Обзорная статья
https://doi.org/10.47470/0016-9900-2021-100-2-172-177

Читать онлайн

Alexandra Ye. Kopach, Olha Ye. Fedoriv, Nataliia A. Melnyk

Effects of the influence of copper and zinc on living organisms (literature review)

Horbachevsky Ternopil National Medical University, Ternopil, 46000, Ukraine

Introduction. *Scientists from Horbachevsky Ternopil National Medical University, Ternopil, and various countries, including state laboratories, have thoroughly studied the biological significance of copper and zinc ions in the body for many years. Nevertheless, the value of the shortage or excess of these metals and their compounds in the body remains mostly underestimated for health.*
Purpose of work*: to study the pathogenesis of traumatic disease occurring due to an imbalance of copper and zinc in the body.*
Methods. *Bibliosemantic and analytical methods were used. A literature search was conducted for the following queries as zinc, copper, heavy metals, negative impact. The investigation was performed with PubMed, Scopus, Web of Science, and Google Scholar for various articles. All publications have been analyzed and included in this review. The importance of these metals' lack or excess and their compounds in the body remains mostly underestimated. Features of the pathogenesis of many diseases occurring due to imbalance of copper and zinc in the body have also been unexplored. The traumatic disorder was no exception, as this was not considered in experimental and clinical medicine.*
Conclusion. *From the analysis of the available scientific literature, no messages were found about the features of the course of traumatic disease in conditions of excessive intake of copper and zinc ions in the body. We can only assume that a violation of the functional ability of the liver, lungs, brain and other organs that occurs against the background of heavy metal ion damage creates an unfavorable background for the occurrence of a serious injury.*

Keywords*: copper; zinc; negative impact; heavy metals; review*

For citation: Kopach A.Ye., Fedoriv O.Ye., Melnyk N.A. Effects of the influence of copper and zinc on living organisms (literature review). *Gigiena i Sanitariya (Hygiene and Sanitation, Russian journal)*. 2021; 100 (2): 172-177. https://doi.org/10.47470/0016-9900-2021-100-2-172-177 (In Russ.)

For correspondence: *Alexandra Ye. Kopach*, MD, PhD., assoc. Prof. of the Department of General Hygiene and Ecology I. Horbachevsky Ternopil National Medical University, Ternopil, 46000, Ukraine. E-mail: kopachole@tdmu.edu.ua

Information about the authors:
Kopach A.Ye., https://orcid.org/0000-0003-3403-6477; Fedoriv O.Ye., https://orcid.org/0000-0001-9860-4889; Melnyk N.A., https://orcid.org/0000-0002-7357-7551

Conflict of interest. The authors declare no conflict of interest.
Acknowledgements. The study had no sponsorship.
Contribution: *Kopach O.Ye.* – writing a text; *Fedoriv O.Ye.* – collection and processing of the material; *Melnyk N.A.* – editing. *Все соавторы* – утверждение окончательного варианта статьи, ответственность за целостность всех частей статьи.

Received: May 18, 2020 / Accepted: September 18, 2020 / Published: March 30, 2021

Копач А.Е., Федорив О.Е., Мельник Н.А.

Эффекты влияния меди и цинка на живые организмы (обзор литературы)

ТНМУ Тернопольский национальный медицинский университет им. И.Я. Горбачевского МОЗ Украины, 46000, Тернополь, Украина

Введение. *Несмотря на то что биологическое значение ионов меди и цинка в организме основательно изучается в течение многих лет учёными разных стран, в том числе в государственных лабораториях, значение нехватки или избытка указанных металлов и их соединений в организме для здоровья в значительной степени остаётся недооцененным.*
Цель работы *– изучить патогенез травматической болезни, возникающей на фоне дисбаланса меди и цинка в организме.*
В работе использованы библиосемантические и аналитические методы. Был проведён поиск литературы по следующим запросам: «цинк, медь, тяжёлые металлы, негативное влияние». Поиск проведён по базам данных PubMed, Scopus, Web of Science и Google Scholar для различных статей. Все публикации были проанализированы и включены в этот обзор.
Важность недостатка или избытка этих металлов и их соединений в организме остаётся в значительной степени недооценённой. Особенности патогенеза многих заболеваний, возникающих на фоне дисбаланса меди и цинка в организме, также не изучены. Травматическое заболевание не было исключением, так как это не учитывалось в экспериментальной и клинической медицине.
Заключение. *Из анализа доступной научной литературе не найдено сообщений об особенностях течения травматической болезни в условиях избыточного поступления ионов меди и цинка в организм. Можно только предположить, что нарушение функциональной способности печени, лёгких, мозга и других органов, которое возникает на фоне поражения ионами тяжёлых металлов, создаёт неблагоприятный фон для протекания тяжёлой травмы.*

Ключевые слова*: цинк; медь; тяжёлые металлы; негативное влияние; обзор*

Для цитирования: Копач А.Е., Федорив О.Е., Мельник Н.А. Эффекты влияния меди и цинка на живые организмы (обзор литературы). *Гигиена и санитария*. 2021; 100 (2): 172-177. https://doi.org/10.47470/0016-9900-2021-100-2-172-177

Для корреспонденции: *Копач Александра Евгеньевна*, доцент кафедры общей гигиены и экологии Тернопольского национального медицинского университета им. И.Я. Горбачевского, 46000, Тернополь, Украина. E-mail: kopachole@tdmu.edu.ua

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов в связи с публикацией данной статьи.
Благодарность. Исследование не имело спонсорской поддержки.
Участие авторов: *Копач А.Е.* – написание текста; *Федорив О.Е.* – сбор и обработка материала; *Мельник Н.А.* – редактирование. *Все соавторы* – утверждение окончательного варианта статьи, ответственность за целостность всех частей статьи.

Поступила 18.05.2020 / Принята к печати 18.09.2020 / Опубликована 30.03.2021

Review article

Introduction

Recently, studies that focus on studying the effects of heavy metals and xenobiotics on the body and, in particular, various processes in the body, which play an important role in critical periods of the development of pathology, such as lipid peroxidation and AO protection [1, 2], the state of the immune system, especially changes in nonspecific reactivity.

The toxicity of copper, zinc and other metals has attracted the attention of many scientific teams; in particular, scientists at the Laboratory of Environmental Toxicology, Tallinn, Estonia, have studied the toxic effects of these metals depending on their size and structure on mammals and on individual cultures cells [3]. As a result of these studies, it was found that the ingress of heavy metals into the environment can pose a threat to living organisms and the degree of this threat depends on the type of organism. So, results were obtained that testify to the high sensitivity of algae, crustaceans, fish, bacteria, yeast, nematodes, protozoa, and also mammalian cell cultures. As a rule, crustaceans, algae and fish turned out to be the most sensitive to the negative effects of silver, copper and zinc, while bacteria showed high resistance to these effects. Unfortunately, the corresponding indices of the average inhibitory concentrations for mammalian cell cultures turned out to be 8–10 times lower, which proved significantly higher sensitivity and vulnerability of organisms of the highest degree of organization, like mammals [3]. However, studies on mammals, the results of which are closer to those in humans, are very few. [3, 4, 5].

Purpose of work: to study the pathogenesis of traumatic disease occurring on the background of an imbalance of copper and zinc in the body.

Bibliosemantic and analytical methods were used in the study. A literature search was conducted for the following queries: «zinc, copper, heavy metals, negative impact». The search was conducted on the databases PubMed, Scopus, Web of Science and Google Scholar for various articles. All publications have been analyzed and included in this review.

The role of heavy metals for humans and other biological species of living organisms is ambiguous: on the one hand, these are substances that are necessary for the life of the organism, on the other - in high concentrations they can be the cause, or the starting or aggravating factor of many diseases. Therefore, in scientific circles, increasing attention is paid to the violation of the balance of copper and zinc, rather than simply reducing or increasing the concentration of these ions in the body [26-27], as well as various mechanisms for regulating the concentration of these substances in the body [3].

Copper and zinc are among the 13 most common pollutants. Studies of Hsieh C.Y., Tsai M.H. (2004) [57] revealed the toxicity of 13 metals of the most dangerous pollutants, including As, Se, Cd, Cr (III and VI), Cu, Pb, Sb, Ag, Tl, Zn, Be, Hg and It is not. The risk of toxic exposure to metals can lie not only in the increased intake of their food compounds, where they come in contact with river, marine organisms, and through soil contamination, which causes a high content of these substances in agricultural products. Even drinking water in some areas contains these compounds at high concentrations, despite the fact that elevated concentrations of copper and zinc in water alter its organoleptic, chemical and biological properties. Thus, at concentrations greater than 5,0mg/l, copper gives tap water a tangy unpleasant binder. At concentrations greater than 1.0 mg / l, the laundry is painted over, corrosion of aluminum and zinc vessels is observed. In this case, opalescence may appear in the water and boiling films may form.

It should also be noted that copper and zinc are some of the essential trace elements that are vital to the body. In particular, it has been proven that copper is an important element in maintaining physical and mental health. Copper is necessary for the metabolism of calcium in the bones, as well as for the adequate functioning of connective tissue elements such as tendons, ligaments, skin, hair, nails, arteries, veins, etc. Therefore, copper imbalances can contribute to the development of osteoporosis, bone spurs, hair and nail diseases. Other symptoms associated with dysfunction of connective tissue in copper imbalance are cardiovascular disease, tendon and ligament diseases, scoliosis, and skeletal imbalance. Copper is also a necessary element for energy production in cells, namely in the final stages of the Krebs cycle. Also important is the involvement of copper in the immune response.

The main symptoms of copper imbalance in the human body are frequent headaches, fatigue, insomnia, depression, skin rashes, and impaired ability to intellectual work. Therefore, in case of copper shortage or imbalance, it is necessary to correct this trace element.

In a detailed study of the effects of trace elements on the body, it is necessary to take into account some features that were observed in the experimental studies. So, in effect largely depends on particle size [6-8, 9] including research scientists of Izrael Borkow G., Zatcoff R.C., Gabbay J.(2009) have shown that small doses of copper nanoparticles can have a positive impact [10, 11], which can be used in diabetes prevention and treatment of skin complications. Patients with this ailment often suffer from skin pathology, especially on the feet. The combination of peripheral vascular disease and neuropathy attenuates the resistance of such patients to infection, so even small cuts and wounds often lead to chronic purulent, fungal skin lesions and severely treatable ulcers. Copper in this case has a positive effect, because it has powerful antibacterial [12-14, 15] and antifungal properties, which is confirmed by many studies of other scientists on various types of microorganisms and fungi. In the works of G. Borkow [10, 11] proved that copper ions that are released from the medical socks or other medical facilities where drugs with nanoparticles coated copper, act locally. This improves the skin condition of patients suffering from diabetes by inducing angiogenesis, expression and stabilization of proteins in addition to their biocidal effect, as well as reducing the risk of fungal and bacterial infection of the diabetic foot. This trend in the use of trace elements has received the approval of other scholars who have made suggestions for practical applications [16].

However, many researchers are attracting the attention of the toxic properties of heavy metals, given the seriousness effects on living organisms of fresh and salt water bodies [17, 18], land animals, in particular mammals [3, 4, 5], of paramount importance for their use has soil contamination with metals and their compounds. Great importance is given to the processes of accumulation of metals, in particular, the toxic effect of the accumulation of copper and zinc compounds in the isthmus organ of different species and different tissues of an individual organism. Scientists Shakibaie M.R., Harati A. (2004) have found that metals are able to accumulate not only within cells but also on the surface of cell membranes. Chinese scientists Cao B., Zheng Y., Xi T. (2012) investigated copper cytotoxicity at high concentrations in mouse fibroblasts in vitro [19]. Zhang J., Song W., and other scientists have conducted a similar study to investigate the effect of ZnO on the alveolar macrophages of mice [20]. Many studies have noted the dependence of the cytotoxic effect of metal ions, in particular copper and zinc, on their concentration, their effect on human fibroblast cell culture [21], and their toxic effect on the genetic material of human lung epithelial cells [22]. Other scientific teams have also evaluated the toxicity and changes in the expression of genes caused by metal nanoparticles, and concluded the role of genes in maintaining the homeostasis of trace elements compounds in living organism, in particular copper, as an example of this regulation of these processes in the intestinal [22, 23].

In the last decade, much attention has been paid to the study of the interaction of metals [24]. Mixtures of copper, zinc and other metals have been proven to have greater toxicity than high concentrations of single metals. On the simplest living organisms, by the example of Tetrahymena thermophila, flow cytometry is used to evaluate the cytotoxicity and generation of reactive oxygen species of single and double mixtures of cadmium, zinc and copper, which partially reveals the mechanisms of toxic action of heavy metals and their mixtures.

It is important to study the characteristics of nanocrystals of copper oxide, zinc and other metals: synthesis, physical, chemical and electrochemical features [25, 26, 27, 29], characteristics of their ability to bioluminescence and influence on this phenomenon [23], antibacterial [12, 15, 28, 29, 30, 31],

https://doi.org/10.47470/0016-9900-2021-100-2-166-171

ntifungal action [32, 33]. Researchers of the National Institute of Chemical Physics and Biophysics of Estonia Heinlaan M. and Ivask A. (2008) studied the characteristics of the effects of ZnO, CuO on living organisms *Daphnia magna* and *Thamnocephalus platyurus*, depending on the particle size. These features have been noted by other researchers [33]. The results of such studies indicate that it is necessary to use very carefully and carefully the use of trace elements, even for therapeutic purposes, since they have the capacity to accumulate in the internal organs, as well as due to their membranotropic and cytotoxic action. To this end, scientists Hernández-Sierra J.F., Ruiz F. (Mexico, 2008) compared the bactericidal and bacteriostatic effect of silver, zinc and gold nanoparticles on *S. Mutans*, while it was possible to establish higher antimicrobial activity of silver at lower concentrations than gold or gold zinc, which will achieve a pronounced clinical effect in the treatment of caries with reduced toxicity. Such work proves the importance of research in this area to prevent the toxic manifestations of heavy metals when used for therapeutic purposes.

It is extremely important in the pathogenesis of many disorders that copper should remain in equilibrium with zinc [35, 36, 37]. This means that, at times, the toxic effects of one of the metals [38] may show symptoms of the lack of another [39, 40]. With copper imbalance, there is a greater tendency for all infections, in particular fungal infections, which are very common today. This is especially relevant for injuries of all kinds and, especially, for combined severe trauma, since traumatic illness is very often complicated by infections. Copper imbalances can also lead to impaired endocrine function (hyperthyroidism, premenstrual syndrome, ovarian cysts, infertility, miscarriages), since copper is closely linked to estrogen metabolism and is required for fertile women's function and pregnancy support.

One of the mechanisms of pathogenetic influence of copper ions is their ability to stimulate the production of neurotransmitters: adrenaline, norepinephrine and dopamine. Copper is also required for the metabolism of monoamine oxidase, an enzyme related to serotonin production. As a result, copper is actively involved in all spheres of influence of the central nervous system, which is of particular importance in such pathogenetic manifestations of traumatic disease, as the development of traumatic shock, syndrome of multiple organ failure [1].

It is interesting to note the fact that people have a variety of symptoms of copper balance disturbances in the body not only when copper deficiency or excess, when the toxic properties of this metal, but with the imbalance of copper and other trace elements. This leads, according to many scientists, the state of violations of bioavailability of copper or other trace elements. Recently, this condition has attracted the attention of scientists in many countries and is called "biounavailability" [37, 39, 40].

Copper is found in products such as meat, eggs, poultry, nuts, seeds and cereals. Some patterns have been identified in the needs of this trace element, depending on age. It is believed that children need much more copper than other age groups. This is mainly due to the peculiarities of metabolism in childhood. It is believed that at a rapid rate of oxidation processes, more copper is required in the body, while during the slow flow of these processes copper may be in excess. In this case, the body is more prone to copper imbalance.

What is biounavailability of copper, zinc and other trace elements? In fact, "biounavailability" translates as "bioavailability"? In this situation, copper, zinc or other trace elements are often present in excess in the body, but they cannot be used for the biological needs of the body. One reason is that minerals such as zinc copper and others must be bound by certain carrier proteins in the body and only then can wines be actively transported and used for the vital needs of the body [4, 2, 42]. Therefore, the bioavailability of copper, zinc and other trace elements is extremely important, although it remains to be fully understood.

Bioavailability is often observed due to a deficiency of copper-binding proteins, ceruloplasmin, or metallothioneins [42]. Without sufficient protein, unbound metal ions can circulate freely in the body, where they can accumulate in the liver, brain and other organs, causing, on the one hand, symptoms of intoxication with this metal, and on the other, signs of deficiency of this trace element. That is, a possible condition when simultaneously exhibit symptoms of toxicity and deficiency of trace elements. In fact, this condition is called "biounavailability". However, some authors believe that the most common symptoms of copper toxicity and "bioavailability" are common.

Each trace element has its specific "target organs" in which these trace elements accumulate at excessive concentration. Most often, the places where copper and zinc accumulate are the liver, brain [4, 43], as well as the lungs, reproductive organs [44, 45, 46]. These organs are often damaged in various types of traumas [1-4, 12, 13], and they also play a key role in the traumatic disease course.

Copper is known to have a significant effect on the central nervous system. This is especially noticeable when there is an imbalance in the body of a given metal. For this reason, copper has been called the "emotional mineral". This is of great importance and should be taken into account for traumatic injuries and especially for severe trauma. The stimulating effect of copper on diencephalon has also been found, so toxic effects, or "biounavailability" of copper in traumatic disease, can negatively affect the course of traumatic disease and its complications, in particula pain and traumatic shock [1].

Interesting was the fact that with excess copper in the body, people show a tendency to violence, possible manifestations of aggressive behavior, signs of blurred consciousness, insomnia, nervousness, irritability, and these are known to be significant factors that can cause increased injuries by creating injuries, aggressive behavior, and can also lead to inappropriate behavior in the early post-traumatic period, which is especially dangerous in the erectile phase of traumatic shock.

Another pathogenetic link of copper biounavailability to the course and prognosis of traumatic disease is anemia, which is quite common, since copper is required to change iron from trivalent to divalent and in the opposite direction, which is necessary for the inclusion of iron in hemoglobin. In this case, prescribing iron for anemia due to copper imbalance, it is impossible to get a positive result, and only the deterioration of the patient's general condition is achieved, since this leads to the development of liver hemosiderosis, which is known to be the body where not only mine and zinc accumulate, but also iron and other trace elements [7].

Copper is also important for aerobic metabolism, which is imbalance contributes to the development of infections, which is especially dangerous in traumas. In addition, copper and zinc are required for a proper immune response. Increased copper concentration or "biounavailability" is often combined with "biounavailability" of zinc in tissues, as shown by studies by G. De Boeck, W. Meeus, and other scientists (2004) [18]. It is important to know that normal concentrations of these metals in the blood can be observed, leading to some diagnostic difficulties. Therefore, many clinics offer additional take on hair analysis.

Copper ions are necessary for the electron transport system, which is very important for energy production in the cell. Chinese scientists have conducted studies on the effect of zinc oxide on mitochondria [47]. These features of the effects of copper and zinc compounds should be remembered in the treatment of traumatic disease, in which disorders in the energy organelles of cells - mitochondria, are also observed. Thus, when copper is inaccessible to the body's cells in sufficient quantity, aerobic metabolism is impaired, while anaerobic metabolism, on the contrary, is activated. That is why when the copper imbalance is often activated by fungal infection in the body. On the other hand, this property of copper has found its application in agriculture: for example, copper sulfate is often sprayed on fields to combat fungal damage to crops, leading to significant soil contamination. Antifungal activity has also been found in zinc compounds [25, 32, 33]. Copper is also used in swimming pools and hot tubs to prevent the propagation of yeast fungi and anaerobic bacteria. This was a significant cause of pollution [2], soil, water, copper and zinc compounds.

Given the significant role played by heavy metals in pollution of natural reservoirs, in recent years, scientists have paid considerable

attention to the search for sensitive bioindication methods and the assessment of their toxicity to various aquatic organisms. Most of the works are devoted to the study of the influence of pollutants on morphological parameters, mortality, reflex-behavioral reactions of organisms. A new area of research was the study of the response to the effect of pollutants at the molecular level with the determination of metallothionein (MT) content [41, 42]. Metallothioneins are specific, cysteine-rich stress proteins that can bind excess heavy metals in the body and perform regulatory function. Determination of metallothionein content in aquatic animal tissues is used for bioindication of water pollution. Scientists are interested in the study of certain biological species of animals that can serve as indicators of environmental pollution, and in particular of rivers. Thus, O.B. Stolyar, G.I. Falfushinskaya etc. (2003) conducted experiments on adults with narrow-cancerous cancer and pond frog. In these studies, the interaction of cancer apothionein (Astacus leptodactylus L.) and frog (Rana esculenta L.) with heavy metal ions along the UV spectra of reconstructed metallothioneins was found. For Pb-MT and Fe-MT of both species, characteristic absorption bands with a maximum of 240 and 235–250 nm, respectively, were detected. The spectra of Cu-MT, Zn-MT, and Cd-MT of cancers and frogs have species-specific features. In the action of a mixture of Cd2 + and Pb2 + ions on T cancer, lead ions are dominant in determining the spectral properties. Determination of the composition of metals in MT by their UV spectra can be used in bioindication of water pollution. It is known that the ability of MT to bind copper and zinc changes to ontogeny. The variability of the MT response of different species to these metals may also depend on the α-, b-cluster organization of the MT structure. It is known that crustaceans are characterized by the b-cluster structure of MT, which is copper-binding [42]. This is consistent with the spectrum features of MT cancer.

By P.M. Linnik, the concentration of copper, zinc and lead in natural reservoirs is, respectively, 10-120, 40-160 and 6.2-64 mcg/l. Therefore, MT of freshwater animals, regardless of species, can be considered as promising biomarkers of lead, iron, and a mixture of ions containing lead ions. And for the bioindication of Cu_2 +, Zn_2 + and Cd_2 + it is necessary to take into account the species characteristics of animals. Correlation analysis of the differential spectra of MT is a convenient form of comparing the binding characteristics of metals with these proteins. Some difficulties with the study of the pathogenic effects of accumulation in the body of copper and zinc ions are due to the fact that the species specific characteristics of animals in terms of the ability to form MT and accumulate these ions in the body are of great importance.

When studying the pathogenetic features of trauma against the background of copper and zinc intoxication, it should be noted that copper is a necessary trace element for the formation of connective tissue elements, in particular collagen. This is of great importance for tissue regeneration processes after traumatic damage. It is noticed that at deficiency of copper in an organism atherosclerosis and other cardiovascular diseases develop. Whereas excess or bioavailability of copper often causes connective tissue problems, preventing the formation of disulfide bonds in the connective tissue elements. Copper also affects the vitamin balance. Copper and vitamin C are known to be direct antagonists. This is one of the reasons that people suffering from the symptoms of copper intoxication feel better by taking in a lot of vitamin C. Oxidation processes are activated at high copper ions, while the vitamin C content in the body decreases. This leads to an increase in the daily requirement of vitamin C of at least about 500 mg per day, which is significantly higher than the minimum daily requirement of this vitamin (about 60 mg). Thus, excess copper can lead to a deficiency of vitamin C in the body and the appearance of many symptoms of a deficiency of this vitamin. In the case of injuries, this is particularly relevant given the significant risk of bleeding.

There is another relationship between copper and zinc: zinc deficiency leads to an increased ability of copper to accumulate. Therefore, when the soil is low in zinc, there is an increased risk of copper toxicity in living organisms.

Z. Emami-Karvani and P. Chehrazi (2011) have shown the antibacterial activity of zinc oxide nanoparticles on gram-positive and gram-negative bacteria [15], as well as on the anti-fungal properties. [32, 33].

Studying the mechanisms of the toxic effect of zinc oxide, Chinese scientists Li Y., Liang J., Tao Z. (2012) concluded that this toxicity is manifested in relation to mitochondria [47]. Zinc oxide (ZnO) nanoparticles are increasingly being used in various industries. It was found that ZnO nanoparticles cause toxic effects at the level of the individual organism, tissues, cells and DNA, and the potential effect of ZnO nanoparticles at the subcellular level is investigated more deeply. The toxicity of ZnO nanoparticles in isolated rat liver mitochondria was investigated [47]. Found that the effect of ZnO nanoparticles on mitochondria is manifested by a decrease in the membrane potential of mitochondria, swelling of the investigated cell microstructures, depression of tissue respiration, and inhibition of the inner permeability of the membrane for hydrogen and potassium ions, changes in ultrasound. These results showed that ZnO nanoparticles can increase the permeability of the inner membrane and adversely affect respiratory chain enzymes, leading to energy deficiency, oxidative stress and even apoptosis. Other Chinese researchers [45] have investigated the toxic effects of ZnO nano- and microparticles on human epithelial lung cells.

Many phenomena of zinc intoxication are based on the competitive ratio of zinc to a number of other metals. One of the most important of these metals is calcium. In this case, the level of calcium in the blood, bones decreases, and the absorption of phosphorus by the body is impaired. As a result of these changes, osteoporosis develops, which is a significant etiologic risk factor for injury. As a confirmation of this, it is a well-known fact that in Japan, in 1981, an outbreak of severe musculoskeletal disease was reported in a population fed on rice grown on irrigation fields using running water heavily contaminated with zinc and cadmium sulfides. Also prohibited for drinking is water stored in galvanized dishes, since zinc ions accumulated in such water have a negative effect on the gastrointestinal tract.

Zinc toxicity is also explained by its high catalytic activity. It should not be forgotten that zinc in high concentrations is a mutagen and an oncogene.

Despite certain features of the influence of copper and zinc ions, scientists have been able to identify some common features of their action on the body. Heavy metals can interact with the proteins of the body and form metal compounds with them. Metal ions are involved in the most important biochemical processes. They stimulate, normalize the metabolism in the body, have a positive effect on growth and reproduction, on the immunobiological activity of the body and life expectancy; participate in redox processes; stabilize and activate enzymes, forming their active centers. Metal ions create a potential difference near the surface of the cell membranes, thereby ensuring the flow of life processes in the cell.

When establishing the negative effect of heavy metals on the body, it should be borne in mind that the toxicity of the substance depends on its state (water-insoluble compounds are practically not transformed in the body). Under natural conditions, a relatively harmless substance can be converted into a highly toxic compound. Also a toxic substance is capable of gradual accumulation in the food chain, resulting in its concentration in the higher links of this chain may be a thousand times greater than the concentration of the substance in the environment as a whole (biological accumulation factor).

From the point of view of predicting the relative toxicity of metal ions, studies using ionic characteristics, in particular bioluminescent analysis, are very valuable.

Increasing reports have been reported of the high toxicity of zinc and copper nanoparticles [48-52]. With the emergence of a new direction of treatment for certain diseases with nanoparticles, or when using dosage forms adsorbed on nanoparticles, which in this case are used as transport forms of active substances, the risk of damage to various structures of the body as metals by the manifestation of their toxicity, and damage, due to the nanostructural features of the substance. It is known that nanoparticles have slightly different physicochemical properties and sometimes have a more aggressive effect.

 https://doi.org/10.47470/0016-9900-2021-100-2-166-171

Kawahara M., Sadakane Y. (2013) investigated possible ways to protect against the toxic effects of metals, which proved that D-histidine and L-histidine protect neurons from the toxic effects of zinc [53]. Protein plays a major role in the disposal of heavy metals, since the structure of proteins is characterized by the presence of several centers of communication. This makes it possible to neutralize a large number of metals entering the body.

Some organisms are able to accumulate metals on the cell surface, as demonstrated in the paper on the accumulation of metals in a Pseudomonas aeruginosa, which occurs in the form of nanoparticles. Song W., Zhang J. and other scientists (2010) have also demonstrated the role of dissolved zinc ions and reactive oxygen species in the cytotoxicity of ZnO nanoparticles [54]. The intracellular distribution of zinc and the significance of the features of this distribution for the manifestations of toxicity of this metal were studied in more detail [55].

Attention is paid to the study of the cytotoxicity of individual chemicals using human cells. Such studies can predict which target organs are typical for which substances. To determine the possibility of predicting liver and kidney damage, target organs, which are most often affected by certain manifestations of toxicity, evaluated the viability of liver cells and kidneys in vitro. The toxic effects of zinc compounds on neuronal cells have been investigated [56].

A deeper study of the pathogenesis of copper and zinc toxicity has been largely contributed by domestic scientists. Thus, in the works of Stolyar O.B. and other scientists the results of the study of the effect of heavy metal ions on the state of antioxidant systems of erythrocytes and blood plasma of carp and hepatopancreas of narrow cancers depending on the concentration of ions in water are presented. The effectiveness of antioxidant protection scientists evaluated the activity of erythrocyte and plasma superoxide dismutase, blood and plasma catalase, content of ceruloplasmin and reduced glutathione, hemoglobin derivatives, formation of lipid peroxidation products. The direct effect of metal ions on hemoglobin and LPO was determined in vitro. It was found that the concentration of ions of each of the metals, which is close to its natural content, causes in the blood of the carp compensatory changes in the state of antioxidant factors. At higher concentrations of metal ions, the individual features of the action of each of them are observed. The ability to activate prooxidant processes decreases among the metals studied in the copper> zinc> lead> manganese series. The action of copper and zinc ions is characterized by a decrease in the erythrocyte SOD activity and an increase in the plasma ceruloplasmin content. Changes in the state of heme proteins are most pronounced in the action of manganese and lead ions. The effect of a mixture of metal ions on the complex of features is most similar to the action of lead ions. For copper and zinc, an essential feature of the development of toxic processes is an increase in the plasma content of ceruloplasmin, the acute phase protein.

Although the biological importance of copper and zinc ions in the body has been extensively studied for many years by scientists from different countries, including, in government laboratories, the importance of the lack or excess of these metals and their compounds in the body remains largely underestimated. Features of pathogenesis of many diseases occurring against the background of the imbalance of copper and zinc in the body have also been unexplored. Traumatic disease was no exception, as this was not considered in experimental and clinical medicine.

Conclusion

From the analysis of the available scientific literature, no messages were found about the features of the course of traumatic disease in conditions of excessive intake of copper and zinc ions in the body. We can only assume that a violation of the functional ability of the liver, lungs, brain and other organs that occurs against the background of heavy metal ion damage creates an unfavorable background for the occurrence of a serious injury.

Referenses / Литература

1. Valko M., Morris H., Cronin M.T.D. Metals, toxicity and oxidative stress. *Curr. Med. Chem*. 2005; 12(10): 1161–208. https://doi.org/10.2174/0929867053764635
2. Fedoriv O.E., Kopach O.E., Melnyk N.A., Lototska O.V., Lototskyy V.V. Influence of nanoparticles of lead on the organizm of suspicious animals when using water with content of sodium and sunpate stearates. *World Med. Biol*. 2019; 68(2): 203–8. https://doi.org/10.26724/2079-8334-2019-2-68-203-208
3. Bondarenko O., Juganson K., Ivask A., Kasemets K., Mortimer M., Kahru A. Toxicity of Ag, CuO and ZnO nanoparticles to selected environmentally relevant test organisms and mammalian cells *in vitro*: a critical review. *Arch. Toxicol*. 2013; 87(7): 1181–200. https://doi.org/10.1007/s00204-013-1079-4
4. Palytsya L.M., Korda M.M., Mudra A.Ye., Fedoniuk L.Ya. C60 fullerenes exacerbate the toxic effect of toluene on the state of the xenobiotic biotransformation enzyme system. *Ukr. Biochem. J*. 2019; 67(1): 178–81. (in Ukrainian)
5. Peralta-Videa J.R., Hernandez-Viezcas J.A., Montes M.O., Keller A.A., Gardea-Torresdey J.L. Microscopic and spectroscopic methods applied to the measurements of nanoparticles in the environment. *Appl. Spectrosc. Rev*. 2012; 47(3): 180–206. https://doi.org/10.1080/05704928.2011.637186
6. Bystrzejewska-Piotrowska G., Golimowski J., Urban P.L. Nanoparticles: their potential toxicity, waste and environmental management. *Waste Manag*. 2009; 29(9): 2587–95. https://doi.org/10.1016/waisman.2009.04.001
7. Yu L.P., Fang T., Xiong D.W., Zhu W.T., Sima X.F. Comparative toxicity of nano-ZnO and bulk ZnO suspensions to zebrafish and the effects of sedimentation, ·OH production and particle dissolution in distilled water. *J. Environ. Monit*. 2011; 13(7): 1975–82. https://doi.org/10.1039/c1em10197h
8. Ma H., Kabengi N.J., Bertsch P.M., Unrine J.M., Glenn T.C., Williams P.L. Comparative phototoxicity of nanoparticulate and bulk ZnO to a free-living nematode Caenorhabditis elegans: the importance of illumination mode and primary particle size. *Environ. Pollut*. 2011; 159(6): 1473–80. https://doi.org/10.1016/j.envpol.2011.03.013
9. Borkow G., Zatcoff R.C., Gabbay J. Reducing the risk of skin pathologies in diabetics by using copper impregnated socks. *Med. Hypotheses*. 2009; 73(6): 883–6. https://doi.org/10.1016/j.mehy.2009.02.050
10. Borkow G., Gabbay J., Dardik R., Eidelman A., Lavie Y., Grunfeld Y., et al. Molecular mechanisms of enhanced wound healing by copper oxide-impregnated dressings. *Wound Repair. Regen*. 2010; 18(2): 266–75. https://doi.org/10.1111/j.1524-475X.2010.00573.x
11. Bondarenko O., Ivask A., Käkinen A., Kahru A. Sub-toxic effects of CuO nanoparticles on bacteria: kinetics, role of Cu ions and possible mechanisms of action. *Environ. Pollut*. 2012; 169: 81–9. https://doi.org/10.1016/j.envpol.2012.05.009
12. Ansari M.A., Khan H.M., Khan A.A., Sultan A., Azam A. Characterization of clinical strains of MSSA, MRSA and MRSE isolated from skin and soft tissue infections and the antibacterial activity of ZnO nanoparticles. *World J. Microbiol. Biotechnol*. 2012; 28(4): 1605–13. https://doi.org/10.1007/s11274-011-0966-1
13. Baker J., Sitthisak S., Sengupta M., Johnson M., Jayaswal R.K., Morrissey J.A. Copper stress induces a global stress response in Staphylococcus aureus and represses sae and agr expression and biofilm formation. *Appl. Environ. Microbiol*. 2010; 76(1): 150–60. https://doi.org/10.1128/AEM.02268-09
14. Emami-Karvani Z., Chehrazi P. Antibacterial activity of ZnO nanoparticle on grampositive and gram-negative bacteria. *Afr. J. Microbiol. Res*. 2011; 5(12): 1368–73. https://doi.org/10.5897/AJMR10.159
15. Alsop D., Wood C.M. Metal uptake and acute toxicity in zebrafish: common mechanisms across multiple metals. *Aquat. Toxicol*. 2011; 105(3–4): 385–93. https://doi.org/10.1016/j.aquatox.2011.07.010
16. Bao V.W., Leung K.M., Qiu J.W., Lam M.H. Acute toxicities of five commonly used antifouling booster biocides to selected subtropical and cosmopolitan marine species. *Mar. Pollut. Bull*. 2011; 62(5): 1147–51. https://doi.org/10.1016/j.marpolbul.2011.02.041
17. Ebrahimpour M., Alipour H., Rakhshah S. Influence of water hardness on acute toxicity of copper and zinc on fish. *Toxicol. Ind. Health*. 2010; 26(6): 361–5. https://doi.org/10.1177/0748233710369123
18. Cao B., Zheng Y., Xi T., Zhang C., Song W., Burugapalli K., et al. Concentration-dependent cytotoxicity of copper ions on mouse fibroblasts in vitro: effects of copper ion release from TCu380A vs TCu220C intra-uterine devices. *Biomed. Microdevices*. 2012; 14(4): 709–20. https://doi.org/10.1007/s10544-012-9651-x
19. Zhang J., Song W., Guo J., Zhang J., Sun Z., Ding F., et al. Toxic effect of different ZnO particles on mouse alveolar macrophages. *J. Hazard Mater*. 2012; 219–220: 148–55. https://doi.org/10.1016/j.jhazmat.2012.03.069
20. Contreras R.G., Sakagami H., Nakajima H., Shimada J. Type of cell death induced by various metal cations in cultured human gingival fibroblasts. *In Vivo*. 2010; 24(4): 513–7.
21. Ahamed M., Siddiqui M.A., Akhtar M.J., Ahmad I., Pant A.B., Alhadlaq H.A. Genotoxic potential of copper oxide nanoparticles in human lung epithelial cells. *Biochem. Biophys. Res. Commun*. 2010; 396(2): 578–83. https://doi.org/10.1016/j.bbrc.2010.04.156
22. Dua P., Chaudhari K.N., Lee C.H. Evaluation of toxicity and gene expression changes triggered by oxide nanoparticles. *Bull. Korean Chem. Soc*. 2011; 32(6): 2051–7. https://doi.org/10.5012/bkcs.2011.32.6.2051

23. Aruoja V., Dubourguier H.C., Kasemets K., Kahru A. Toxicity of nanoparticles of CuO, ZnO and TiO_2 to microalgae Pseudokirchneriella subcapitata. *Sci. Total Environ*. 2009; 407(4): 1461–8. https://doi.org/10.1016/j.scitotenv.2008.10.053
24. Patra P., Mitra S., Debnath N., Goswami A. Biochemical-, biophysical-, and microarray-based antifungal evaluation of the buffer-mediated synthesized nano zinc oxide: an *in vivo* and *in vitro* toxicity study. *Langmuir*. 2012; 28(49): 16966–78. https://doi.org/10.1021/la304120k
25. Hassan M.S., Amna T., Yang O.B., El-Newehy M.H., Al-Deyab S.S., Khil M.S. Smart copper oxide nanocrystals: synthesis, characterization, electrochemical and potent antibacterial activity. *Colloids Surf. B. Bioinerfaces*. 2012; 97: 201–6. https://doi.org/10.1016/j.colsurfb.2012.04.032
26. Majzlik P., Strasky A., Adam V., Nemec M., Trnkova L., Zehnalek J., et al. Influence of zinc(II) and copper(II) ions on Streptomyces bacteria revealed by electrochemistry. *Int. J. Electrochem. Sci*. 2011; 6(1): 2171–91.
27. Harrington J.M., Boyd W.A., Smith M.V., Rice J.R., Freedman J.H., Crumbliss A.L. Amelioration of metal-induced toxicity in Caenorhabditis elegans: utility of chelating agents in the bioremediation of metals. *Toxicol. Sci*. 2012; 129(1): 49–56. https://doi.org/10.1093/toxsci/kfs191
28. Mortimer M., Kasemets K., Heinlaan M., Kurvet I, Kahru A. High throughput kinetic Vibrio fischeri bioluminescence inhibition assay for study of toxic effects of nanoparticles. *Toxicol. In Vitro*. 2008; 22(5): 1412–7. https://doi.org/10.1016/j.tiv.2008.02.011
29. Liu Y., He L., Mustapha A., Li H., Hu Z.Q., Lin M. Antibacterial activities of zinc oxide nanoparticles against *Escherichia coli* O157:H7. *J. Appl. Microbiol*. 2009; 107(4): 1193–201. https://doi.org/10.1111/j.1365-2672.2009.04303.x
30. Xie Y., He Y., Irwin P.L., Jin T., Shi X. Antibacterial activity and mechanism of action of zinc oxide nanoparticles against *Campylobacter jejuni*. *Appl. Environ. Microb*. 2011; 77(7): 2325–31. https://doi.org/10.1128/AEM.02149-10
31. Mirhosseini M., Firouzabadi F.B. Antibacterial activity of zinc oxide nanoparticle suspensions on food-borne pathogens. *Int. J. Dairy Technol*. 2013; 66(2): 291–5. https://doi.org/10.1111/1471-0307.12015
32. He L., Liu Y., Mustapha A., Lin M. Antifungal activity of zinc oxide nanoparticles against *Botrytis cinerea* and *Penicillium expansum*. *Microbiol. Res*. 2011; 166(3): 207–15. https://doi.org/10.1016/j.micres.2010.03.003
33. Lipovsky A., Nitzan Y., Gedanken A., Lubart R. Antifungal activity of ZnO nanoparticles-the role of ROS mediated cell injury. *Nanotechnology*. 2011; 22(10): 105101. https://doi.org/10.1088/0957-4484/22/10/105101
34. Hoheisel S.M., Diamond S., Mount D. Comparison of nanosilver and ionic silver toxicity in *Daphnia magna* and *Pimephales promelas*. *Environ. Toxicol. Chem*. 2012; 31(11): 2557–63. https://doi.org/10.1002/etc.1978
35. Mortimer M., Kasemets K., Kahru A. Toxicity of ZnO and CuO nanoparticles to ciliated protozoa *Tetrahymena thermophila*. *Toxicology*. 2010; 269(2-3): 182–9. https://doi.org/10.1016/j.tox.2009.07.007
36. Kasemets K., Ivask A., Dubourguier H.C., Kahru A. Toxicity of nanoparticles of ZnO, CuO and TiO_2 to yeast *Saccharomyces cerevisiae*. *Toxicol. In Vitro*. 2009; 23(6): 1116–22. https://doi.org/10.1016/j.tiv.2009.05.015
37. Smith S.R. A critical review of the bioavailability and impacts of heavy metals in municipal solid waste composts compared to sewage sludge. *Environ. Int*. 2009; 35(1): 142–56. https://doi.org/10.1016/j.envint
38. Poynton H.C., Lazorchak J.M., Impellitteri C.A., Smith M.E., Rogers K., Patra M., et al. Differential gene expression in *Daphnia magna* suggests distinct modes of action and bioavailability for ZnO nanoparticles and Zn ions. *Environ. Sci. Technol*. 2011; 45(2): 762–8. https://doi.org/10.1021/es102501z
39. Stolyar O.B., Zin'kovs'ka N.Z., Mudra A.Y. The role of low weight proteins and thiols of hepatopancreas in the protection of carp organs from copper uptake. In: *Metals and Cell Symposium*. Canterbury; 2001.
40. Käkinen A., Bondarenko O., Ivask A., Kahru A. The effect of composition of different ecotoxicological test media on free and bioavailable copper from $CuSO_4$ and CuO nanoparticles: comparative evidence from a Cu-selective electrode and a Cu-biosensor *Sensors*. 2011; 11(11): 10502–21. https://doi.org/10.3390/s111110502
41. Wang P., Lutton A., Olesik J., Vali H., Li X. A novel iron- and copper-binding protein in the Lyme disease spirochaete. *Mol. Microbiol*. 2012; 86(6): 1441–51. https://doi.org/10.1111/mmi.12068
42. Valls M., Bofill R., Gonzales-Duarte R. A new insight into metallothionein (MT) classification and evolution. *J. Biol. Chem*. 2001; 35(276): 32835–43. https://doi.org/10.1074/jbc.m102151200
43. Riggio M., Filosa S., Parisi E., Scudiero R. Changes in zinc, copper and metallothionein contents during oocyte growth and early development of the teleost *Danio rerio* (zebrafish). *Comp. Biochem. Physiol*. 2003; 135(2): 191–6. https://doi.org/10.1016/s1532-0456(03)00107-8
44. Kim Y.H., Fazlollahi F., Kennedy I.M., Yacobi N.R., Hamm-Alvarez S.F., Borok Z., et al. Alveolar epithelial cell injury due to zinc oxide nanoparticle exposure. *Am J. Respir. Crit. Care. Med*. 2010; 182(11): 1398–409. https://doi.org/10.1164/rccm.201002-0185OC
45. Lin W., Xu Y., Huang C.C., Yinfa Ma, Shannon K.B., Chen D.R., et al. Toxicity of nano and micro-sized ZnO particles in human lung epithelial cells. *J. Nanopart. Res*. 2009; 11(1): 25–39. https://doi.org/10.1007/s11051-008-9419-7
46. Wu J., Wang L., He J., Zhu C. In vitro cytotoxicity of Cu_2^+, Zn_2^+, Ag^+ and their mixtures on primary human endometrial epithelial cells. *Contraception*. 2012; 85(5): 509–18. https://doi.org/10.1016/j.contraception.2011.09.016
47. Li J., Liu X., Zhang Y., Tian F.F., Zhao G.Y., Yu Q.L.Y., et al. *Toxicol. Res*. 2012; 1(2): 137–44. https://doi.org/10.1039/c2tx20016c
48. Kasemets K., Suppi S., Künnis-Beres K., Kahru A. Toxicity of CuO nanoparticles to yeast *Saccharomyces cerevisiae* BY4741 wild-type and its nine isogenic single-gene deletion mutants. *Chem. Res. Toxicol*. 2013; 26(3): 356–67. https://doi.org/10.1021/tx300467d
49. Manusadžianas L., Caillet C., Fachetti L., Gylytė B., Grigutytė R., Jurkonienė S., et al. Toxicity of copper oxide nanoparticle suspensions to aquatic biota. *Environ. Toxicol. Chem*. 2012; 31(1): 108–14. https://doi.org/10.1002/etc.715
50. Mortimer M., Kasemets K., Vodovnik M., Marinsek-Logar R., Kahru A. Exposure to CuO nanoparticles changes the fatty acid composition of protozoa *Tetrahymena thermophila*. *Environ. Sci. Technol*. 2011; 45(15): 6617–24. https://doi.org/10.1021/es201524q
51. Ma H., Bertsch P.M., Glenn T.C., Kabengi N.J., Williams P.L. Toxicity of manufactured zinc oxide nanoparticles in the nematode *Caenorhabditis elegans*. *Environ. Toxicol. Chem*. 2009; 28(6): 1324–30. https://doi.org/10.1897/08-262.1
52. Naddafi K., Zare M.R., Nazmara S. Investigating potential toxicity of phenanthrene adsorbed to nano-ZnO using *Daphnia magna*. *Toxicol. Environ. Chem*. 2011; 93(4): 729–37. https://doi.org/10.1080/02772248.2011.552505
53. Kawahara M., Sadakane Y., Koyama H., Konoha K., Ohkawara S. D-histidine and L-histidine attenuate zinc-induced neuronal death in GT1-7 cells. *Metallomics*. 2013; 5(5): 453–60. https://doi.org/10.1039/c3mt20264j
54. Song W., Zhang J., Guo J., Zhang J., Ding F., Li L., et al. Role of the dissolved zinc ion and reactive oxygen species in cytotoxicity of ZnO nanoparticles. *Toxicol. Lett*. 2010; 199(3): 389–97. https://doi.org/10.1016/j.toxlet.2010.10.003
55. Wang W.X., Guan R. Subcellular distribution of zinc in *Daphnia magna* and implication for toxicity. *Environ. Toxicol. Chem*. 2010; 29(8): 1841–8. https://doi.org/10.1002/etc.229
56. Pavlica S., Gaunitz F., Gebhardt R. Comparative *in vitro* toxicity of seven zinc-salts towards neuronal PC12 cells. *Toxicol. In Vitro*. 2009; 23(4): 653–9. https://doi.org/10.1016/j.tiv.2009.03.003
57. Hsieh C.Y., Tsai M.H., Ryan David K., Pancorbo O.C. Toxicity of the 13 priority pollutant metals to *Vibrio fisheri* in the Microtox chronic toxicity test. *Sci. Total Environ*. 2004; 320(1): 37–50. https://doi.org/10.1016/s0048-9697(03)00451-0