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CLINICAL ASPECTS OF THE EFFECTS OF CADMIUM AND

LEAD COMPOUNDS IN THE LIVER (LITERATURE REVIEW)

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Annotation. *The important scientific problem of modern science is the issue of abilities and mechanisms of regulating the public health by influencing the environment, which contamination has become a global, stable and permanent factor, regardless today's development of science and technology. Some heavy metals, particularly lead and cadmium, are considered to be the main pollutants. They are mentioned in the «List of Controlled Toxic Substances» of the United States Environmental Protection Agency (US EPA). One of the main "targets" of Pb/Cd-induced toxicity is liver tissue. The use of biometals (zinc, iron, magnesium) prevents, reduces or completely eliminates the Pb/Cd-induced specific and nonspecific effects on the organ, cellular and molecular levels.*

Keywords: *biometals, cadmium, lead, metallothioneins, hepatotoxicity, environment.*

Formulation of the problem. In recent years, the problems of strategic and tactical approaches to improving the health of the population of different countries, including Ukraine, have become increasingly important. One of the most important scientific problems of our time is the question of the possibility and mechanisms of regulating the level of health of the population by influencing the quality of the living environment.

According to the United States Environmental Protection Agency (US EPA) and the European Chemical Agency (ECHA), the priority pollutants listed in the "List of Controlled Toxic Substances" are heavy metals [1].

The greatest health risks are heavy metals and their compounds, which are extremely dangerous and dangerous chemicals (hazard classes 1 and 2), in particular, lead (Pb) and cadmium (Cd) [2]. These toxicants are characterized by a high prevalence in the environment and the ability to harm the body with prolonged use, even in concentrations not exceeding existing hygienic standards. The danger of lead and cadmium is determined by the polytropism of their negative impact: accumulating in the body, they have the ability to interfere with metabolic cycles, quickly change its chemical form when moving from one environment to another, not subject to biochemical decomposition, enter into numerous chemical reactions with each other and with other chemical compounds, can cause a deficiency of essential elements, displacing them from the connection with

protein components [3]. This can lead to polysystemic involvement in the pathological process of vital organs and systems with the formation of functional and organic damage at the organ, cellular and molecular levels.

The purpose of the article. Analyze and evaluate pathophysiological, histological and histochemical changes in the liver, induced by toxic effects of lead and cadmium compounds, and identify promising ways to correct and prevent them based on available literature.

Analysis of recent research and publications. Direct hepatotoxic effects, which are inherent in lead, are realized by the direct action of xenobiotics on the processes of lipid peroxidation in liver tissue [4, 5]. Under conditions of chronic lead intoxication is the activation of lipid peroxidation processes with a simultaneous decrease in the activity of antioxidant enzymes, which leads to increased DNA fragmentation. Such deviations are also accompanied by changes in blood biochemical parameters (increased concentration of total bilirubin, alanine aminotransferase, γ-glutamyltranspeptidase and alkaline phosphatase) [6].

Lead-mediated hepatic hypercholesterolemia is associated with enzyme activation, involved in the synthesis of cholesterol (3-hydroxy-3-methylglutaryl-CoA reductase, farnesyl diphosphate synthase, squalene synthase), with a simultaneous decrease in the activity of enzymes (7-alpha-hydroxylase), which have a catabolic effect on cholesterol [7].

In the experimental work of A.A. Berrahal et al. it was demonstrated that the severity of functional and morphological changes in the liver in chronic lead intoxication depends on age. It was shown that in young animals exposed to the toxicant, a significant increase in the concentration of alanine aminotransferase and alkaline phosphatase was observed in the blood plasma, which was accompanied by a simultaneous decrease in albumin levels compared with the older group of animals [8].

The hepatotoxic effect of lead is confirmed by the formation of histological and histochemical pathological changes in the liver tissue. According to the results of studies by B.M. Jarrar et al., under conditions of chronic Pb-induced intoxication in hepatocytes revealed a significant nuclear polymorphism, moreover, some changes in Pb-associated pleomorphism resemble those usually observed in liver dysplasia and its carcinomatous lesions. Apoptic changes of hepatocytes are accompanied by edema of organelles, especially mitochondria, endoplasmic reticulum and rupture of lysosomes with leakage of lysosomal hydrolytic enzymes, causing hydropic cytoplasmic degeneration as an initial sign of liver cell necrosis [9, 10].

Chronic lead intoxication causes Kupffer cell hyperplasia, which usually correlates with the level of hepatocyte damage caused by the toxicant, and is considered by some authors to be a consequence of increased autophagy in liver tissue, which helps to eliminate the accumulated lead and is a protective mechanism of detoxification [9, 11]. A team of researchers led by A. Hegazy demonstrated that in animals that received for 8 weeks a 0.13% aqueous solution of lead acetate, there were changes in hepatocytes in the form of abundant lymphocytic infiltration, enhanced cell polymorphism, pyknotic nuclei

and areas of cell necrosis with overt moderate periportal fibrosis and severe vacuolar degeneration, which is associated with significant depletion of glycogen content. Ultrastructural examination revealed mitochondrial edema, appearance of interstitial inflammatory cells and scattered lead electron-dense inclusion bodies. Scientists believe that such Pb-induced pathomorphological changes in organ tissue can subsequently be naturally transformed into liver cirrhosis [12].

Lead has been reported to cause depletion of glycogen in hepatocytes, which may be due to the toxicant's effect on glucose absorption or on the activity of enzymes involved in glycogenesis and / or glycolysis [9, 12]. Chronic lead intoxication causes an increase in alkaline phosphatase activity, primarily in the canalicular membranes of hepatocytes [6, 8, 9, 12]. According to D.S. Aksu et al., Such an increase in alkaline phosphatase activity may indicate the need to transfer lead ions across cell membranes, where the enzyme is involved in the absorption and transmembrane transport of electrolytes [13].

The development of cadmium-induced hepatocellular trauma has many features in common with the formation of Pb-associated hepatotoxicity. The negative effect of cadmium on the hepatobiliary system is also mediated primarily by the formation of bonds with SH groups of molecules of mitochondrial protein structures and the development of oxidative stress, which causes depletion of cellular GSH content. In addition, cadmium competes with essential metals (zinc Zn, selenium Se, copper Cu and calcium Ca) [14], displacing them from metal-containing complexes, causing metabolic disorders, inhibition of energy generation by mitochondria and reducing the energy potential of cells, affects DNA repair systems and redox state, alters intercellular adhesion, inducing dissociation of the E-cadherin / β-catenin complex [15, 16].

The negative effect of cadmium on the hepatobiliary complex is closely related to the development of inflammatory foci in the liver, accompanied by infiltration of the organ by polymorphonuclear neutrophils, which, along with Kupffer cells, release pro-inflammatory substances and cause the development of necrosis. Studies by T. Yamano et al., conducted in the early XXI century, show that activated Kupffer cells, releasing a number of inflammatory mediators, subsequently increase the expression of adhesion molecules, which initiate a cascade of cellular and humoral responses leading to inflammation and secondary Cd-induced liver damage [15, 17].

The functioning of signaling systems for the expression of genes of pro-inflammatory and adhesion molecules provide active forms of oxygen, enhancing the activity of nuclear factor κB (NF-κB) and activator protein-1 (AP-1). In response to the increase in the level of pro-inflammatory factors in the liver, the production of glycoprotein of the acute phase of inflammation - C-reactive protein, the content of which shows a clear positive correlation with the level of serum cadmium accumulation [15, 18, 19].

As demonstrated by in vitro studies on rat, mouse and human hepatocytes, apoptosis plays an important role in cadmium hepatotoxicity, primarily due to the interaction of the toxicant with thiol groups in mitochondria. In a study on isolated liver mitochondria in mice, cadmium was shown to directly inhibit adenosine diphosphate-induced respiration, increases the ionic permeability of mitochondrial membranes, reduces their

transmembrane potential, causes the release of cytochrome C and induces the activation of caspases [20, 21].

In liver cells, cadmium causes the activation of caspase-9 and caspase-3, probably due to the release of cytochrome C from damaged mitochondria. Caspase-independent apoptosis may occur due to Cd-mediated effects on the tumor suppressor protein of p53, because Cd++ can replace Zn++ in the p53 structure, thereby compromising the recovery of p53-induced DNA damage or cell cycle arrest. Cadmium can also activate Ca++-a dependent protease of calpain, which plays an important role in the development of early stages of Cd-induced caspazone-independent apoptosis in hepatocytes [22, 23].

The main morphological manifestation of Cd-associated hepatocellular trauma is considered to be an increase in the hepatosomatic index and the formation of structural pathological changes in the liver tissue. Chronic cadmium intoxication causes general hydropic and local balloon dystrophy of hepatocytes, development of monocellular foci of necrobiosis and necrosis of liver cells with reactive moderate infiltration by lymphocytes and macrophages, phenomena of periportal fibrosis and vacuolar degeneration, uneven expansion of the lumen of sinusoids and a significant increase in their bulk density. Electron microscopic examination reveals changes in the shape and swelling of mitochondria, as well as signs of their biodegradation, reducing the bulk density of the profiles of the granular cytoplasmic network, which was accompanied by their degranulation, focal vacuolization, as well as the presence of small diffuse lipid inclusions in the cytoplasm [24, 25].

Since chronic intoxication with heavy metal compounds, in particular lead and cadmium, leads to the formation of pronounced functional and morphological changes in the liver, it is important to find effective means of prevention and elimination of their hepatotoxic effects.

Currently, one of the priority areas of medical science is the search for and use of biometals - biological antagonists of cadmium and lead, which would reduce the negative impact of these toxicants at the organ, cellular and molecular levels. Currently, the most studied biometals, which have antagonistic properties against cadmium and lead, are selenium, magnesium, iron and zinc [26].

Zinc is an important trace element that plays a key role in counteracting the toxic effects of heavy metals. Experimental work in mice, fish and hamsters proved the role of copper-zinc superoxide dismutase 1 (SOD1) and glutathione-associated enzymes in Zn-mediated protection against CD-induced cytotoxicity. SOD1 has been shown to protect cells from apoptosis by inhibiting caspase-9 activation and mitochondrial cytochrome C release, as well as by reducing chronic endoplasmic reticulum stress and glutathione by preventing cadmium intake by reducing its ZIP8 expression also helps protect against oxidative stress caused by heavy metals, including lead and cadmium [27].

A potential mechanism of Zn-mediated protection against Cd-induced cytotoxicity is competition for the system of ion transporters. In addition, G. Jacquillet et al. cadmium has been shown to induce apoptosis by activating caspase 3 in the cortical layer of the kidney, and zinc prevents apoptosis and necrosis by inhibiting it [28].

Zinc and iron (Fe), which are major scavengers of free radicals, play an important role in maintaining prooxidant and antioxidant status. The results obtained by J. Obaiah et al. indicate that Zn and Fe or their combinations reduced cadmium-induced oxidative stress in the liver and kidneys of rats. The use of zinc and iron both alone and in combination inhibited the formation of malonic dialdehyde in the liver and kidneys of experimental animals. The maximum decrease in malonic dialdehyde content was observed in the liver tissue of Cd-associated rats, in which zinc and iron were added to the diet for 15 and 30 days [29]. Based on the available literature publications, it has been suggested that Zn and Fe maintain the bioavailability of essential trace elements, thereby playing a role in the displacement of cadmium from metal-containing sites of enzyme binding. Zn and Fe have also been reported to protect against Cd-induced changes in both renal and hepatic tissue by direct or indirect induction of metallothioneins (MT), blocking the oxidative chain reaction and inhibiting the formation of lipid peroxidation products [30]. The increase in the level of metallothioneins in both studied tissues was probably due to the differential expression of the MT gene. The combined addition of Zn and Fe to the diet was more effective in the synthesis of metallothioneins and attenuation of Cd-induced cytotoxicity than the individual use of these trace elements [29].

Conclusions. Chronic lead and cadmium intoxication causes polysystemic involvement of vital organs and systems in the development of pathological processes at the organ, cellular and molecular levels.

The use of biometals - biological antagonists of cadmium and lead helps to prevent, attenuate or eliminate Pb / Cd-induced adverse specific and non-specific effects due to direct and indirect induction of metallothioneins, activation of the antioxidant defense system and reduction of the generation of reactive oxygen species.

Prospects for further research. Given the above, the analysis and evaluation of morphological changes in rat liver in the isolated exposure of lead acetate and its combinations with iron and zinc succinates is an urgent task of modern experimental medicine.

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HISTORY