazabenzole, then inorganic salts of copper were used on different animals affected with carcinomatosis (Brada & Altman, 1978). Later as antitumoral compounds on the experimental tumors of Sarcome 180 and Ehrlich ascites were used Cu(II)(3,4,7,8,-tetramethyl-1,10-phenanthroline)$_2^{2+}$, (Dwyer, Mayhew, Roe, Shulman, 1965), Cu(II)(2-keto-3-ethoxybutyraldehyde bisthiosemicarbazone)$_2^{2+}$ (Rao, Saryan, Antholine, Petering 1980), Cu(II) complexes 2-formylpyridine- and 1-formylisoquinoline- thiosemicarbazones, (Monti et al, 1990) copper derivative of doxorubicin (Monti et al, 1990), aminoacids and peptides (Pickartet al, 1980) Schiff derivative of aroilhydrazides and amino acids (Sreedhara, Freed, Cowan, 2000; Pickart, Goodwin, Burgua, Murphy, Johnson, 1983; Казарян, 2010; Гаспарян, Казарян, Аракелова, 2010; Arakelova et al, 2010).

Having relatively low potential for oxidation metallocomplexes with copper ions take acitve part in many reactions with electron transfer, including catalyzing recovery of organic radicals and breakdown of peroxides, while some of these compounds have superoxidedismutase activity (Sorenson, 1984; Dillon et al, 2003;).

Cu(II) chelate of 3,5-diisopropylsalycinic acid [$Cu(II)(3,5\text{-}DIPS)_4$] shows high antitumoral and SOD mimetice effect on experimental tumors of Erhlich carcinoma and Sarkoma 180 (Oberley et al, 1982).

Cu(II) Compunds as Antiulcer Means

Changes in quantitative content of copper in blood and its removal from the organism are well studied for such diseases as stomach ulcer and small intestines ulcer (Sorenson, 1978; Парашак,1965; Alberghina et al, 1982). On the other hand, it turns out that Cu(II) chelates used for treatment of inflammatory processes of organism, can be used quite successfully to treat stomach ulcer and small intestines ulcer. Experiments are conducted with the use of inorganic compounds (Rainsford, 1981), as well as in case of Cu(II) chelates of anthroic and nicotine acids as aminoacids and peptides, like D- and L-tryptophan, L-valine, L-proline, L-lysine, L- histidine, L- histidine, L- isoleucine, L-serine, glycyl- histidyl -glycine, carnosine (Rainsford, 1981; Kimura, Koike, Shimizu, Kodama, 1986), while Cu(II) $(tryptophan)_2$ and $Cu(II)(aspirin)_2$ were used in case of such ulcers which were inclined to form tumour cells (Craven, Pfanstiel, De Rubertis, 1986). This and other studies prove that the accumulation of superoxides and other oxyradicals play an important role in the process of aetiology and pathology by formating stomach ulcer and small intestines ulcer and propose to use such compounds which possess Superoxide Dismutase Mimetic Activity (Brigelius et al, 1974; Weser, Richter, Wendel, Younes 1978; Lengfelder, Fuches, Younes, Weser 1979; West, 1982).

Cu(II) Complexes as Anticonvulsive Substances

It's known that stimulation caused by different stimulants (intramuscular injection of camphor, coffeine, irritation with electric current) leads to the decrease in quantitative copper content in the tissues of brain (Rose & Lombroso, 1970; Oxbury & Whitty, 1971). Consequently, it may be assumed that in case of stimulation of the central nervous system copper in the brain tissue gets out of proteine complexes and it may be assumed that shifts of copper content in the whole blood, spinal fluid and brain tissue in case of schizophrenia have a direct relation with the pathogenesis of this disease. This is proved by the fact that introduction of bluestone into organism managed to improve the condition of people ill with schizophrenia (Ботвиникова, 1966). This phenomenon was observed also in the experiment with $CuCl_2$ and $Cu_2(acetate)_2$ in case of convulsions caused by maximum electric shocks (Sorenson et al, 1980).

Among diseases of nervous system connected with metabolic disturbance of copper, hepatolenticular [lenticular progressive] degeneration is best studied. This disease ic characterized by high content of copper in liver, brain, skin and cornea; at the same time discharge of copper with urine increases for this disease. It is also characterized by decrease in copper content in the blood serum (Horn, Heydorn, Damsgaard, 1978). It has been established that brain tissue pathogenesis is directly connected with inflamamtory processes of organism, and anti-inflammatory substances can successfully be used at the initial stage of brain tissue disease. Thus, it has been established that such derivatives of salycilic acid have anticonvulsive effect as $Cu(II)(salicylate)_2$, $Cu(II)(4\text{-amino salicylate})_2$, $Cu(II)(4\text{-tertiary butylsalicylate})_2$, $Cu(II)(4\text{-nitrosalicylate})_2$, $Cu(II)(3,5\text{-diisopropyl-salicylate})_2$, $Cu(II)(adamantylsalicylate)_4$, $Cu(II)(acetylsalicylate)_4$ (Sorenson, Rauls,

Ramakrishna, Stull, Voldeng, 1979; Dollwet, McNicholas, Pezeshk, Sorenson, 1987), as well as Cu(II) chelates of such amino acids such as L-threonine, L-valine, L-alanine, L-phenylalanine, L-cystine, L-serine, L-tryptophan, L- glutamic acid, L- leucine, L-isoleucine (Sorenson et al, 1979; Dollwet et al, 1987).

These experiments *in vivo* on convulsions caused by maximum electric shocks prove that Cu(II) chelates of such anticonvulsion medicines as phenobarbital, dilantin, valproic acid, lorazepam have higher anticonvulsion effect than initial substances (Sorenson et al, 1979; Dollwet et al, 1987). Cu(II) chelates of different Schiff-aminoacids and their ethers have anticolvusion effect (Казарян, Григорян, Пароникян, Тадевосян, 2008; Казарян et al 2010; Казарян, 2010).

Copper (II) and Antibacterial Activity

Streptococcus pyogenes and Staphylococcus aureus are the most frequent causative agents of skin and other soft tissues. The range of these infections is rather large: from erysipelas and cellulitis to necrotizing fasciitis (Goppa, Eng, Giuge, 1983). The most important component for treatment patients with necrotizing fasciitis caused by Streptococcus pyogenes is the surgical treatment of primary focus of infection, and it supposes maximally complete removal of nonviable tissues. Antibacterial therapy is the integral part of treatment of surgical infections. Bacteriemia is very rarely detected for those patients who have the syndrom of toxic shock developed together with fasciitis, which is referred to the production of certain stams of streptococci of ectotoxin (Ahchondg, Yip, Lee, Chiu, 1994).

In the course of recent 15 years Staphylococcus aureus is one of the leading post-operational and post-traumatic festering wound aftereffects in traumotology and orthopaedics such as osteomyelitis and abscess. In regard with frequent generation of a large number of antibiotic resistance of Staphylococcus auceus stams it is necessary to look for new highly effective antibacterial preparations (Белобородов, 2003). Copper nanoparticles are among such preparations (Богословская, Астротина, Байтукалов, 2006). Copper preparations introduced into the organisms of animals in the form of nanoparticles have prolonged effect and less toxicity as compared with salts. When introduced into organism copper nanoparticles stimulate mechanisms for regulating microelement composition and activity of antioxidant ferments (Арсентьева, Зотова, Фолманис, 2007). Studies were conducted on 10 stams of Staphylococcus aureus. Unlike antibiotics copper nanoparticles don't cause selection of resistent stams that enables to recommend for further use of treating festering wounds caused by poly-antibiotics-resistant stams of golden staphylococci. Antibacterial activity was studied for Cu(II) chelates of salicylidene anthranilic acid, salicylidene -o-aminophenol, salicylidene -o-aminopyridine (Hodnett & Dunn, 1970), salicylidene-and nicotinyl –amino acids (Пароникян, Степанян, Григорян, Казарян, 2006; Степанян, Пароникян, Григорян, Казарян, 2009; Степанян, Пароникян, Григорян, Аракелова, Казарян, 2010; Chohan & Kausar, 2000), some salicylidene hydrazones (Chohan, Farooq, Iqbal 2000), as in case of gram-positive Staphylococcus aureus, as well as gram-negative Esherichia coli bacteria, and fungi bacteria Aspergillus niger, Aspergillus nidulense and Candida albicans by limiting dilution method.

Cu(II) complex of thioisonicotinealhydrazone pyridine-2-carbaldehyde possesses antibacteral activity in regard with Cholerae, E. Coli, Klebsiella pneumoniae.

On the example of hydrazone complexes, Cu(II) complexes particularly show how physiologically active substances are constructed (sulfanilamide and its analogues ethazol and aziridine) with assigned acitivities, particularly anticancer (in case of aziridine), atimicrobial preparations (sulfanilamide, ethazole), substances for treating blood diseases etc. It turned out that Cu(II) salycilidenehydrazones as compared with the aforementioned known medicines not only preserve the effectiveness against gram-positive bacteria characteristic for additional ligands, but also successfully supress stams of gram-negative microorganisms (Хорсеева, Алексеев, Зеленин, 1991).

Finally, among hydrazones there are a number of known antibacterial means, such as furacilin, ftivazide, as well as strong antiviral mean - metisazone (thisemicarbazone N-methylizatine). There is marked synergism of metisazone action in combination with cations Zn, Fe and especially Cu (Fox, Bopp, Pfau, 1977; Rohde, Cordell, Webster, 1977).

Recently the synthesis of Cu(II) complex enoxacin (1-ethyl-6-fluorine-1,4-dehydro-4-oxo-7-(1- piperazinyl)-1,8-naphthyridine-3- carboxylic acid) has been carried out, which is the inhibitor of bacterial enzyme of DNA spiral. The obtained complex showed anitbacterial activity on 11 different different gram-positive and gram-negative bacteria (Wood, 1989; Arayne, Sultana, Haroon, Mesaik, 2009).

Radioprotective Action of Cu(II) Complexes

Live tissue contains 60-90% of water, that's why it's natural when ionizing radiations interact with organism tissues, the significant part of energy is absorbed by water molecules. In water radiolysis under the effect of γ-radiation not only superoxide anion O_2^{*-} can be formed, but also hydroxyradical OH*, perhydroxyradical HO_2^*, radical H* according to the following equations: $hv+H_2O \rightarrow e^- + H^* + H_3O^+ + HO^* + H_2O_2$, then radical H* enters into reaction with organism oxygen $H^* + O_2 \rightarrow HO_2^* \rightarrow H^+ + O_2^-$, as well as $e^- + O_2 \rightarrow O_2^-$ (Czapski, 1971; Okada, 1970), alkyl-radical-R* can also be formed (Gui-min et al, 2001), alcoxyl-radical (lipid) LO*, peroxyl-radical (lipid) LO_2^*, lipid radiotoxins - (lipid peroxygenation products) LOOH, R-LO_2, L-LO. If the effect of H_2O_2, O_2^{*-} was studied at the time of studying the effect of ionizing radiation, exremely active oxidyzer – hydroxy radical HO* has recently became the object for studies (Floyd, Watson, Wong, 1986). Affecting on the thiol protein molecules, OH* denatures them and inactivates ferments. In nucleic acids, hydroxyl-radical enters into reaction with bases thus forming products of damage in genome, as well as destroys carbohydrate bridges between nucletides and cause DNA and RNA chain break. So OH* is capable of causing mutation and death of cells (Владимиров, 2000). Biological changes may take place in the radiated organism at different levels, below are given some of these changes/modifications:

- Damage of macromolecules of ferments, DNA and RNA and their effect on exchange processes.
- Damage of cellular membranes, nuclei, chromosome, mitochondrion and lysosomes.
- Termination of cell division and death: transformation into malignant cells.

- Changes of genetic characteristics of separate individuals under effect of genetic and chromosomal mutations.
- Death or reduction of lifespan caused by radiation.

Based on the abovementioned considerations in the affection of ionizind radiation, control should be exercised on toxic accumulation of forming radicals, lipid peroxygenation products in biological membrances so as to prevent irreversible character of DNA structure degeneration for short time period.

At the stages of formation of primary radicals in water and lipids, antiradical protective resources of the organism decrease formation of free radicals, destroy or prevent their formation in the cell – this is so called antiradical mechanism of protection (Владимиров, 2000; Кудряшов, 2000). At the stage of forming oxidative radicals protective mechanisms are switched on which are capable of cutting down the access of oxygen from blood into the cell, for example, met- and carboxy-haemoglobin-formation, vasoconstriction (Гончаренко & Кудряшов, 1985), to regulate the level of active forms of oxygen – for example, SOD activation– superoxide dismutase (Вартанян, С.Н. Гуревич, А.И. Козаченко, 2000). There are more active low-molecular antioxidants, i.e. thiols: reduced glutathione, cysteine; biogenic amins: serotonin, histamine, catecholamines, corticosteroids; peptides: carnosine, anserine; vitamins: ascorbic acid in cytosol of cells, tocopherol, β-carotin and other lipochromes localized in the lipids of biological membranes; other antioxidants: phospholipids, ubiquinone, urates, bilirubin, phenols, microelemtns, metal ions of variable valency (Гончаренко & Кудряшов, 1985; Владимиров, 2000; Скулачев, 1996; Болдырев, 1998). It should be noted that there are many effective means from radiation-stricken effect among different chemical substances, compounds, biological preparations and formulas. Among them there are vitamins, antibiotics, nitrites, cyanides, amino acids, alkaloids, flavonoids, polysaccharides, serum-containing substances, analetpics, narcotic, stimulators of nervous system, kholine and acridic derivatives, local anesthetic, indolylalkylamins, aminothiols etc (Казарян, 2006;2009). Among the abovementioned substances superoxide dismutase (SOD) is one of the main components of antioxidant protective system of the organism. (Halliwell & Gutteridge, 1986).

Superoxide dismutase (SOD) refers to the group of antioxidant ferments which is a copper-containing protein and was called hemocrupein, then this protein was renamed into erythrocuprein. Later similar proteins were isolated from other tissues (hematocrupein, cerebrocrupein) and it was detected that all they together with Cu(II) also contain Zn(II). Further studies of superoxide dismutase (SOD) are tightly connected with Fridovich's name (1986). As a matter of fact, Cu(II) - Zn(II) (SOD) is a ferment from the family of metallothioneins rich in cysteine localized in the cell nucleus (Miles, Hawksworth, Geattie, Rodilla, 2000). They present certain interest as they are in the role of interceptors and dampers of free oxygen radicals (Sato & Bremner, 1993; Vukovic, Say-Ry Pheng, Stewart, 2000). Under modern assumptions metallothioneins may impact on the protective effect in regard of radiation-conditioned geno- and cytotoxicity (Cai, Satoh, Tohyama, Cherian, 2000) and to prevent the formation of DNA breaks and apoptosis (Cai, Cherian, Iskander, 2000; Vukovic, Say-Ry Pheng, Stewart, 2000). The tight connection of the survival rate of mice should be mentioned that were exposed to radiation after introducing salts of heavy metals, Cu(II), Co(II), with increase in content of metalloc metallothioneins in the backbone (Miura, Satoh, Imura, Naganuma, 1998).

The radioprotective effect is observed in case of intravenous induction of the ferment into mice (Petkau, Kelley, Chelack, Barefoot, 1976). In case of Cu-Zn SOD this phenomenon was also checked on different bacterial cultures (Nagasawa, Little, 1981). It should be noted that like Cu-Zn SOD, Cu (II) complexes with different molecular weights in case of weights and different chemical structures which mainly possess antitumoral activity, to some extent possess both radioprotective and antioxidant activities (Monti et al, 1990; Oberley et al, 1982).

Though the velocity of these complexes to trap forming radicals is much less than the constant of Cu-Zn SOD reaction rate which is equal to 2*·10msec which is close the magnitude of the constant of reaction rate controlled by diffusion. When using ferments isolated from the blood of animals as antioxidant preparations, probably problems of immune compatibility emerge, meanwhile complex compounds, which are not proteins, can't generate undesirable ractions in the immune system. Complex compounds of Cu(II) have another advantage: they can penetrate inside the cell due to their small size, while ferment acts only in the intercellular environment. Besides, as compared with ferments, complex conpounds are more accessible.

As radioprotective mean Cu(II) chelate 3,5-diizopropylsalycinic acid [Cu(II)(3,5-DIPS)4] (Monti et al, 1990; Oberley et al, 1982; Sorenson, 1984; Sorenson, Soderberg, Chung, Walker, 2001; Soderberg, Barnett, Baker, Salari, Sorenson, 1987) and Cu(II) complex 5-diethylsulphonamoilsalycinicacids [Cu(II)(5-DESS)] (Kuykendall, III et al, 1999) are rather intensively checked in different doses both before the exposure of radiation of experimental animals and after it. Certain interest presents rather up-to-date0 information about antioxidant and radiprotevtive activities of Cu(II) complexes of nitrogen-containing compounds (Fujimori et al, 2005; Sheepskin et al, 2006) and salycidene-aminoacids (Kazaryan et al, 2001; Малакян et al, 2003).

Thus when analyzing the aforementioned information it can be said that Cu(II) must be present in the organism in strictly certain quantity as: first of all, its deficit is the cause of rheumatoid arthritis (Taylor, Williams, 1998), inadequate production of ferments of superoxide dismutase (SOD), NO-synthases (NOS) and several other immunobiological ferments (Sorenson, 1989; Weder et al, 2002; Kaim & Rall, 1996;); secondly, Cu(II) can affect on the activities of other necessary microelements meanwhile promoting formation of metalloenzymes of (Magnani & Solioz, 2007) 3rd group (Zn, Ni, Cu, Co, Cd, Fe(II), Fe(III), Mn) (Percival, 1998); 3), thirdly, Cu(II) surplus or deficit can determine the course of disease developments in different organs (liver, kidney, spleen, lungs, heart, eyes, muscles, bones, adrenal gland, pancreas and thyroid gland) etc; 4) and fourthly, the content of Cu(II) in blood can be used as an indicator for organism health.

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