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CONTENTS

EXPERIMENTAL DETERMINATION OF THE INFLUENCE OF CADMIUM SALT ON CARDIOGENESIS OF A RAT

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Annotation. *The results of an experimental effect on the cardiogenesis of intragastric administration of cadmium chloride / cadmium citrate to pregnant female rats are discussed in the article. Except for groups of isolated cadmium salts administration, there were groups of combined administration of cadmium with citrates of germanium, cerium and composite iodine + sulfur. The second task was to study the effect of the studied salt solutions on the cardiogenesis of rat embryos, for which serial histological sections of the heart were made and the thickness of the chambers of the heart and interventricular septum were measured. The thickness of the compact myocardium of the heart chambers was measured as the main indicator of cardiogenesis.*

The effect of the indicated doses of cadmium salts on cardiogenesis in rats influenced differently on the thickness of the myocardial layer of various chambers of the heart: cadmium chloride thickened the wall of the left and right ventricle, both atriums with thickening of the interventricular septum. Cadmium citrate provokes thinning of the myocardium of the walls of both ventricles and local thickening of the interventricular septum. In the groups of combined administration, indicators of the thickness of the compact myocardium recovered, which indicates the modifying effect of citrates of the studied microelements on the cardiotoxicity of cadmium salts.

Key words: *rat embryo, cardiogenesis, cadmium, metal citrate, heart.*

Formulation of the problem. Increasing urbanization will inevitably complicate the environmental situation in areas occupied by industrial enterprises, transport highways together with adjacent territories. The influence of heavy metal compounds during prenatal development period, when major morphogenetic events occur and restructuring of the structural components of the embryo happen, birth defects are formed was studied. Data collected during this age period is of particular importance concerning the development and formation of the organism.

Among the urgent fundamental and applied problems of modern morphology, the attention of researchers is attracted by the study of regularities of the basic processes of morphogenesis and organogenesis under the influence of adverse environmental factors, among which heavy metal compounds are the most harmful [1,2].

Analysis of recent research and publications. Human activity has led to the redistribution of microelements, increase of the pollution of the environment with toxic substances, that is why modern medical researchers are paying more attention to

microelements and microelementosis. The stability of the chemical composition is one of the most important and necessary conditions for the normal functioning of the body. Deficiency of vital microelements and increased concentration of toxic in the environment lead to adverse effects on human life and the course of embryogenesis and organogenesis [3, 4]. The mechanisms by which cadmium may contribute to cardiovascular disfunction are being actively investigated: increase of blood pressure, increase of blood cholesterol level, increase of mutations in arterial wall cells [5, 6]. Cadmium, as some other metals, directly affects the vascular endothelium, which is accompanied by endothelin secretion, to which mast cells have specific receptors. The mechanism of action of endothelin is associated with activation of calcium ion input through potential-dependent calcium channels [7]. Contineous influense of cadmium cloride on the bodies of experimental animals leads to considerable morphological changes of the myocardium at all levels of its structural organization. Together with significant increase in the mass of different parts of the heart, dilatation of their chambers, injury of cardiomyocytes, endothelial cells, reduction of the reserve volumes of the ventricles, reduction of the capacity of the arteries, expansion of the venous part of the heart, hypoxia, etc. [8, 9, 10, 11], however, the effect of cadmium on the development of the heart during embryogenesis remains a poorly understood area. Thus, an actual trend in morphological experimental studies is to identify the spectrum of cardiogenesis disorders under the influence of cadmium salts on pregnant females and during compensation.

The purpose of the article – to determine experimentally the effect of cadmium salts administration on the course of cardiogenesis of rats. And to compare the influence when administration of cadmium salts is isolated and in combination with metal citrate.

Materials and methods. Experimental studies were performed on female rats of the strain Wistar (ursery «Далі», c. Kiev). Before the experiment, all animals were examined, weighed. Their motor activity and skin condition were taken into account. After external inspection and culling, the experiment started simultaneously with the control group. Rats were in the vivarium of State Institution Dnipropetrovsk medical academy of Health of Ukraine before and during the experiment. At a temperature of 20-25oC, humidity of not less than 50%, in ventilated rooms and day / night light mode in standard plastic cages no more than 3-4 species in each. On a standard diet. For carrying out the embryological experiment, females with a dated pregnancy calculated by the method of vaginal smears. To simulate the effects and toxic effects of exposure to cadmium salts, we administered enteral solutions of the test substances daily to pregnant females of the Wistar rats throughout pregnancy. The solutions of germanium citrate, cerium, sulfur composite and iodine obtained by aquananotechnology were used in experimental models. Citrates (citric acid salts) of biometals are safe. Moreover, they have antioxidant and radioprotective effect, have a positive effect on the cardiovascular and immune systems of the body. All rats were divided into 8 groups:

Group 1 - control (n females = 8; n 13th day embryos = 77; n 20th day embryos = 76); Group 2 - animals that were administered a single solution of cadmium chloride at a dose of 1.0 mg / kg (n females = 8; n 13th day embryos = 68; n 20th day embryos

= 63); Group 3 - animals that were administered a single solution of cadmium citrate at a dose of 1.0 mg / kg (n females = 8; n 13th-day embryos = 69; n 20th-day embryos = 70); Group 4 - animals who were administered a solution of cadmium chloride at a dose of 1.0 mg / kg and a solution of cerium citrate at a dose of 1.3 mg / kg (n females = 8; n embryos of the 13th day = 70; n embryos of the 20th day == 68); Group 5 - animals that were administered a solution of cadmium citrate at a dose of 1.0 mg / kg and a solution of cerium citrate at a dose of 1.3 mg / kg (n females = 8; n embryos of the 13th day = 71; n embryos of the 20th day = 72); Group 6 - animals who were administered a solution of cadmium chloride at a dose of 1.0 mg / kg and a solution of germanium citrate at a dose of 0.1 mg / kg (n females = 8; n embryos of the 13th day = 70; n embryos of the 20th days = 68); Group 7 - animals who were administered a solution of cadmium citrate at a dose of 1.0 mg / kg and a solution of germanium citrate at a dose of 0.1 mg / kg (n females = 8; n embryos of the 20th day = 71); Group 8 - animals who were administered a solution of cadmium chloride at a dose of 1.0 mg / kg and a solution of citrate sulfur and iodine at a dose of 0.003 mg / kg (n females = 8; n embryos of the 13th day = 71, n embryos of the 20th days = 73),

On the 13th and 20th day of embryogenesis, an operative slaughter of animals was performed. Embryos were removed from the uterus, weighed, length was measured, photographed, and the heart was removed for further histological examination. Taking into account the specificity of the goal of the study, the following indicators of cardiogenesis were quantified on the histological sections :

- cardiofetal index (%), M±m; which we calculated by the formula:

$$КФИ = \frac{m}{M} \times 100\%$$

- where CFI – cardiofetal index;
- m – weight of the heart;
- M – the weight of the rat embryo.

- thickness of compact atrial and ventricular myocardium of normal embryo heart and in experiment (μm), M±m;

- thickness of the interventricular septum of normal embryo heart and in experiment (μm), M±m;

A camera for light microscopy ZEISS Axiocam ERc 5s with adapter P95-C 1/2" 0,5x was used to obtain digital images with subsequent size calculation of structures. Determination of heart structures sizes was performed using ZEN 2.0 software, which is software for ZEISS Primo Star series light microscopes. We used software tools to measure the linear dimensions of structures.

Statistical analysis and analysis of results were performed according to conventional methods using licensed statistical analysis software Statistica v.6.1 (StatSoft Inc., Serial

No. AGAR909E415822FA) and Microsoft Excel. The probability of statistical studies was performed using Student's t-test.

Animal studies were conducted in accordance with the "General Ethical Principles for Animal Experiments" (Kyiv, 2001), which are consistent with the European Convention for the Protection of Experimental Animals (Strasbourg, 1985).

Results and Discussions. All experimental females survived, normally consumed food, moved actively, had no external signs of disease. We have not detected external injuries, ectopia, hernias and other defects after the administration of indicated doses to embryos. Cosequently, cadmium salts and other test substances did not cause teratogenic effect with this route of administration and doses.

Disruption of the course of cardiogenesis in the experiment was already detected at the level of determination of the heart weight of embryos of rats, namely: in the cadmium intoxication group, not only the weight loss of the embryos was observed, but also a significant decrease in the weight of the heart. In order to eliminate errors regarding the effect of weight loss of embryos and heart weight on cardiotoxicity indices, we calculated the cardiofetal index. According to analysis of the results obtained, there are changes not only in the number of live embryos in the afterbirth, but also changes in the massometric parameters of the embryos themselves when pregnant female is exposed to cadmium chloride. Thus, with respect to the control group, a significant decrease in the number of live embryos was determined in the cadmium salts influence group, although the average fetal and heart mass values did not have a significant difference (table 1).

Table 1

Indicators of the number and weight of rat embryos and cardiofetal index on the 20th day of embryogenesis in groups of isolated administration

Indicator	Control	Influenced groups	
		Cadmium chloride	Cadmium citrate
Number of live fetuses per female	9,50±0,13	7,88±0,40*	8,75±0,27*
Body weight of 1 fetus, g	2,76±0,07	2,72±0,08	2,64±0,05
Embryo heart mass, mg	34,08±0,53	34,80±0,58	31,10+1,29*
Cardiofetal index	1,23±0,02	1,33±0,04*	1,22±0,06

*Note. * - $p<0,05$; in relation to control.*

At the same time, the quantitative indices of the embryos in the cadmium citrate exposure group were closer to the controls, and the heart mass decreased compared to both groups. An increase in the index of cardiofetal index in the group of exposure to cadmium chloride indicates an increase in weight indicators of the heart in the group while reducing the body weight of the embryo due to intoxication. In the cadmium citrate exposure group, the index of cardiofetal index was almost equal to the control value, although embryo body weight was the lowest of the studied groups.

Analysis and calculation of changes in the mean values of fetus number, heart mass,

and cardiofetal index in the groups of combined administration of cadmium chloride with metal citrate and iodine + sulfur composite showed the following dynamics (Table 2). The highest number of fetuses per female was observed in the group of combined introduction of sulfur and iodine. This indicator had no significant difference with the control group, but was significantly higher than the isolated cadmium chloride administration group ($p \leq 0,001$).In groups with combined administration of cerium citrate and germanium the number of embryos was significantly fewer than in the control group($p \leq 0,05$), but still higher than the cadmium chloride isolated administration group. The weight of the embryo in the presented groups did not have a significant difference, but we found a tendency to increase of the heart mass in the groups of combined administration. The highest indicator was in the group with iodine and sulfur. This situation led to a significant increase in cardiofetal index to 1,97±0,11, which exceeded not only the control values, but also this indicator in the group of isolated administration of cadmium chloride (table 2).

Table 2

Indicators of the number and weight of rat embryos and cardiofetal index on the 20th day of embryogenesis in groups with administration of cadmium chloride in different combinations.

Indicator	Cadmium chloride + cerium citrate	Cadmium chloride + germanium citrate	Cadmium chloride + composite iodine + sulfur
Number of live fetuses per female	8,25±0,40	8,50±0,20	9,13±0,13
Body weight of 1 fetus, g	2,71±0,05	2,71±0,04	2,68±0,04
Embryo heart mass, mg	33,04±3,41	40,01±1,82	46,10+3,59
Cardiofetal index	1,22±0,06	1,48±0,03	1,97±0,11

Comparison of the presented data demonstrates the modifying effect of metal citrate and iodine + sulfur composite on the embryotoxicity and cardiotoxicity of cadmium chloride when combined in rats at indicated doses and route of administration.

The analysis of the studied indicators in the groups of combined introduction of these elements with cadmium citrate had the following trends (table.3). As you can see from the calculations, the highest number of embryos is observed in these groups. That is, cerium citrate and germanium reduce the embryotoxic effects of cadmium citrate compared to the isolated administration group. Average values of embryo mass and heart mass also increase, which in turn leads to an increase in cardiofetal index in embryos that have undergone the influence of these factors. Compared to control group, the cardiofetal index increases in the following directions: in the group of cadmium citrate + cerium citrate in 1.18 times, and in the group of cadmium citrate + germanium citrate in 1.19 times. This indicates a possible myocardial hypertrophy and dilation of the heart chambers in the experimental embryos. Such data can be considered as a result of the compensatory action of germanium and cerium on the cardiotoxicity of cadmium citrate.

Table 3

Indicators of the number and weight of rat embryos and cardiofetal index on the 20th day of embryogenesis in in groups with administration of cadmium citrate in different combinations

Indicator	Cadmium citrate + cerium citrate	Cadmium citrate + germanium citrate
Number of live fetuses per female	9,00±0,29	8,88±0,24
Body weight of 1 fetus, g	2,78±0,06	2,73±0,05
Embryo heart mass, mg	40,04±5,80	40,06±2,53
Cardiofetal index	1,45±0,07	1,46±0,07

Based on the results of the calculation of the number and weight of embryos of all the experimental groups, we can conclude that the cadmium citrate is less embryotoxic compared to cadmium chloride and determine the modifying effect of cerium citrate, germanium, iodine + sulfur on embryotoxicity and cardiotoxicity.

To achieve this goal, we conducted morphometric studies of the histological sections of the embryos hearts of all experimental groups. To determine the morphogenetic changes of the heart chambers under the influence of cadmium salts, we determined the thickness of the compact ventricular myocardium, interventricular septum and atrium on the 13th and 20th days of the experiment.

Investigating the heart-formation processes of rats on the 13th day of embryogenesis and the formation of the walls of the heart chambers, we made serial histological sections of the whole embryo to determine the correspondence to the normal course of cardiogenesis. The process of heart septation begins with delamination of the upper part of the ventricular myocardium. Endocardial cushions play a significant role in the formation of the cusps. Endocardial cushions are transient organs for future atrial-ventricular valves. Together with the formation of valves of the atrioventricular orifice, the formation of the papillary-trabecular apparatus of the ventricles and the atrium of the heart of the embryo occure.

The myocardium of the ventricles is divided into 2 plates due to the delamination: internal, which together with the remnants of the endocardial cushions initiates the formation of valve cusp. It forms the primary tendon string, and the primary mastoid muscles. The formation of tendon strings, trabecular myocardium, and ventricular pelvic muscles is the process that occurs together with the formation of valve cusps during the delamination process. The endocardial cushions continue into the conotrunk in the form of endocardial ridges that further participate in the distribution of total conotrunk on the aorta and pulmonary trunk. Particulary during this period of cardiogenesis the primary myocardial layer of the ventricles of the embryonic heart is rebuilt and compact and trabecular layers of the wall of the heat are formed. In general, the heart of the embryo is formed for this period of development, the ventricles are separated from the atrium by the atrioventricular valve, the endocardial cushions are filled with mesenchymal cells. We also investigated the processes of septation of the chambers of the heart, namely

the formation of the interventricular septum. The muscular part of the interventricular septum, which was formed as an outgrowth of the myocardium of the primary ventricles to the atrioventricular orifice, was determened during the study period. The upper part of the septum (membranous) has a completely different origin. It is an outgrowth of endocardial cushions of atrioventricular canal. Combining these two sources gives begining to the interventricular septum.

Investigating the results of the influence on the development of the heart of cadmium salts, we compared ventricular myocardial thickness and determined the compliance of the heart development with the standart criteria. Under the influence of cadmium chloride administration on the 13th day of embryogenesis we determined a 26-29% thickening of the ventricular wall in comparison with the control group. Although no significant changes in ventricular wall thickness were detected in the cadmium citrate exposure group, but the thickness of the atrium increased significantly in comparison with the control group. The primary venous sinus is the source of the origin of the embryonic human atrium and the formation of the atrium in time is lagging behind the formation of the ventricles, where cardiomyocytes develop and specialize earlier. Therefore, in response to the influence of the exogenous factor, the response of early atriums and ventricles is quite different.

The study of morphometric parameters demonstrated the influence of the investigated cadmium salts on cardiogenesis on the 13th day of embryonic development. Determining the thickness of the atrium in the influenced groups, we measured the thinnest and thickest sections of the walls due to the significant heterogeneity of the structure of these heart chambers. In the control group this indicator reached 25,38 ± 1,60 μm and 43,75 ± 1,06 μm, when exposed to cadmium chloride, the atrium wall was 30.63 ± 1.28 μm and 53.25 ± 1.92 μm therefore the the thickness was determined at this stage ($p \leq 0.05$). Exposure to cadmium citrate did not show a significant difference with the control group and was 21.38 ± 0.64 and 42.85 ± 0.71 μm, respectively. But it should be noted that in 27.3% of embryos the thickness of the atrium clearly increased compared to the control group($p \leq 0.05$). Namely, it was 28.31 ± 2.52 μm and 67.75 ± 4.14 μm, respectively, in the thin and thick regions.

The thickness of the ventricular wall of the early embryonic heart (13th day) in the control group was 61.13 ± 2.44 μm, and when exposed to cadmium chloride, it thickened to 64.87 ± 1.24 μm. The effect of cadmium citrate did not lead to a significant difference with this indicator in control group and constituted 61.88 ± 1.28 μm. The study of the formation processes of the interventricular septum showed no disorder in the formation of this structure, which is important for the septation of the heart. The interventricular septum at this stage of development consisted of a muscular ridge that grew in the direction of the longitudinal axis of the heart from the apex to the atrioventricular canal. The measurements were carried out in the middle part of the interventricular septum and showed the following changes in the formation of the thickness of the myocardial septum: in the control group it was 420.75 ± 7.82 μm, in the group of exposure to cadmium chloride it was 441.16 ± 3.06 μm, and under the influence of cadmium citrate it

was 415.50 ± 2.77 μm. Thus, according to the results of morphometric studies in 13-day-old embryos that have been exposed to cadmium salts, the following changes occur in the development of heart chambers: administration of cadmium chloride to females leads to increased thickness of the atrium, ventricles, and interventricular septum, and the effect of cadmium citrate is not significant in comparison with control group.

The thickness of the ventricle on the 20th day of embryogenesis was determined taking into account the peculiarities of the structure of the heart chamber in 3 zones: apical part, middle part and basal part. In the control group, the lowest indicators of the thickness of the compact myocardium of the ventricles were determined in the apical part of the left and right ventricles and were respectively: 241.38 ± 10.34 μm and 163.38 ± 4.11 μm. The most significant is the compact myocardium of the middle part of the ventricles, which thickness in the control group reached 512,13 ± 3,98 μm in the left and 314,88 ± 5,17 μm in the right. The thickness of the interventricular septum (in its middle part) in this group was 420.75 ± 7.82 μm. The atria had a distinctly heterogeneous thickness, so measurements were made of the thinnest and thickest sections of the wall for further calculation. The thickness of the myocardium of the right atrium ranged from 40.25 ± 1.33 μm, 133.63 ± 2.79 μm, the left - 52.13 ± 1.86 and 142.63 ± 3.71 μm. At this stage of development well-formed trabeculae and considerable epicardial layer were in control group.

In the ventricles, the compact myocardium contains advanced vessels, and the trabecular layer consists of separated formed trabeculae. The epicardium fits snugly the myocardium. The interventricular septum is fully formed.

Histological examination showed that in the group of exposure to cadmium chloride changes in the structure of the atrium and ventricles were detected. In 12.3% of the studied objects, atrium endocardial hyperplasia was detected, but ventricular endocardium remained normal. Processes of hyperplasia may indicate the formation of compensatory mechanisms by the endothelium in response to the toxic effect of cadmium chloride during embryogenesis. There was no endothelium hyperplasia in the cadmium citrate exposure group. Exposure to cadmium chloride also led to a local thickening of the atrial wall during this development period. The heterogeneity of the thickness of the atrium wall prompted us to measure the thickest and thinnest sections of the atrium. If in the control, the average thickness of the right atrium was 40.25 ± 1.33 μm in the thin sections,but when exposed to cadmium chloride, a thickening of up to 49.88 ± 1.72 μm was observed, and in the cadmium citrate exposure group, the thinning of the wall was determined up to 35.50 ± 2.30 μm.

Under the influence of cadmium chloride, the thickness of the interventricular septum of the heart of the embryo increased from 420.75 ± 7.82 μm in control to 494.16 ± 6.71 μm, and in the group influenced by cadmium citrate a decrease in the thickness of the interventricular septum was determined to 381.50 ± 8.11 μm although a local thickening of the middle part of the septum was observed in 12.4%.

Thus, different heart chambers respond to the influence of cadmium salts in different ways, which is explained by the different hemodynamic load of the heart chambers.

The right half of the heart does not carry a large haemodynamic load in the embryo due to the presence of arterial duct and lack of gas exchange in the lungs. The small circulatory system does not work and the effect on the myocardium of this part of the organ is not significant. The left half is more damaged, which is associated with a large circulation and has a higher hemodynamic load. It should be said that at the time of the embryo's birth, the rat's heart is not the definitive organ. Vessels, the valve apparatus and the myocardium are finally formed within the first 2 weeks after birth. But when exposed to equal doses of different salts of cadmium, different directional processes of cardiac development were determined, namely: exposure to cadmium chloride led to an increase in the compact layer of the myocardium of all the chambers of the heart and the interventricular septum, and the administration of cadmium citrate reduced the thickness of the walls of the chambers and septum together with heart weight loss. In the groups of combined administration of cadmium salts with citrates of the investigated microelements the indicators of compact myocardium recovered, which testifies the antagonistic nature of the influence of the tested substances on the cardiotoxicity of cadmium.

Conclusions. 1. The effect of indicated doses of cadmium salts on cardiogenesis in rats influenced morphogenesis of different heart chambers in different ways: cadmium chloride led to an increase in heart mass by increasing the thickness of the myocardial layer of the ventricles and atrium walls with local thickening of the interventricular septum. The administration of cadmium citrate led to a decrease in heart mass in embryos due to thinning of the myocardium wall of both ventricles and interventricular septum.

2. In groups of combined administration of cadmium salts with citrates of metals recovery of cardiofetal index and thickness indicators of compact myocardium were determined. The data obtained indicate the reduction of cardiotoxicity of cadmium salts due to administration of citrates of germanium, cerium, iodine + sulfur during pregnancy in a rats experiment.

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