DOI 10.26724/2079-8334-2025-1-91-191-198
UDC 611.12–053.13:546.48'131:546.461.4:616–091.8–092.9

V.F. Shatorna, L.L. Lomyha, O.S. Shevchenko
Dnipro State Medical University

THE INFLUENCE OF CADMIUM CHLORIDE ISOLATED ADMINISTRATION AND IN COMBINATION WITH COPPER OR ZINC SUCCINATE ON CARDIOGENESIS OF RATS

e-mail: verashatornaya67@gmail.com

Today cadmium is one of the most common pollutants among heavy metals in the Dnipro region. The negative impact of cadmium on the human cardiovascular system throughout life is generally recognized, however, there are still few results of research into the chronic impact of cadmium on cardiogenesis and the identification of effective bioantagonists capable of exerting a modifying effect on cadmium toxicity and restoring standard indicators of heart development. We conducted a study of the effect of cadmium chloride on cardiogenesis in embryos of "Wistar" rats with chronic isolated administration and in combination with copper or zinc succinate during the entire period of female pregnancy. The removed embryos and their hearts were weighed, fixed and embedded in paraplast for further histological studies. The obtained results confirmed the general tendency of the toxic effect of cadmium on cardiogenesis, which was reflected in the delay in the formation of compact myocardium, endothelial-mesenchymal transformations and reduction of cardiogel on the 13th day of embryogenesis. On the 20th day of the experiment, an increase in the thickness of the compact myocardium of the middle part of the ventricles and uneven thickening of the atrial myocardium was observed, which plays a compensatory role in chronic hypoxia of the myocardium. In the groups of combined administration of cadmium chloride with copper or zinc succinate, an antagonistic effect of these metals was observed in relation to the cardiotoxicity of cadmium chloride, which was reflected in the reduction of myocardial hypertrophy, especially in the group of the combination of cadmium and zinc.

Key words: heart, cardiogenesis, myocardium, cadmium, zinc, copper, rats, experiment.

В.Ф. Шаторна, Л.Л. Ломига, О.С. Шевченко

ВПЛИВ ІЗОЛЬОВАНОГО ВВЕДЕННЯ ХЛОРИДУ КАДМІЮ ТА У ПОЄДНАННІ З СУКЦИНАТОМ МІДІ АБО ЦИНКУ НА КАРДІОГЕНЕЗ ЩУРІВ

На сьогодні кадмій є одним з найпоширеніших полютантів серед важких металів у Дніпровському регіоні. Негативний вплив кадмію на серцево-судинну систему людини протягом життя є загальновизнаним, однак і досі мало результатів дослідження хронічного впливу кадмію на хід кардіогенезу та визначення ефективних біоантагоністів, що здатні здійснювати модифікуючу дію на токсичність кадмію і відновлювати стандартні показники розвитку серця. Нами проводилось дослідження впливу хлориду кадмію на хід кардіогенезу у ембріонів щурів лінії Wistar при хронічному ізольованому введенні та у поєднанні з сукцинатом міді або цинку впродовж всього періоду вагітності самиць. Вилучені ембріони та їхні серця зважувались, фіксувались та заливались у парапласт для подальших гістологічних досліджень. Отримані результати підтвердили загальну тенденцію токсичного впливу кадмію на хід кардіогенезу, що відображалось у затримці формування компактного міокарду, ендотеліально-мезенхімних перетворень та редукції кардіогелю на 13-ту добу ембріогенезу. На 20-тій добі експерименту спостерігалось збільшення товщини компактного міокарду середньої частини шлуночків та нерівномірне потовщення міокарду передсердь, що відіграє компенсаторну роль при хронічній гіпоксії міокарду. У групах комбінованого введення хлориду кадмію з сукцинатом міді або цинку спостерігався антагоністичний ефект зазначених металів відносно кардіотоксичності хлориду кадмію, що відображалось у зниженні гіпертрофії міокарду, особливо у групі поєднання кадмію та цинку.

Ключові слова: серце, кардіогенез, міокард, кадмій, цинк, мідь, щури, експеримент.

The work is a fragment of the research project "Biological bases of morphogenesis of organs and animals under the influence of microelements and ultramicroelements in the experiment", state registration No. 0118U006635.

Cardiovascular diseases are still the leading cause of death worldwide (ischemic heart disease – 13 % and the first place among all causes of death, stroke – 10 % and the third place) [13], in European countries the part of deaths from cardiovascular diseases is 42.5 %annually [8], in Ukraine the statistics are even more disappointing – 64.3 % of deaths are caused by cardiovascular diseases and this is one of the highest indicators among the countries of the world [3]. Over the decades, basic clinical, morphological, biological and statistical studies have identified age, heredity, sex, bad habits (smoking and excessive alcohol consumption), stress, nutrition, hypodynamism, obesity, diabetes and environmental pollution. Some studies have established that particles in the air, which contain an increased amount of heavy metals, are potentially dangerous for the cardiovascular system [7].

Cadmium is one of the most dangerous toxicants, as it is almost impossible to eliminate it from the environment, therefore it mostly accumulates in soils and enters the body of animals and humans through trophic chains [4]. With a half-life and elimination period of 10 to 30 years, cadmium has been classified as a Class I carcinogen (International Agency for Research on Cancer, 2012) and its using is restricted by international law. As a result of absorption of cadmium by the body, it is widely transported and distributed

in tissues and organs. Even in low doses, cadmium has a toxic effect on the body's immune response [9], reproductive system [1], cardiovascular system [14], etc.

A number of studies confirm the negative effect of cadmium on embryogenesis of humans and experimental animals [2, 5, 11], while there is less data on the effect of cadmium on cardiogenesis. Previous studies of the influence of cadmium on the development of the heart and blood vessels during embryogenesis have shown that different chambers of the heart react differently to the introduction of cadmium salts. Since the right side of the heart does not carry a large hemodynamic load during embryogenesis, the pulmonary blood circulation does not work at full strength, the effect of cadmium on the myocardium of this part of the heart is weakly expressed, while the left side, which is connected to the large blood circulation, has obvious damage. Cadmium chloride led to an increase in the layer of compact myocardium of all chambers of the heart and interventricular septum. In the same experiment, the combined effect of cadmium salts in combination with citrates of trace elements (germanium, cerium, and iodine+sulfur composite) was investigated as possible bioantagonists of cadmium toxicity. In these research groups the parameters of the compact myocardium were restored, which indicates the antagonistic nature of the effect of the studied substances on the cardiotoxicity of cadmium [5].

The purpose of the study was to determine the chronic effect of cadmium chloride on the early histo- and morphogenesis of the heart of rat embryos when administered isolated and in combination with copper or zinc succinate.

Materials and methods. The research was conducted on female 'Wistar' rats, which were kept in the vivarium of the State Medical University in accordance with the norms of the "European Convention for the Protection of Vertebrate Animals Used in Experiments and Other Educational Purposes" (Strasbourg, 18.03.1986), the principles of the Declaration of Helsinki, the General Assembly of the World Medical Association (2000), the Council of Europe Convention on Human Rights and Biomedicine (1997), the relevant provisions of the WHO, the "General Ethical Principles of Experiments on Animals", approved by the First National Congress of bioethics (Kyiv, 2001).

All pregnant female rats were divided into 4 groups and received the appropriate solutions daily intragastrically (through a probe): Group I – control (a physiological solution of the appropriate volume was administered; Group II – isolated administration of a solution of cadmium chloride at a dose of 2.0 mg/kg; III group – combined administration of cadmium chloride solution at a dose of 2.0 mg/kg and zinc succinate solution at a dose of 5 mg/kg; IV group – combined administration of cadmium chloride solution at a dose of 2.0 mg/kg and copper succinate at a dose of 0.1 mg/kg. 16 females in each group. Operative slaughter and collection of embryonic material took place on the 13th and 20th day of embryogenesis. Rats were removed from the uterus, weighed, photographed and fixed in 10 % neutral formalin solution for subsequent embedding in paraffin and preparation of histological preparations. Fixed embryos and hearts were embedded in paraplast and serial histological sections were made, which were stained with histological dyes, and a ZEISS Axiocam ERc 5s light microscopy camera with a P95-C 1/2" 0.5x adapter attached to the ZEISS Primo Star microscope was used to obtain digital images. In accordance with the tasks of the experiment, the main anatomical and morphological indicators of cardiogenesis were observed, described and measured on the 13th day, namely, the thickness of the myocardium of the ventricles, atria and trabeculae, their compactness, the presence of cardiogel, etc.; and the 20th day of the experiment – the thickness of the myocardium of the middle part of the ventricles, the thickness of the myocardium of the atria, to calculate the cardiofetal index (%), the weight indicators of the embryo as a whole were measured (mg), M±m; weight indicators of the isolated embryo heart (mg), M±m, which was calculated according to the formula: KFI=m/M *100 %, where KFI is the cardiofetal index, m – the mass of the embryo heart (mg), M – the mass of the rat embryo (mg).

Statistical analysis was carried out according to generally accepted methods using licensed statistical analysis programs Statistica v.6.1 (StatSoft Inc., serial number AGAR909E415822FA) and Microsoft Excel. Statistically significant differences between mean values in experimental groups were evaluated using ANOVA variance analysis. Differences between groups were considered significant at a value of $p<0.05$.

Results of the study and their discussion. In our experiment all females survived, remained active, consumed food well, and their fur was shiny and clean. On the 13th day the first part of the pregnant females was surgically removed. Embryos were removed from the uterus, carefully examined, the correspondence of the stage of development to the term of pregnancy was determined according to the classical international criteria of Hamburger end Hamilton (HH). 13-day-old embryos were subject to fixation with subsequent pouring into the paraplast for histological examination of the early embryonic heart.

The heart is one of the first organs that is laid during early embryogenesis, therefore the influence of environmental factors on the physiological state of the mother's body is extremely important for the normal development of the cardiovascular system during embryogenesis and postnatal development. The rat heart is formed from the mesoderm on the 9–10th day (11th stage of embryogenesis according to the HH) in the form of two hollow lateral tubes, which are modified very quickly: they merge into one, shift to a medial position and take the form of a simple endothelial tube, which begins abbreviation. Areas of splanchnotomes adjacent to the endothelial lining of the heart turn into myoepicardial plates, from which the myocardium and epicardium will be formed in the future. Due to increased growth in length, the heart forms bends (S-shaped heart stage), which give rise to the formation of the atrium and ventricle. The posterior end of the tube expands and forms a venous sinus and is separated from the anterior narrowed end – the arterial trunk – by a transverse band. Large veins flow into the venous sinus, and the abdominal aorta originates from the arterial trunk. Gradually, the venous sinus shifts cranially, covers the arterial cone and lays the formation of the atria, while the arterial trunk shifts caudally, actively grows and lays the formation of the ventricles of the heart. After the formation of sagittal partitions, the heart becomes four-chambered, trabeculae are formed in the ventricles. The heart and liver form a well-visible cardio-hepatic tubercle in the embryo, and at the 16th stage of development, which corresponds to the 13th day of rat embryogenesis, a four-chambered heart is normally observed (Fig. 1).

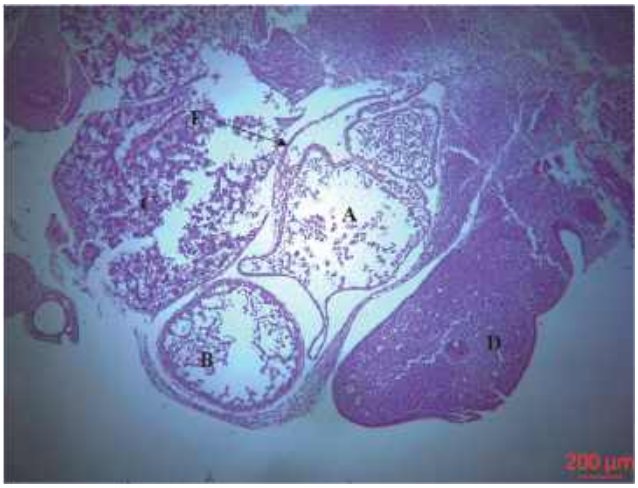

Fig. 1. Microphotograph of the heart-hepatic tubercle of a scour embryo fixed in preparation on the 13th day of the experiment. Magnification 4x10. A – embryonic atrium, B – embryonic ventricle, C – liver, D – tongue anlage, E – diaphragm anlagen.

Such complex locational and histological transformations cause a high level of vulnerability and affectivity of cardiogenesis to the influence of negative environmental factors, especially in regions with a significant industrial load. Research in recent decades has proven that heavy metals, even in small concentrations, are able to cross the placental barrier, accumulate in the tissues and organs of the mother and fetus, cause hypoxia and have a distant impact on postnatal development.

Analysis of histological sections of rat embryos on the 13th day of development revealed differences in indicators of embryonic heart development in different groups.

Thus, the average value of the thickness of the ventricular myocardium in the group of isolated introduction of cadmium chloride was 13.46±0.40 μm, which was statistically significantly different from the same indicator in the control group, in which the average thickness of the myocardium was 21.49±1.03 μm. That is a significant decrease in the thickness of the myocardium of the ventricles of the embryonic heart was observed. At the same time, in the groups of combined administration of cadmium chloride in combination with zinc succinate or copper, the formation of a ventricular myocardium layer with an average thickness of 22.10±1.09 μm in the group of cadmium chloride in combination with zinc succinate and 24.13±1.16 μm in the group was noted cadmium chloride in combination with copper succinate. These indicators had statistically significant differences in comparison with the group of isolated introduction of cadmium chloride.

Comparison of these parameters with the control group showed the mean value of ventricular myocardium thickness in the group of combined administration of cadmium chloride with copper succinate was statistically significantly higher than in the control group, and the average values of ventricular myocardium thickness in the group of combined administration of cadmium chloride with zinc succinate compared to controls did not have such a difference. Thus, on the 13th day of the experiment, the mediated isolated effect of cadmium chloride led to the thinning of the myocardium thickness of the ventricles of the heart of the embryos, the delay of cardiogenesis, which indicates the toxic effect of cadmium. And the combined administration of copper and zinc succinates with cadmium restored the investigated parameters of the heart. That is zinc succinate and copper succinate have a modifying effect on the cardiotoxicity of cadmium chloride in the specified doses and method of administration in an experiment on rats.

Also on the 13th day of cardiogenesis, we determined a different degree of formation and development of trabeculae in the ventricles of the heart of rat embryos and their formation was almost

absent in the atria. The different number of layers of cardiomyocytes in the structure of trabeculae and the density of their placement led to sufficient variability in their thickness and length indicators. The average value of the trabeculae thickness in the group of isolated exposure to cadmium chloride was 9.54±0.24 μm, which has a statistically significant difference from the average thickness of the trabeculae in the control group – 11.52±0.42 μm. In the groups of combined administration, the thickness of trabeculae was 10.84±1.15 μm when combining cadmium with zinc succinate, which has no statistically significant difference compared to the group of isolated administration of cadmium chloride and differs from the control group; and 13.92±1.12 μm in the group of combined administration of cadmium chloride with copper succinate, which, on the contrary, has a statistically significant difference in comparison with the group of isolated exposure to cadmium chloride and does not have such a difference with the control group.

Thus, it can be concluded that copper succinate and zinc succinate have pronounced bioantagonistic properties in relation to the negative effect of cadmium chloride on the formation of the trabecular myocardium of the heart of rat embryos in the experiment. However, the combined administration of cadmium with copper succinate leads to thickening of the wall and the thickness of the trabeculae of the embryonic heart on the 13th day of the experiment.

Comparison of the average values of atrial myocardium thickness indicates statistically significant differences in groups and, at the same time, does not have such a wide range of indicators as in ventricular myocardium, which is quite logical. Thus, in the control group, the average thickness of the atrial myocardium was 9.14±0.20 μm, while in the group of isolated exposure to cadmium chloride, this indicator was statistically significantly lower and was 8.00±0.27 μm. A significant difference was also observed between the indicators of the thickness of the atrial myocardium in the control group and the group of combined administration of cadmium chloride in combination with zinc succinate, since in the group of combined administration the thickness of the atrial myocardium increased to 12.66±0.45 μm. At the same time, when comparing the indicators of this parameter of the control group and the group of combined administration of cadmium with copper succinate, no statistically significant differences were observed, since the average value of the thickness of the atrial myocardium was 8.87±0.46 μm.

Thus, the influence of copper succinate and zinc succinate in combination with cadmium chloride had a rather pronounced multidirectional effect on the development of different chambers of the heart of rat embryos in the experiment. If in the ventricles of the embryonic heart in the group of combined exposure with zinc, the investigated indicators (thickness of the ventricles and thickness of the trabeculae) were restored towards the control ones, then in the atria a significant thickening of the myocardium was determined. And in the group of combined administration of cadmium with copper succinate, on the contrary, the indicators of the thickness of the wall of the atria of the embryonic heart were restored, and the thickness of the ventricles and the thickness of the trabeculae was the highest among all experimental groups on the 13th day of the experimental study.

Comparison of the average values of atrial myocardium thickness indicates statistically significant differences in groups and, at the same time, does not have such a wide range of indicators as in ventricular myocardium, which is quite logical. Thus, in the control group the average thickness of the atrial myocardium was 9.14±0.20 μm, while in the group of isolated exposure to cadmium chloride, this indicator was statistically significantly lower and was 8.00±0.27 μm. A significant difference was also observed between the indicators of the thickness of the atrial myocardium in the control group and the group of combined administration of cadmium chloride in combination with zinc succinate, since in the group of combined administration the thickness of the atrial myocardium increased to 12.66±0.45 μm. At the same time, when comparing the indicators of this parameter of the control group and the group of combined administration of cadmium with copper succinate, no statistically significant differences were observed, since the average value of the thickness of the atrial myocardium was 8.87±0.46 μm.

Thus, the influence of copper succinate and zinc succinate in combination with cadmium chloride had a rather pronounced multidirectional effect on the development of different chambers of the heart of rat embryos in the experiment. If in the ventricles of the embryonic heart in the group of combined exposure with zinc, the investigated indicators (thickness of the ventricles and thickness of the trabeculae) were restored towards the control ones, then in the atria a significant thickening of the myocardium was determined. And in the group of combined administration of cadmium with copper succinate, on the contrary, the indicators of the thickness of the wall of the atria of the embryonic heart were restored, and the thickness of the ventricles and the thickness of the trabeculae was the highest among all experimental groups on the 13th day of the experimental study.

In addition to the quantitative indicators, the difference in the density of the myocardium and the level of the extracellular matrix (cardiogel) residues drew attention. Cardiogel is an extremely important substance in the embryonic development of the heart of birds and mammals. Cardiogel contains glycosaminoglycans, which ensure the transport of cells formed by epithelial-mesenchymal transformations and are a substrate for the development of tissues of the early embryonic heart and its valvular apparatus. At the later stages of cardiogenesis, cardiogel is reduced and the degree of its reduction is one of the parameters of normal heart development. Thus, on the 13th day of the experiment in the group of isolated exposure to cadmium chloride, we observed a looser structure of the myocardium of the ventricles and trabeculae, as well as significant remnants of cardiogel around the trabecular structures in comparison with the control group, where cardiogel was visually observed only around the central trabeculae. In addition, the number of trabeculae in the group of isolated exposure to cadmium chloride was significantly lower than in the control group.

Taking into account the tendency to decrease the thickness of the ventricular myocardium and the delay in the reduction of the cardiogel, it can be assumed that cadmium chloride slows the growth and development of the heart in early embryogenesis with chronic exposure in the indicated dose and method of administration in rats.

In order to achieve the set purpose and fulfill the tasks of experimental research, we studied and calculated heart parameters at the end of embryogenesis of experimental animals. At the time of the birth of rat pups, their heart does not have a definitive state, because the structures of the valve apparatus and the septa of the chambers are not finally formed. Therefore, one of the most indicative parameters is the calculation of the cardiofetal index, which is the ratio of the weight of the heart to the weight of the embryo. For this purpose, on the 20th day of the experiment, we removed, weighed and prepared embryos in all experimental groups, removed the heart-lung complex, and inspected for signs of normal development. We then isolated the heart and weighed it on a torsion balance and fixed it for further histological studies.

Calculation of the cardiofetal index revealed the following trends. As the analysis and comparison of the obtained results showed, the isolated chronic exposure to cadmium chloride on a pregnant female leads to a decrease in the weight indicators of the weight of the heart of the embryos on the 20th day of the study. This difference is significant in comparison to the control group. In the group of combined exposure with copper succinate, heart mass was restored and had no significant difference from the control. When exposed to zinc succinate in combination with cadmium, the weight parameters of the heart were unreliably lower than the parameters of the group exposed to cadmium alone (Fig. 2).

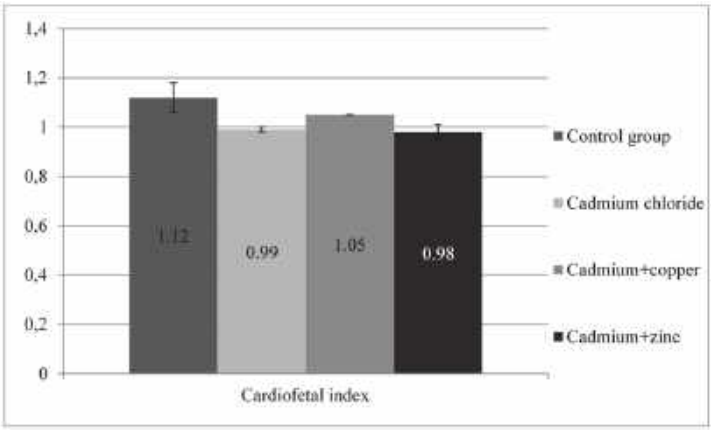

Fig. 2. Cardiofetal index of rat embryos on the 20th day of embryogenesis in all experimental groups.

To further investigate the isolated effect of cadmium chloride and in combination with copper or zinc succinates, we conducted histological studies of the obtained samples of rat embryonic heart. As the analysis of histological studies showed, in contrast to the results of the measurement of the thickness of the myocardium of the embryonic heart on the 13th day of the experiment in the group of isolated exposure to cadmium chloride, on the 20th day of the experiment we noted a significant increase in the thickness of the myocardium of the ventricles relative to the indicators of the control group. Thus, on the 20th day of embryogenesis, the thickness of the myocardium of the left ventricle in the group exposed to cadmium was 361.51±3.66 μm, while in the control group the average thickness of the myocardium was only 314.77±7.39 μm.

In the group of combined administration of cadmium chloride in combination with copper succinate we observed a statistically significant decrease in the thickness of the myocardium of the left ventricle not only in relation to the group of isolated administration, but also to the control group, and this indicator was 301.17±2.06 μm, while in in the group of combined administration with zinc succinate, the thickness of the myocardium reached 341.71±3.12 μm, which was statistically lower than the isolated injection group, and the indicator approached the control data.

The parameters of the wall thickness of the right ventricle differed from those of the left ventricle for groups of combined administration. If in the left ventricle with combined administration we observed a decrease in the thickness of the myocardium, then in the right ventricle this indicator did not have a statistically significant difference with the group of isolated administration of cadmium chloride and was 221.52±4.79 μm, in the group of administration of cadmium chloride – 218.54 ±4.92 μm. In the control group the thickness of the myocardium of the right ventricle was 183.50±11.26 μm, which indicates a significant difference both with the group of isolated introduction of cadmium chloride and in combination with copper succinate. In the group of combined exposure to cadmium chloride and zinc succinate, the thickness of the myocardium of the right ventricle decreased to the control indicators and was 194.85±3.07 μm.

Histological studies of the thickness of the atrial walls showed quite unexpected results, although the trend for both the left and right atria is quite distinct (Fig. 3).

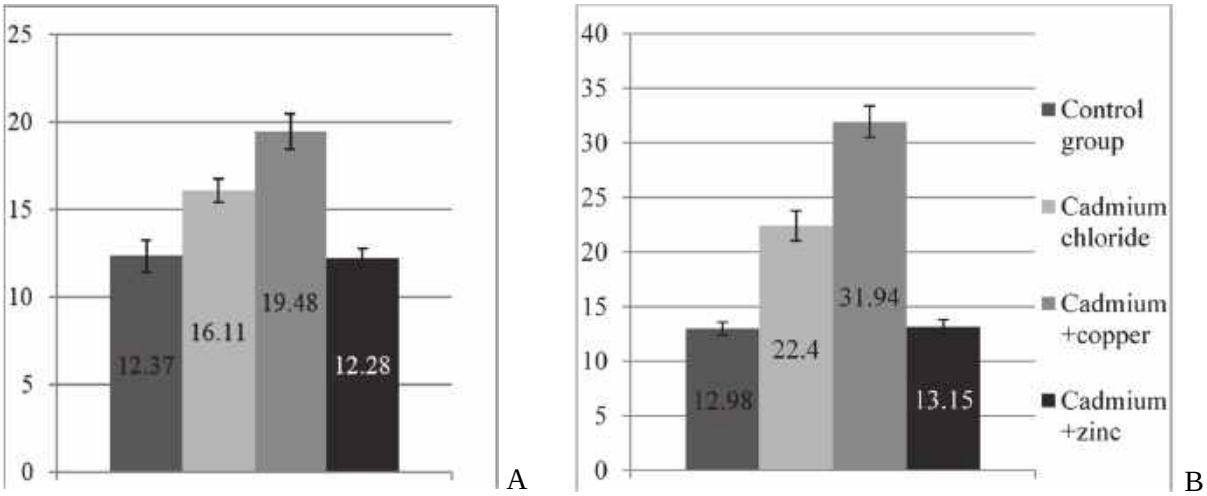

Fig. 3. Average thickness of the myocardium of the left (A) and right (B) atrium of the heart of rat embryos in all experimental groups on the 20th day of embryogenesis.

Simultaneous administration of cadmium chloride with copper succinate increased the tendency to thicken the myocardium of the left atrium, while the combination of cadmium chloride with zinc succinate, on the contrary, reduced this indicator to the level of the control group.

Thus, analyzing the quantitative indicators of the development of the myocardium of different chambers of the heart of rats at the final stage of embryogenesis, it can be assumed that zinc succinate has a more pronounced modifying effect on the cardiotoxicity of cadmium chloride, while no pronounced bioantagonistic properties were observed with the combined administration of cadmium and copper in a chronic experiment.

In addition to determining the quantitative parameters of the embryonic heart on the 20th day of the experiment we conducted a detailed study of structural changes in the myocardium and blood vessels. On histological preparations, a high level of blood filling of the cavities of the chambers of the heart and blood vessels was visually determined in the group of isolated exposure to cadmium chloride compared to the control. We explain this fact by the hypoxic state of heart structures, which provokes chronic exposure to cadmium. As a reactive response of the organ to hypoxia, the diameter of blood vessels expands, their level of blood filling increases, which is reflected in the photo.

According to the results of histological studies, we determined the expansion of the diameter of subepicardial vessels with a high level of blood filling, which is a peculiar marker of the hypoxic state of the embryo. Since the establishment and development of these vessels occurs in parallel with compaction of the compact myocardium, the degree of their blood supply is a certain criterion for assessing the functional state of the ventricles and indicates an increased level of blood circulation in the embryonic heart. In both groups of the combined effect of succinates with cadmium chloride on the 20th day of embryogenesis, a high level of blood filling of vessels and chambers of the heart was also observed, an increase in the diameter of subepicardial vessels was determined, which indicates that the myocardium is suffering from hypoxia. We explain this condition of the walls of the heart by the continuation of the negative effect of cadmium chloride upon combined administration in a chronic experiment on rats.

Thus, experimental studies proved that both the isolated chronic exposure to cadmium chloride and the combined administration of cadmium with copper and zinc succinates provoke a hypoxic state of the

myocardium of the ventricles, which is manifested by the expansion of blood vessels and a high level of their blood filling.

The results obtained during the experiment confirm the general trend regarding the cardiotoxic effect of cadmium chloride during the embryogenesis of rats, which was already reflected in a number of publications [5, 11, 12]. It was confirmed that chronic intragastric administration of cadmium chloride to pregnant female rats slows down the development of the myocardium during early embryogenesis, as well as hypertrophy of the walls of the embryonic heart at the final stage of development. This indicates a significant hypoxic effect of cadmium and the presence of compensatory mechanisms during cardiogenesis.

The combined administration of cadmium chloride with copper or zinc indicated the bioantagonistic nature of the interaction between cadmium and zinc, which was also recorded in previous studies [6, 10]. Unfortunately, it is currently quite difficult to compare the results obtained by us on the modifying effect of copper on the course of cardiogenesis during chronic exposure to cadmium chloride, since there is lack of data on the simultaneous effect of these metals on cardiogenesis in experimental animals. In addition, the concentrations, duration, and methods of administration of cadmium, zinc, and copper varied significantly.

Conclusions

The results obtained by us allow us to draw the following conclusions and generalizations:

1. Cadmium chloride in a dose of 2 mg/kg with chronic isolated administration slows down the development of the heart during early embryogenesis, which is characterized by a decrease in the thickness of the myocardium of the ventricles and distinct remnants of cardiogel on the 13th day of the experiment. At the final stages of embryogenesis, cadmium chloride increases the thickness of the myocardium of all heart chambers and has a hypoxic effect on the walls and vessels of the embryonic heart.

2. The combined administration of cadmium chloride in a dose of 2 mg/kg with copper succinate 0.1 mg/kg had a multidirectional effect on the development of the heart of rat embryos: on the 13th day of the experiment, the index of the thickness of the myocardium of the atria and trabeculae approached the control group and had a statistically significant difference with the isolated exposure group. At the same time, the thickness of the myocardium of the ventricles of the embryonic heart at this stage of cardiogenesis exceeded the indicator of both the isolated injection group and the control group. On the 20th day of the experiment, we observed the opposite effect: in the left and right atria, the highest myocardial thickness indicators were recorded in the group of simultaneous administration of cadmium chloride and copper succinate, where the myocardial thickness indicators significantly exceeded this indicator in both the isolated administration group and the control group. The comparison of the average values of the thickness of the myocardium of the left and right ventricles in the group of combined administration of cadmium and copper to the groups of isolated exposure and control group was unexpected. We observed a tendency to restore the indicator in the right ventricle to the control indicators, and in the left ventricle a significant decrease of this indicator relative not only to the group of isolated introduction of cadmium chloride, but also to the control group.

3. The combined administration of cadmium chloride at a dose of 2 mg/kg and zinc succinate at a dose of 5 mg/kg showed the following results: during early cardiogenesis in this group, a tendency to decrease the negative effect of cadmium chloride was observed, as the thickness of the ventricular myocardium approached the control indicators and was statistically significant in relation to the group of isolated introduction. At the same time, the thickness of the trabecular myocardium was lower than the control values, but higher than the group of isolated exposure, the thickness of the atrial myocardium, on the contrary, statistically exceeded the control values. On the 20th day of cardiogenesis we observed the modifying effect of zinc succinate on the formation of the myocardium of all chambers of the rat heart, because the indicators of wall thickness were statistically significantly lower than the group of isolated exposure and approached the control values.

4. Analyzing the modifying effect of copper and zinc succinate on the cardiotoxic effect of cadmium chloride, it can be noted that both metals have bioantagonistic properties in relation to cadmium and cause a corrective effect on rat cardiogenesis both in early and late embryogenesis. Particular attention was paid to the indicators of the thickness of the myocardium on the 20th day of the experiment when cadmium chloride was combined with zinc succinate in the indicated doses, since the indicators of this group approached the corresponding indicators in the control group.

Prospects for further research. In our opinion, studies on the accumulation of cadmium in embryos of different groups and immunohistochemical studies of basic histogenetic processes in the heart of the embryo and their changes during embryonic development are promising.

References

1. Kolosova I. Nakopychennya kadmiyu v yayechnykakh shchuriv pry izol′ovanomu vvedenni soley kadmiyu ta v kombinatsiyi z tsytratamy tseriyu y hermaniyu. Visnyk problem biolohiyi i medytsyny, 2020;4(158):60-65. DOI:10.29254/2077-4214-2020-4-158-60-65 [in Ukrainian].
2. Rudenko KM, Kolosova II. Vplyv khlorydu kadmiyu ta suktsynatu midi na pokaznyky smertnosti v embriohenezi bilykh shchuriv. The 3 rd International scientific and practical conference «Topical issues of modern science, society and education» (October 3-5, 2021) SPC – Sci-conf.com.ua, Kharkiv, Ukraine. 2021;1096 p. [in Ukrainian].
3. Sertsevo-sudynni zakhvoryuvannya – holovna prychyna smerti ukrayintsiv. Vysnovky z doslidzhennya Hlobal′noho tyaharya khvorob u 2019 rotsi. Public Health Center of the Ministry of Health of Ukraine https://phc.org.ua/news/sercevo-sudinni-zakhvoryuvannya-golovna-prichina-smerti-ukrainciv-visnovki-z-doslidzhennya [in Ukrainian].
4. Chorna VI, Voroshylova NV, Syrovatko VO. Rozpodil kadmiyu v gruntakh Dnipropetrovs′koyi oblasti ta yoho akumulyatsiya v produktsiyi roslynnytstva. Ukrainian Journal of Ecology, 2018;8(1):910–917. DOI:10.15421/2018_293 [in Ukrainian].
5. Azarov OI, Nefodova OO, Halperin OI, Solomenko MV, Zhitniy MI, Kononova II, Frolova GM. Effect of metal citrates on indicators of the embryotoxicity of cadmium salts in rats with combined introduction. World of Medicine and Biology. 2021;1(75):176-181. DOI 10.26724/2079-8334-2021-1-75-176-181.
6. Erdem O, Yazihan N, Kacar Kocak M, Sayal A, Akcil E. Influence of chronic cadmium exposure on the tissue distribution of copper and zinc and oxidative stress parameters in rats. Toxicol Ind Health. 2016;32(8):1505-1514. DOI: 10.1177/0748233714566875.
7. Fine LJ, Joubert B, Nadadur S. Stimulating intervention research to reduce cardiopulmonary impacts of particulate matter in air pollution among high-risk populations. 2020, October 5. https://grants.nih.gov/grants/guide/notice-files/NOT-HL-20-788.html.
8. Kryuchkov I. Cardiovascular diseases kill 10 000 people in the WHO European Region every day, with men dying more frequently than women. Copenhagen, Denmark, 15 May 2024. World Health Organization https://www.who.int/europe/news/item/15-05-2024-cardiovascular-diseases-kill-10-000-people-in-the-who-european-region-every-day--with-men-dying-more-frequently-than-women
9. Kulas J, Ninkov M, Tucovic D, Popov Aleksandrov, Ukropina M. Subchronic Oral Cadmium Exposure Exerts Both Stimulatory and Suppressive Effects on Pulmonary Inflammation/Immune Reactivity in Rats. Biomed. Environ. 2019;32 (7):508–519. DOI: 10.3967/bes2019.068.
10. Nasiadek M, Stragierowicz J, Kilanowicz A. An Assessment of Metallothionein–Cadmium Binding in Rat Uterus after Subchronic Exposure Using a Long–Term Observation Model. International Journal of Molecular Sciences. 2022; 23(23):15154. https://doi.org/10.3390/ijms232315154
11. Nefedova OO, Halperin OI, Shatorna VF, Shevchenko IV, Demidenko YUV, Pridius IO, Myasoyed YUP. Experimental determination of the accumulation of cadmium salts in the heart of the embryo of rat and their effect on rat cardiogenesis. Medychni perspektyvy. 2020;25(3):8-16. https://doi.org/10.26641/2307-0404.2020.3.214628.
12. Nefodova O, Zadesenets I, Shevchenko O. The effect of cadmium salts on the development of vessels and atrioventricular valves of rat heart under the conditions of zinc citrate correction. Modern Science – Moderni věda 2020;2:116-123.
13. The top 10 causes of death. World Health Organization https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death
14. Tinkov AA, Filippini T, Ajsuvakova, OP, Skalnaya, MG, Aaseth J, Bjørklund G. Cadmium and Atherosclerosis: A Review of Toxicological Mechanisms and a Meta-Analysis of Epidemiologic Studies. Environ. Res. 2018;162:240–260. DOI: 10.1016/j.envres.2018.01.008.

Стаття надійшла 27.01.2024 р.