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FEATURES OF THE FORMATION OF MICROELEMENTAL DISELEMENTOSIS OF THE HEART OF RATS UNDER THE CONDITIONS OF CHRONIC CADMIUM CHLORIDE INTOXICATION

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The aim of the work was to assess the features of cadmium, zinc and iron deposition in the myocardium of the heart of pregnant female rats under conditions of isolated and combined chronic intake of cadmium chloride with succinates of biogenic metals. For 20 days, pregnant rats were administered solutions intragastrically daily. 4 experimental groups were formed: control, isolated cadmium chloride and its combinations with succinates of zinc or iron. The content of metals in the organs was determined by polyelement analysis. It was established that the concentration of cadmium in the hearts of rats of all experimental groups exceeded the control values. Intensive accumulation of the toxicant by the myocardium was accompanied by a change in the microelement balance, namely zinc and iron at both studied periods with isolated administration of the toxicant. Simultaneous administration of cadmium with iron succinate caused a significant decrease in the level of cadmium accumulation by the myocardium in the first half of pregnancy, while combined administration of cadmium with zinc succinate reduced cadmium accumulation at both terms compared to the group of isolated administration. Thus, the experiment proved the modifying effect of zinc and iron succinates on the level of cadmium accumulation in a chronic experiment on rats in the studied doses and method of administration. This study is aimed at forming a theoretical basis for creating effective means of neutralizing the cardiotoxic effect of cadmium when it is excessively ingested into the body.

Key words: experiment, rats, cardiovascular system, heart, cadmium, zinc, iron, succinates, bioantagonism.

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ОСОБЛИВОСТІ ФОРМУВАННЯ МІКРОЕЛЕМЕНТНОГО ДИСЕЛЕМЕНТОЗУ СЕРЦЯ ЩУРІВ ЗА УМОВ ХРОНІЧНОЇ ІНТОКСИКАЦІЇ ХЛОРИДОМ КАДМІЮ

Метою роботи було оцінити особливості депонування кадмію, цинку та заліза в міокарді серця вагітних самиць щурів за умов ізолюваного та комбінованого хронічного надходження хлориду кадмію з сукцинатами біогенних металів. Протягом 20-ти діб вагітним щурам щодня внутрішньошлунково вводили розчини. Сформовано 4 експериментальні групи: контрольна, ізолюваного хлориду кадмію та його комбінацій із сукцинатами цинку або заліза. Вміст металів в органах визначали поліелементним аналізом. Встановлено, що концентрація кадмію в серцях щурів усіх дослідних груп перевищувала контрольні значення. Інтенсивне кумулювання токсиканта міокардом супроводжувалося зміною мікроелементного балансу, а саме цинку та заліза на обох досліджуваних термінах при ізолюваному введенні токсиканта. Одночасне введення кадмію з сукцинатом заліза викликало достовірне зниження рівню накопичення кадмію міокардом в першій половині вагітності, в той час як комбіноване введення кадмію з сукцинатом цинку знижувало кумуляцію кадмію на обох термінах порівняно з групою ізолюваного введення. Таким чином, експеримент довів модифікуючий вплив сукцинатів цинку та заліза на рівень кумуляції кадмію в хронічному експерименті на щурах в досліджуваних дозах та способі введення. Це дослідження спрямоване на формування теоретичної бази для створення ефективних засобів нейтралізації кардіотоксичного впливу кадмію при його надмірному надходженні в організм.

Ключові слова: експеримент, щури, серцево-судинна система, серце, кадмій, цинк, залізо, сукцинати, біоантагонізм.

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Environmental heavy metals are dangerous cumulative pollutants that affect the cardiovascular, nervous, and urinary systems. A particular threat is posed by cadmium, whose cardiotoxic effect manifests even at subtoxic doses. Accumulating in the myocardium through oxidative stress, inflammation, and apoptosis, it induces hypertension, atherosclerosis, and cardiogenesis defects [1, 2, 9]. The primary mechanism of cadmium toxicity is the competitive replacement of essential divalent cations, which disrupts the microelement homeostasis of the heart [4, 5]. The severity of these alterations depends on the dose, exposure time, and physiological state (in particular, pregnancy). A key factor in the pathogenesis of chronic heavy metal intoxication is their deposition in target organs, particularly in the cardiac muscle, followed by the disruption of tissue homeostasis [6, 8]. Upon entering a

biosystem, exogenous xenobiotic ions interact with cellular macromolecules, transforming fundamental metabolic processes. Assessing the dynamics of the heart's microelement profile based on cadmium, zinc, and iron levels in experimental animals allows for verifying the severity of organ damage and the temporal parameters of dysmicroelementosis development. At the same time, this creates a rationale for the pathogenetic substantiation of the cardioprotective efficacy of novel biometal succinate compounds.

Zinc succinate and iron succinate are not antioxidants in the classic chemical sense; they do not scavenge free radicals as vitamins C, E, or resveratrol do. However, in vivo, they act as potent indirect antioxidants and membrane protectors. In experimental toxicology, especially during cadmium intoxication, their protective effect is based on two

fundamental mechanisms [11, 12]. Cadmium blocks mitochondrial enzymes, shutting down cellular respiration, which leads to renal cellular energy starvation – specifically, ATP deficiency and a secondary burst of oxidative stress. Succinate serves as a Krebs cycle substrate that maintains the function of the mitochondrial respiratory chain by bypassing the sites blocked by cadmium. The second mechanism involves competitive potentiation and the anti-dysselementosis action of essential metals. Zinc is a direct component of the cell's primary antioxidant enzyme, superoxide dismutase [13]. Furthermore, zinc triggers the synthesis of the metallothionein protein, which binds and detoxifies cadmium. Zinc succinate restores this metal to the organism, reinstating the cell's natural antioxidant shield. Iron is a component of another key antioxidant enzyme, catalase, as well as cytochromes. Cadmium blocks iron absorption, causing tissue anemia and renal hypoxia, whereas iron succinate restores this balance [3, 10]. In this regard, the search for effective cadmium bioantagonists among biometal succinates is pathogenetically justified and highly relevant.

The purpose of the study was to compare the levels of cadmium, zinc, and iron in the hearts of experimental animals and to determine the relationship between the accumulation of cadmium, iron, and zinc in the heart under conditions of isolated cadmium chloride administration, as well as the combined effect of cadmium with zinc or iron succinate, to identify potential bioantagonistic properties of metal succinates against cadmium chloride cardiotoxicity in a chronic experiment.

Materials and methods. The experimental part of the study was conducted on pregnant female Wistar rats aged 2.5–3 months, obtained from the specialized breeding facility "Dali 2001" LLC (Kyiv). The study was performed as a chronic experiment. Pregnant females entered the experiment and were divided into the following experimental groups within each cohort: Control group, receiving 0.5 mL of physiological saline; Isolated cadmium chloride administration group, receiving cadmium chloride solution at a dose of 3.0 mg/kg; Combined administration groups: the third group received a combination of cadmium chloride solution at a dose of 3.0 mg/kg + zinc succinate at a dose of 6.0 mg/kg; the fourth group received a combination of cadmium chloride solution at a dose of 3.0 mg/kg + iron succinate at a dose of 0.2 mg/kg. All experimental procedures on rats were carried out in accordance with international and national bioethical standards (EU Directive 2010/63/EU, ARRIVE guidelines) and were approved by the Bioethics Committee of Dnipro State Medical University. Adequate methods of anesthesia and humane endpoints were applied to minimize animal suffering.

One of the criteria for the chronic impact of cadmium salts on the body is determining the accumulation level of this element and the disruption of quantitative indicators of other microelements in the heart to establish potential dysselementosis. Sample measurements were performed at the State

Enterprise "Ukrainian Research Institute of Transport Medicine of the Ministry of Health of Ukraine" (Odesa) pursuant to a scientific and technical cooperation agreement. Sample preparation and metal content measurements were carried out in accordance with GOST 30823-2002.

The concentration of metals in biomaterials was evaluated using atomic emission spectrometry on an automated EMAS-200 CCD complex. This modern computerized system minimizes operator involvement in calculations by performing them automatically. Experimental samples were collected on days 13 and 20 of the study. All excised hearts were frozen without prior chemical fixation. A reference spectral buffer mixture prepared according to GOST 30823-2002 was used as a solvent during sample preparation. Cadmium content was determined at a wavelength of 228.802 nm, zinc at 213.856 nm, and iron at 328.754 nm. The arc discharge current was kept constant at 15 A for all measurements, and the optical slit width of the instrument was 0.4 for cadmium and zinc, and 0.1 for iron.

Results of the study. Among xenobiotics, a special place is occupied by cadmium, which exhibits pronounced cardiotoxicity even at low doses. Chronic transport of this metal leads to its accumulation in the cardiac muscle, accompanied by a profound imbalance of essential microelements. The ability of cadmium to substitute divalent cations or block their excretion directly depends on the dose, duration of intoxication, and the physiological state of the organism. In this regard, the analysis of changes in the heart's microelement status across experimental groups allows for evaluating the degree of the metal's destructive impact and identifying the timing and severity of dysmicroelementosis formation under conditions of cadmium intoxication, as well as during the search for potential novel protectors among biometal succinates.

The study of cadmium, iron, and zinc accumulation in the heart was carried out in pregnant females on days 13 and 20 of the experiment across all experimental groups. This approach enabled a comprehensive assessment of the redistribution features of the xenobiotic and essential elements, taking into account the intoxication period and the physiological state of the organism.

Analysis and comparison of the obtained results revealed the following. On day 13 of the experiment, the highest level of cadmium accumulation in female hearts was observed in the isolated cadmium chloride exposure group, reaching $0.131 \pm 0.0213 \mu\text{g/g}$, which was 2.3 times higher than the control values ($0.0562 \pm 0.004 \mu\text{g/g}$). Combined administration of the same cadmium dose with zinc or iron succinates quite effectively reduced the level of cadmium accumulation in female hearts. Administration of cadmium with zinc succinate reduced the cadmium level at this stage of the study toward the control value, amounting to $0.0958 \pm 0.0134 \mu\text{g/g}$ (Fig. 1).

However, the most pronounced reduction in myocardial cadmium accumulation was observed in the group receiving combined simultaneous exposure to the toxicant and iron succinate – 0.0814 ± 0.0152

µg/g. This indicates a modifying effect of biogenic metal succinates on the retention level of cadmium during their simultaneous intake into the organism at the studied doses and route of administration in the rat experiment. Thus, as early as day 13 of daily chronic administration of the test substances to rats,

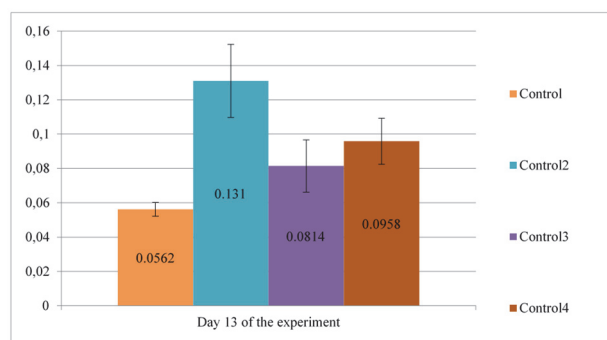


Fig. 1. Cadmium accumulation level (µg/g) in the hearts of pregnant female rats in the experimental groups on day 13 of the experiment.

We attribute this increase to the fact that the experiment was conducted in a cadmium-burdened region of Ukraine. Concurrently, the accumulation rate in the isolated cadmium administration group also expectedly increased, reaching 0.1964 ± 0.0054 µg/g. A rather unexpected shift was observed in the cadmium accumulation trend within the combined administration groups. While on day 13 the most pronounced reduction in cadmium levels was observed under the combined effect of cadmium and iron succinate, by the final stage of the study, this group exhibited higher levels compared to the combination group with zinc. On day 20, the lowest cadmium accumulation level was observed in the combination with zinc (0.1342 ± 0.0145 µg/g) relative to the isolated cadmium chloride exposure group, although it still exceeded the control value by 1.85 times.

Thus, the analysis and comparison of multi-element analysis results at both experimental time points demonstrated that the combined administration of cadmium with iron succinate or zinc succinate reduces the cadmium accumulation level in the hearts of adult females, confirming the modifying effect of succinates on the capacity of cadmium to be retained in the myocardium.

The next stage of our study was to determine the zinc content in the cardiac tissues of pregnant females across all experimental groups. Zinc belongs to the category of essential microelements critical for ensuring fundamental vital processes. This microelement participates directly in carbohydrate and lipid metabolism, gene expression regulation, and the maintenance of the structural and functional integrity of the immune, reproductive, and nervous systems. Zinc is of particular importance for the cardiovascular system, where it acts as a potent endogenous cardioprotector. This cation is an integral component of superoxide dismutase – a key enzyme of myocardial antioxidant defense that mitigates the destructive effects of free radical processes and prevents the development of oxidative stress. Furthermore, zinc is involved in regulating

varying levels of cadmium accumulation were observed in the hearts of pregnant females.

As revealed by the multi-element analysis on day 20 of the experiment, the cadmium accumulation level in female hearts nonsignificantly increased even in the control group, reaching 0.0711 ± 0.0024 µg/g (Fig. 2).

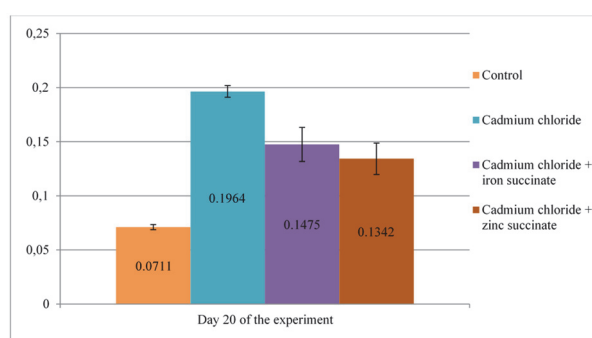


Fig. 2. Cadmium accumulation level (µg/g) in the hearts of pregnant female rats in the experimental groups on day 20 of the experiment.

intracellular signaling and calcium homeostasis in cardiomyocytes, maintaining adequate myocardial contractility and vascular tone stability. It ensures the stability of myocardial cell membranes and vascular endothelium, protecting them from apoptosis and xenobiotic-induced toxic damage. In view of this, evaluating the dynamics of zinc content in the heart under conditions of metallotoxicity is fundamentally important for understanding the mechanisms underlying the formation of secondary cardiomyopathies.

Analysis of the zinc content in the cardiac tissues of pregnant females on day 13 of the experiment revealed significant changes in this parameter under the influence of the toxicant and under conditions of its combined administration with bioelements (Fig. 3).

In control animals, the zinc concentration in the myocardium was 46.7 ± 3.16 µg/g. Isolated administration of cadmium chloride led to a rapid and statistically significant increase in the zinc level in the cardiac muscle – up to 92.3 ± 10.36 µg/g, which is almost twice the control value. Such a response may indicate compensatory mobilization of endogenous zinc or activation of zinc-dependent antioxidant defense systems in response to xenobiotic-induced acute toxic stress.

The co-administration of cadmium chloride with iron was accompanied by a less pronounced accumulation of zinc in the myocardium (63.7 ± 4.32 µg/g) compared to the pure metallotoxicity group, although this value remained higher than the control. This indicates a partial mitigating effect of iron on the processes of zinc redistribution in cardiac tissues. In the group of animals receiving cadmium chloride alongside zinc, the content of the studied microelement in the heart was 81.34 ± 8.11 µg/g. This level is predictably higher than the control due to exogenous element intake, yet nonsignificantly lower than that of the isolated cadmium exposure group. We believe that this latter finding may indicate that supplemental zinc administration partially prevents

the pathological destruction of tissue stores and the chaotic redistribution of intrinsic endogenous zinc within the myocardium under xenobiotic exposure.

On day 20 of the study, a decrease in heart zinc levels was observed across all experimental groups of

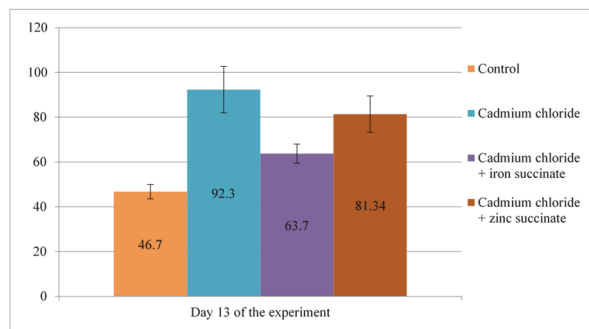


Fig. 3. Zinc accumulation level (µg/g) in the hearts of pregnant female rats in the experimental groups on day 13 of the experiment.

We attribute the decrease in the level of this essential microelement to the physiological requirements of the pregnant female, metabolic remodeling, and embryonic development. In the isolated cadmium administration group, the zinc level was 79.52 ± 6.3 µg/g, which was 1.2-fold lower than the level recorded on day 13 of the experiment. A nonsignificant decrease in cardiac zinc levels in pregnant females compared to the previous time point was also observed in the group with combined cadmium and iron succinate administration. In the experimental group combining cadmium with zinc, a further increase in myocardial zinc concentration in females was recorded; however, due to the specifics of the experimental protocol, these results were not directly compared. Thus, prolonged administration of cadmium chloride, both alone and co-administered with metal succinates, alters the pattern of zinc accumulation in the cardiac tissue of pregnant animals.

Analysis of iron accumulation results in the myocardium of pregnant females showed that under cadmium chloride exposure, iron levels decreased as early as day 13 of the experiment to 278.9 ± 13.50 mg/kg, representing a 28.7 % reduction compared to control values (387.4 ± 10.47 mg/kg). In the group with combined cadmium and iron succinate intake, the parameter was restored toward control values (340.3 ± 21.10 mg/kg), which was logical given the daily administration of iron itself according to the experimental design. In the cadmium and zinc succinate co-administration group, a partial preservation of iron stores was also observed, reaching 320.7 ± 16.91 mg/kg. This indicates a modifying effect of iron and zinc succinates on cadmium chloride cardiotoxicity, as these microelements maintained mineral homeostasis in the hearts of experimental animals in our rat study. At the next observation period – at the end of rat pregnancy (day 20) – cardiac iron levels in adult females were distributed as follows. In the control group, this parameter nonsignificantly increased (411.46 ± 10.51 mg/kg), which we attribute to active changes in the microelement balance of the pregnant female prior to parturition. However, chronic

pregnant female rats compared to the previous observation period (Fig. 4). This trend was evident even in the control group, where zinc levels nonsignificantly decreased compared to day 13 of the experiment.

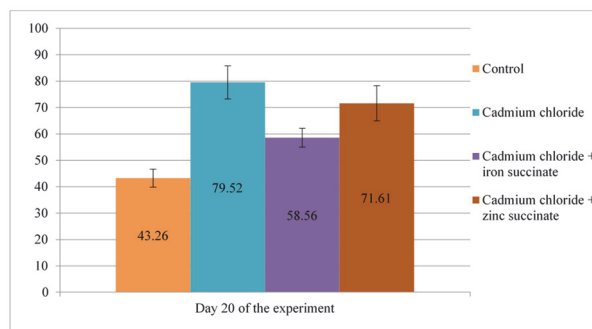


Fig. 4. Zinc accumulation level (µg/g) in the hearts of pregnant female rats in the experimental groups on day 20 of the experiment.

excess intake of cadmium continued to reduce iron levels in the hearts of the cadmium intoxication group (287.51 ± 12.47 mg/kg), reaching a 30.1 % reduction compared to control. Thus, the downward trend in iron levels persisted throughout the gestation period in the experimental group with isolated cadmium chloride exposure.

The use of multi-element analysis of the hearts of pregnant female rats allowed us to conclude that the administration of cadmium chloride leads to changes not only in cadmium levels but also causes zinc and iron dyselementosis. Calculation and comparison of the obtained experimental results demonstrated the modifying effect of zinc and iron succinates on the degree of microelement accumulation in the hearts of adult females when co-administered with cadmium in the rat experiment.

Discussion. Intensive accumulation of cadmium by the myocardium was accompanied by alterations in the microelement balance – specifically of zinc and iron—at both study time points under isolated administration of the toxicant. Co-administration of cadmium with iron succinate induced a statistically significant reduction in myocardial cadmium accumulation during the first half of pregnancy, whereas the combination of cadmium with zinc succinate reduced cadmium accumulation at both time points compared to the isolated administration group. Thus, the experiment demonstrated the modifying effect of zinc and iron succinates on the level of cadmium accumulation in a chronic rat study at the investigated doses and administration route. We believe that iron succinate and zinc succinate can be considered substances with antioxidant and antihypoxic properties that attenuate myocardial dyselementosis in experimental animals upon simultaneous intake with cadmium chloride. Similar research directions have been encountered in studies by international researchers, which demonstrated that zinc induces metallothionein and reduces cadmium toxicity in mouse cardiac tissues [3, 10]. Hypotheses were considered stating that zinc administration reduced apoptosis and the inhibition of cardiomyocyte

contractions, and mechanisms of competitive cadmium and zinc transport were investigated [7, 14]. The experimental data we obtained are consistent with current literature: zinc and iron succinates can indeed reduce cadmium accumulation in the myocardium and exhibit antioxidant and antihypoxic properties. This confirms the promise of their application for correcting dyselementosis during cadmium intoxication [8].

Evaluating the dynamics of cadmium, zinc, and iron content in the heart of experimental animals allows for determining the degree of myocardial damage and pathogenetically substantiating the cardioprotective effect of novel biometal succinates. The search for novel potential bioantagonists against toxic ecopollutant microelements among biogenic metals remains ongoing.

Conclusions

1. Isolated administration of cadmium chloride at the specified dose and route leads to an increase in cadmium accumulation levels in the heart tissues of adult females on both day 13 and day 20 of the experiment. Combined administration of cadmium with iron succinate and zinc succinate reduces the cadmium accumulation level in the myocardium of pregnant females. The obtained data allow for considering zinc and iron succinates as complexes with metalloprotective and antioxidant properties that can be investigated as potential bioantagonists of cadmium chloride.

2. Isolated chronic administration of cadmium leads to an increase in zinc levels in the hearts of pregnant females on day 13 of the experiment up to $92.3 \pm 10.36 \mu\text{g/g}$, which is nearly twice the control values. However, on day 20, a nonsignificant decrease in zinc levels compared to the previous time point was observed ($79.5 \pm 6.3 \mu\text{g/g}$), which we attribute to the physiological requirements of the pregnant female for this essential microelement, metabolic remodeling, and embryonic development.

3. In the cadmium and iron succinate co-administration group, a decrease in heart zinc levels in pregnant females was observed compared to the intoxication group, whereas the results of zinc succinate combined with cadmium were not evaluated in this context due to exogenous zinc intake. Thus, prolonged administration of cadmium chloride, both alone and co-administered with metal succinates, alters the pattern of zinc accumulation in the cardiac tissue of pregnant animals.

4. Cadmium chloride exposure reduces myocardial iron levels in female hearts by 28.7 % compared to control values. In the groups receiving combined cadmium with either iron or zinc succinate, this parameter was restored toward control values, indicating a modifying effect of iron and zinc succinates on cadmium chloride cardiotoxicity, as these microelements maintained mineral homeostasis in the hearts of experimental animals in our rat study.

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Conflict of interest. The authors have no conflicts of interest to declare.

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