

EFFECT OF CADMIUM CHLORIDE ON KIDNEY MORPHOLOGY IN RATS IN ISOLATED INTRODUCTION AND IN COMBINATION WITH COPPER AND ZINC SUCCINATES

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An important area of morphological experimental research is the search for new possible bioantagonists of cadmium toxicity among microelements. The aim of the experimental study was to determine the morphological changes in the kidneys and to determine the degree of cadmium accumulation in the kidneys of female rats and embryos with cadmium chloride (2,0 mg/kg) isolated and in combination with zinc and copper succinates. The study was performed on pregnant female rats, which were divided into 4 groups: the first – control; the second – the isolated injection of cadmium chloride; third – combined injection of cadmium chloride + zinc succinate (5 mg/kg); fourth – combined administration of cadmium + copper succinate (0,1 mg/kg). The effect was performed daily from the 1st to the 19th day of pregnancy intragastrically once a day. Elements of nephrons were studied on histological preparations of kidneys: diameter of a renal corpuscle, area of a capsule of a nephron. The degree of accumulation of cadmium was determined using polyelement analysis. There was a significant increase in the accumulation of cadmium in the kidneys of female rats in all experimental groups, the highest level was determined in the group of the combination of cadmium with copper succinate. Rat embryos in the group of isolated administration of cadmium chloride accumulated 10,2 times more cadmium than the control values, and in the groups of combined injection, the level of cadmium accumulation significantly decreased compared to the group of isolated exposure. Isolation of cadmium at the histological level showed capsule dilation and compaction of the nephron's glomeruli female kidney. In the groups of combined administration, there was no increase in the area of the nephron capsule, which we considered as a compensatory effect of succinates on the nephrotoxicity of cadmium. The obtained results allow considering succinates of zinc and copper as potential bioantagonists of cadmium chloride in a chronic experiment on rats.

Key words: kidneys, rats, embryo, nephron, cadmium, copper, zinc.

Relationship of the publication with planned research works. The experimental study was performed as part of research work of the Department of Medical Biology, Pharmacognosy and Botany SI "DMA" "Biological basis of morphogenesis of organs and animals under the influence of microelements and ultramicroelements in the experiment" (№ state registration 0118U006635).

Introduction. Since the middle of the XX century in the world science began to grow interest in research on the effects of anthropogenic activities on the environment. Heavy metals have a high ability to a variety of chemical, physicochemical, and biological reactions, some of them have variable valence and are involved in redox processes. Their compounds can move and re-

distribute, in other words, migrate as an organo-mineral component of the biogeocenosis [1, 2, 3].

The problem of embryotoxicity and fetotoxicity of microelements have great practical importance because a significant number of women work in industry and production conditions and are often exposed to heavy metals, which is very dangerous for the fetus and offspring in general. Embryo death can be associated with both an excess of some elements and their deficiency, and pathological conditions caused by excess, deficiency, or imbalance of micronutrients in the body, called dyselementosis [4, 5, 6]. Currently, the influence of maternal microelements on the development of the embryo and fetus has been established, and teratogenic effects on the offspring can have any type of maternal microelements [7, 8]. Excess of cadmium can provoke chromosomal abnormalities, cause embryotoxic effects, abnormalities in the structure of the face and neural tube, skeletal changes.

Not sufficiently researched chronic influence on the course of embryogenesis of cadmium salts with microelements that have bioantagonistic properties about the toxicity of heavy metals [8, 9]. Thus, an important area of morphological experimental research is the search for new possible bioantagonists of cadmium toxicity among trace elements that can affect dyslementosis, maintaining homeostasis, including during pregnancy.

An important feature of heavy metals and cadmium salts is the ability to bioaccumulate in the body and the ability to lead to severe damage to the reproductive, cardiovascular, urinary, and respiratory systems. The kidneys are the main organ that excretes toxins from the body. It is known that toxic metals accumulate mainly in the cells of the proximal tubules, causing structural and functional damage, which disrupts the processes of reabsorption and secretion. The most common manifestations of its nephrotoxicity are oxidative stress associated with the accumulation of free radicals, mechanisms of apoptosis, and necrosis [10, 11, 12]. The vulnerability of tubules to nephrotoxins is due to the fact that chemical agents absorbed by pinocytosis are concentrated in lysosomes, where they undergo hydrolytic cleavage, but some toxicants inhibit the proteolytic process, leading to their accumulation and damage to the tubular epithelium, [13, 14, 15]. The mechanism of urgent adaptation to hypoxia in critical conditions develops with a characteristic decrease in succinate, which allows to correct its deficiency with the prospect of increasing oxygen consumption, activation of aerobic oxidation, and restoration of processes within cellular aerobic metabolism [16, 17]. For energy support of animal cells in conditions of oxygen starvation in anoxia and hypoxia, it is advisable to use substrates that can participate in the anaerobic formation of succinate, while in hypoxic conditions it makes sense to use succinates [18].

The aim of the study. To investigate the accumulation of cadmium in the kidneys of adult female rats and embryos when cadmium chloride is administered in isolation and to search for possible bioantagonists among zinc and copper succinates when combined with cadmium chloride in a chronic experiment in rats. Identify morphological changes in the kidneys of experimental animals.

Object and methods of research. The study was conducted on 64 females of Wistar rats (kennel "Dali 2000" Kyiv), weighing 180-300 g. Using the method of vaginal swabs we received females with a date of pregnancy, which allowed us to obtain embryos with a certain date of development.

All pregnant females were divided into the following groups: the first group – control; the second group – isolated administration of a solution of cadmium chloride at a dose of 2.0 mg/kg; the third group – the combined introduction of a solution of cadmium chloride at a dose of 2.0 mg/kg + zinc succinate at a dose of 5 mg/kg; the fourth group – the combined introduction of a solution of cadmium chloride at a dose of 2.0 mg/kg + copper succinate 0.1 mg/kg. In each group of 16 females, on the 13th and 19th day of pregnancy the females underwent surgery. Zinc succinate and copper succinate were chelated compounds widely used in chemistry and medicine. Succinate solutions were nanoscale, so we used nanoaquachelates of copper and zinc obtained under the agreement on scientific and technical cooperation in the Research Institute of Nanobiotechnology and Resource Conservation of Ukraine (Kyiv).

The influence of the studied factors of female rats was performed daily from the 1st to the 19th day of pregnancy by administering the solution intragastrically, through a tube once a day. During the experiment, we recorded the condition and behavior of female rats, rectal temperature, dynamics of body weight, duration of pregnancy.

Determination of the degree of cadmium accumulation was performed using polyelement analysis. Samples were measured at the State Enterprise "Ukrainian Research Institute of Transport Medicine of the Ministry of Health of Ukraine" (Odesa) under the agreement on scientific and technical cooperation. Preparation of samples and measurement of metal content was carried out following GOST 30823-2002. Quantitative measurement

of metal content in the samples was performed on the atomic emission spectrometer Emas-200 CCD, which is a modern analytical instrument, controlled by a computer and performs all necessary calculations independently with minimal involvement of the operator. To perform this study, the kidneys of females on 13 and 19 days and embryos of 19 days, which were subjected to freezing without fixation, were removed during the experiment.

To determine changes in the morphogenesis of the kidneys under the influence of the studied substances, we removed the kidneys of females and embryos, fixed them in 10% formalin solution, then poured into the paraplast and made histological sections. Elements of nephrons were studied on histological preparations: diameter of the renal corpuscle, area of nephron capsule. These parameters were measured on microphotographs. We used a ZEISS Axiocam ERc 5s light microscopy camera to obtain digital images and then calculate the size of the kidney structures. Measurements were performed on histological photographs using the ZEISS Axiocam ERc 5s light microscopy program with a P95-C 1/2 "0.5x adapter connected to a ZEISS Primo Star microscope. This program ZEN 2.0 is licensed for histological measurements and allows morphometric studies of both linear parameters (diameter of the glomerulus) and the calculation of the spline contour (glomerular capsule area, etc.). The obtained results were processed by the method of variation statistics. The probability of statistical studies was assessed using Student's t-test.

The research was carried out in accordance with the principles of the Declaration of Helsinki adopted by the General Assembly of the World Medical Association (2000), the Council of Europe Convention on Human Rights and Biomedicine (1997), relevant WHO regulations, the International Council of Medical Societies and the International Code of Medical Ethics (1983), "Ethical Guidelines for the Use of Animals in Research", approved by the First National Congress of Bioethics (Kyiv, 2001) in accordance with the provisions of the "European Convention for the Protection of Vertebrate Animals used in Experiments and Other Educational Purposes" (Strasbourg, March 18, 1986).

Research results and their discussion. To determine the effect of the studied compounds on the morphology of the kidneys of pregnant females, we on the 13th and 19th day promptly removed the kidneys, weighed and recorded for further histological sections. The calculation of metric mass indicators revealed the following: the right kidney has a larger mass compared to the left in all groups, so we calculated the average of both kidneys. To exclude the error in the dynamics in the rat weight changes and kidney mass, we calculated the body mass index (kidney) (KMI), that is the ratio of wet kidney mass to female rat weight. The average weight of both kidneys in the control group was on the 13th day of the experiment 0.737 ± 0.019 g, and on the 19th day – 0.790 ± 0.03 g, and the KMI was 0.316 ± 0.005 on the 13th day and 0.322 ± 0.008 on the 19th respectively. Thus, at the end of embryogenesis,

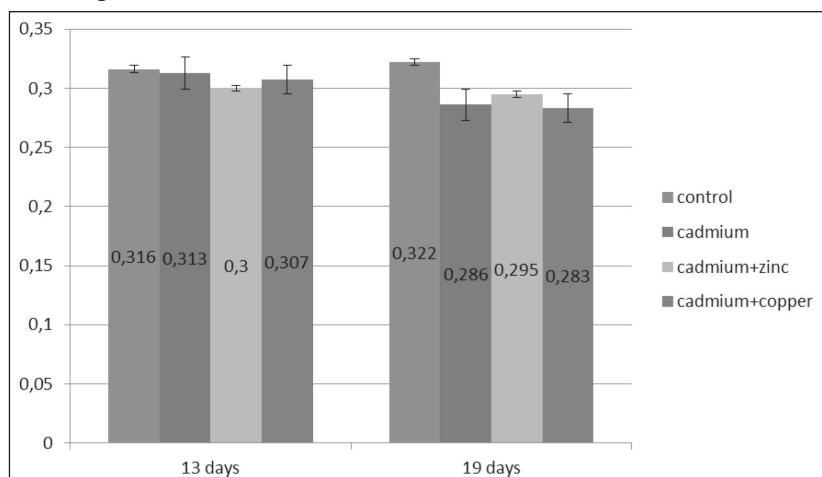


Figure 1 – Dynamics of changes in the renal mass index in all experimental groups.

the kidney mass of a pregnant female increased unreliable, which was reflected in the KMI. In the group of isolated administration of cadmium chloride, the average weight of female kidneys on the 13th day of embryogenesis was 0.730 ± 0.015 g, and KMI 0.313 ± 0.001 (fig. 1), which was unreliable below the control values. At the end of the experiment (19th day), the KMI was significantly lower than the control ($p < 0.05$) and was determined at the level of 0.286 ± 0.010 , which shows a decrease in renal weights with isolated administration of cadmium chloride. In the groups of combined administration of cadmium chloride with metal succinates, the renal mass index on the 13th day of administration had no significant difference with the control and the group of isolated administration, and on the 19th day was significantly ($p < 0.05$) lower than control, but not had a significant difference with the group of isolated administration of cadmium chloride (fig. 1). This situation indicates kidney damage in the experimental groups and significantly emphasizes the decrease in the weight of the kidneys of females with chronic administration of the studied factors during pregnancy.

Analysis of histological serial sections of the kidney in all groups showed the following morphological shifts in the structure of the renal parenchyma. When isolated with cadmium chloride, the area of the nephron capsule increased, which we considered as a possible result of capsule edema and a symptom of nephron damage. Also in the group of isolated exposure to cadmium chloride was determined by edema of the nephron tubules, which led to the parenchyma compaction. In the groups of combined administration, the studied parameters of the parenchyma did not differ significantly from the control, which we regarded as a positive effect of copper and zinc succinates on the nephrotoxicity of cadmium chloride.

Measurements of the area of the nephron capsule and the glomerular area by the spline contour method allowed to calculate the renal corpuscle index of the nephron, which allowed to estimate the degree of damage to the structural and functional unit of the kidney – the nephron. During pregnancy, morphofunctional changes occur in the kidneys of the female rats: at the end of pregnancy in the control, there is a decrease in the ratio of the area of the capsule to the area of the glomerulus of the nephron. Such changes are physiological and associated with an increased morpho-physiological load on the kidneys of pregnant females. Already on the 13th day in the group of isolated exposure to cadmium was determined by an increase in the area of the nephron capsule, which led to a significant decrease ($p < 0.001$) ratio. In the groups of combined administration of cadmium with succinates, this figure also decreased, indicating renal impairment in all experimental groups in the first half of pregnancy. But in the end in the group of combined administration of cadmium with copper succinate, the ratio of capsule area to glomerular area approached the control values, which we con-

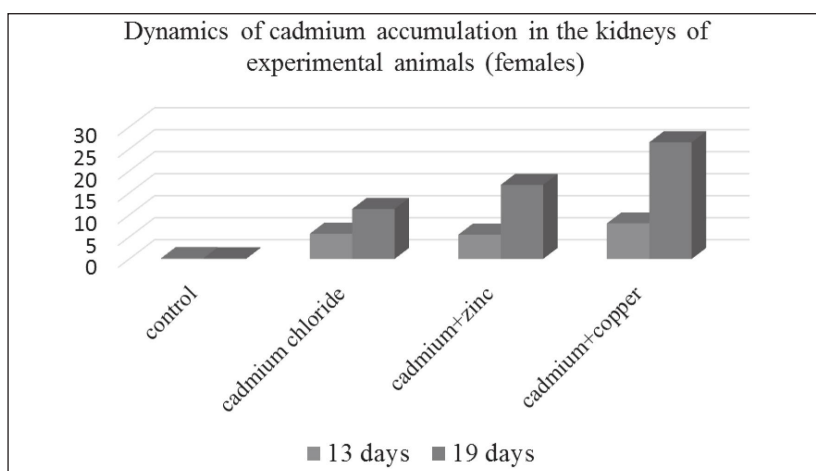


Figure 2 – Indicators of cadmium accumulation ($\mu\text{g/g}$) in the kidneys of females of the experimental groups on the 13th and 19th days of embryogenesis with daily chronic enteral administration.

sider as a compensatory effect of copper succinate on the nephrotoxicity of cadmium chloride in these doses in experiments on rats.

Analysis of cadmium accumulation was performed in two directions. The first direction is the accumulation of cadmium in the kidneys of female rats on the 13th and 19th days of the experiment. The kidneys are an excretory organ where cadmium is excreted in the urine, so, logically, the level of accumulation of this trace element will be higher than in other organs. The second area of research is the accumulation of cadmium in embryos of the 19th day that is at the end of embryogenesis and experiment. It is well known that the placenta retains some cadmium, so the level of accumulation in the embryo will be several orders of magnitude lower than in the kidneys of female rats. As shown by the results of the use of polyelement analysis, the level of cadmium accumulation in the kidneys of female rats of different groups of the experiment was higher than the control values (fig. 2).

The amount of cadmium in the kidneys of female rats significantly ($p \leq 0.05$) increased in the groups of isolated exposure to cadmium in both studied terms, which was logical and predictable. But in the groups of combined exposure, the amount of cadmium in the kidneys of female rats increased even more and this increase was significantly higher ($p \leq 0.001$) than the control indicators and significantly exceeded the indicators of isolated exposure to cadmium. The highest level of accumulation was determined in the group of combinations of cadmium with copper succinate. It is possible that such data indicate more active processes of cadmium retention by the kidneys and increased excretion of this toxicant from the body, as evidenced by the level of cadmium accumulation by the embryo itself.

Analysis of the results of cadmium accumulation in 19-day-old embryos of experimental groups in a comparative aspect showed the following. With chronic daily exposure to a pregnant female in the group of isolated administration of cadmium chloride, embryos at the end of embryogenesis ($0.168 \mu\text{g/g}$) accumulate cadmium 10.2 times more than the control values ($0.01645 \mu\text{g/g}$). And with the combined introduction of cadmium chloride with succinate copper/zinc, the level of cadmium accumulation is significantly reduced ($p \leq 0.05$)

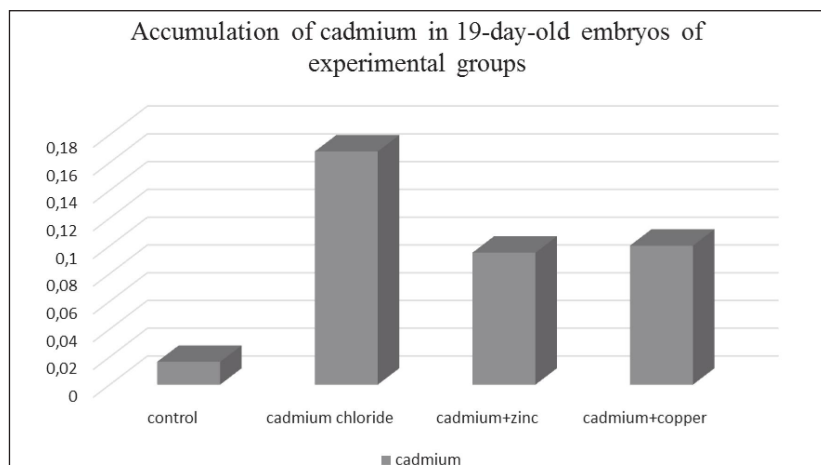


Figure 3 – Indicators of cadmium accumulation (µg/g) in rat embryos on the 19th day of the experiment in all experimental groups.

compared with the group of isolated exposure to cadmium. In the group of the combination of cadmium with zinc succinate, the accumulation level is 1.8 times lower (0.09515 µg/g) compared to the isolated administration of cadmium. And at a combination of cadmium with copper, the similar indicator decreases in 1,7 times (0,1002 mk/g) (fig. 3).

Thus, the combined administration of succinates of zinc or copper on the background of cadmium intoxication of pregnant females significantly reduces the level of cadmium accumulation in rat embryos in the experiment of chronic enteral administration of the studied factors in these doses. The obtained results demonstrate that zinc and copper succinates can be considered as potential bioantagonists of cadmium chloride, which promote the excretion of this trace element from the embryo when combined with metal succinates in an experiment on rats.

group of isolated exposure.

The nephrotoxicity of cadmium chloride in isolated administration was manifested at the histological level in the expansion of the nephron capsule and the compaction of the nephron glomeruli of the female kidney. In the groups of combined administration of cadmium chloride with succinates of copper or zinc at the histological level was not recognized increase in the area of the nephron capsule, which we considered as a compensatory effect of succinates on the nephrotoxicity of cadmium.

The obtained results allow us to consider succinates of zinc and copper as potential bioantagonists of cadmium chloride in a chronic experiment in rats.

Prospects for further research. In our opinion, complex histological studies of female kidneys and rat embryos in experimental groups are perspective.

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ВПЛИВ ХЛОРИДУ КАДМІЮ НА МОРФОЛОГІЮ НИРОК У ЩУРІВ ПРИ ІЗОЛЬОВАНОМУ ВВЕДЕННІ ТА В КОМБІНАЦІЇ З СУКЦИНАТАМИ МІДІ ТА ЦИНКУ

Шаторна В. Ф., Краснов О. О.

Резюме. Малодослідженими є аспекти хронічного впливу на хід ембріогенезу солей кадмію з мікроелементами, які мають біоанатагоністичні властивості відносно токсичності важких металів. Актуальним напрямком морфологічних експериментальних досліджень є пошук нових можливих біоантагоністів токсичності кадмію серед мікроелементів, що здатні впливати на диселементози, підтримуючи гомеостаз організму в тому числі і під час вагітності.

Метою експериментального дослідження було виявлення ступеню накопичення кадмію та визначення морфологічних змін в нирках дорослих самиць щурів та в ембріонах при введенні хлориду кадмію ізольовано та при комбінованому введенні з сукцинатами цинку і міді в хронічному експерименті на щурах.

Дослідження проведено на вагітних самицях щурів, які розподілялись на 4 групи: перша – контроль; друга – ізольованого введення розчину хлориду кадмію у дозі 2,0 мг/кг; третя – комбінованого введення хлориду кадмію + сукцинат цинку в дозі 5 мг/кг; четверта – комбінованого введення хлориду кадмію + сукцинат міді 0,1мг/кг. Вплив досліджуваних чинників самиць щурів проводили щоденно з 1-го по 19-й день вагітності введенням розчину внутрішньошлунково, через зонд один раз на добу. Ступінь накопичення кадмію визначали з використанням поліелементного аналізу. Для визначення змін в морфогенезі нирок виготовлялись гістологічні зрізи нирок. На гістологічних препаратах досліджувались елементи нефронів: діаметр ниркового тільця, площа капсули нефрону.

Виявлено достовірне зростання накопичення кадмію в нирках самиць щурів в групі ізольованого впливу хлоридом кадмію і в групах комбінованого впливу. Найвищий рівень накопичення визначався в групі комбінації кадмію з сукцинатом міді. Ембріони щура у групі ізольованого введення кадмію у 10,2 рази накопичували кадмій більше за контрольні показники. А в групах комбінованого введення хлориду кадмію з сукцинатами міді/цинку рівень накопичення кадмію достовірно зменшувався у порівнянні до групи ізольованого введення.

Нефротоксичність хлориду кадмію при ізольованому введенні проявлялась на гістологічному рівні у розширенні капсули нефрону та ущільненні структур клубочків нефрону нирки самиці. В групах комбінованого введення хлориду кадмію з сукцинатами міді або цинку на гістологічному рівні не визначилось збільшення площі капсули нефрону, що розцінювались нами як компенсаторний вплив сукцинатів на нефротоксичність кадмію. Отримані результати дозволяють розглядати сукцинати цинку та міді як потенційні біоантагоністи хлориду кадмію в хронічному експерименті на щурах

Ключові слова: нирки, щури, ембріон, нефрон, кадмій, мідь, цинк.

EFFECT OF CADMIUM CHLORIDE ON KIDNEY MORPHOLOGY IN RATS IN ISOLATED INTRODUCTION AND IN COMBINATION WITH COPPER AND ZINC SUCCINATES

Shatorna V. F., Krasnov O. O.

Abstract. The problem of embryotoxicity and foetotoxicity of microelements is of great practical importance, because a significant number of women work in industry and production conditions and are often exposed to heavy metals, which is very dangerous for the fetus and offspring in general. Aspects of chronic influence on the course of embryogenesis of cadmium salts with microelements, which have bioantagonistic properties in relation to the toxicity of heavy metals, have been little studied. An important area of morphological experimental research is the search for new possible bioantagonist of cadmium toxicity among trace elements that can affect dyselementosis, maintaining homeostasis, including during pregnancy.

The aim of the experimental study was to determine the degree of cadmium accumulation in the kidneys of adult female rats and embryos when cadmium chloride was administered in isolation and in combination with zinc and copper succinates in a chronic experiment in rats. Determination of morphological changes in the kidneys of experimental animals.

The study was performed on 64 female Wistar rats weighing 180-300 g. All pregnant females were divided into 4 groups: first – control; the second – isolated administration of a solution of cadmium chloride at a dose of 2.0 mg/kg; third – combined administration of cadmium chloride at a dose of 2.0 mg/kg + zinc succinate at a dose of 5 mg/kg; fourth – combined administration of cadmium chloride at a dose of 2.0 mg/kg + copper succinate 0.1 mg/kg. The influence of the studied factors of female rats was performed daily from the 1st to the 19th day of pregnancy by administering the solution intragastrically, through a tube once a day. The degree of cadmium accumulation was determined using multi-element analysis on an atomic emission spectrometer Emas-200 CCD. To conduct this study, the kidneys of females on days 13 and 19 and embryos of days 19, which were frozen without fixation, were removed during the experiment. To determine changes in the morphogenesis of the kidneys, we removed the kidneys of females and embryos, recorded, poured into the paraplast and made histological sections. Elements of nephrons were studied on histological specimens: diameter of renal corpuscle, area of nephron capsule.

There was a significant increase in the accumulation of cadmium in the kidneys of female rats in the groups of isolated exposure to cadmium chloride, but in the groups of combined exposure, the amount of cadmium in the

kidneys of females also increased significantly. The highest level of accumulation was determined in the group of combinations of cadmium with copper succinate. Rat embryos that were indirectly affected in the cadmium chloride isolation group accumulated 10.2 times more cadmium than controls. And in the groups of combined administration of cadmium chloride with copper/zinc succinates, the level of cadmium accumulation is significantly reduced compared to the group of isolated exposure.

The nephrotoxicity of cadmium chloride in isolated administration was manifested at the histological level in the expansion of the nephron capsule and the compaction of the nephron glomeruli of the female kidney. In the groups of combined administration of cadmium chloride with copper or zinc succinates at the histological level there was no increase in the area of the nephron capsule, which we considered as a compensatory effect of succinates on cadmium nephrotoxicity. The obtained results allow to consider succinates of zinc and copper as potential bioantagonists of cadmium chloride in a chronic experiment on rats.

Key words: kidneys, rats, embryo, nephron, cadmium, copper, zinc.

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The authors confirm that there is no conflict of interest in this article.

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