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## EXPERIMENTAL STUDY OF THE INFLUENCE OF ADVERSE EXTERNAL FACTORS ON THE HISTOLOGICAL STRUCTURE OF BONE TISSUE COMPONENTS OF RATS

**Abstract.** Environmental contamination is becoming an increasingly serious problem for humanity every year. One of the most dangerous, long-acting and stable pollutants are heavy metals, the most common man-made associations of which are represented by salts of mercury, cadmium and lead. Cadmium and its compounds enter the body mainly through the respiratory tract (10-40%). In areas with cadmium-contaminated soils, dust is a potentially important source of the toxicant entering the body. The natural content of cadmium in the most important food products is small and is in the range of 0.001 - 1.5 mg/kg (the exception is the kidneys of animals: up to 40 mg/kg), but it can be much higher due to anthropogenic pollution. Chronic cadmium intoxication, mediated by the above-mentioned Cd-induced mechanisms of cytotoxicity, can cause the development of asthenovegetative, asthenoneurotic and neurasthenic syndromes with vegetative disorders, cadmium parkinsonism, progressive pneumosclerosis and emphysema of the lungs, gastrointestinal disorders, kidney and liver dysfunction, damage to the testicles, adrenal glands, hypochromic anemia and lesions of bone and cartilage tissue. Currently, the use of succinates (preparations based on succinic acid) is one of the priorities of modern fundamental and practical medicine. Drugs containing succinic acid (metal succinates, mexidol, reamberin, etc.) are drugs of metabotropic type of action, the pharmacotherapeutic effects of which are aimed at restoring biochemical metabolic reactions disrupted by pathological processes. Succinic acid is an intracellular metabolite that is involved in metabolic processes in the body and

acts as a substrate for oxidative phosphorylation in the mitochondrial cycle of tricarboxylic acids, performing a catalytic function, reduces the concentration of lactate, pyruvate and citrate, the level of which increases energy. required for normal cell function. This intermediate refers to low-toxic compounds and has no mutagenic or teratogenic effects. Succinates, by restoring the balance of activity of pro- and antioxidant systems, inhibiting the excessive generation of reactive oxygen species and weakening the processes of lipid peroxidation, can potentially eliminate or significantly reduce the manifestations of Cd-induced toxicity, the leading mechanism of which is considered oxidation. Given the above, experimental study of morphological Cd-induced pathological changes in rat bones and evaluation of the possibility of correction of cadmium-associated osteotoxicity by using succinic acid preparations, in particular, iron and zinc succinates as potential biological antagonists of cadmium, is urgent and urgent.

**Keywords:** osteotoxicity, bone tissue, rats, experiment, histological changes, morphology, different types of bones, femur, mandible, environmental pollution, succinates, cadmium.

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### **ЕКСПЕРИМЕНТАЛЬНЕ ВИВЧЕННЯ ВПЛИВУ ЗОВНІШНІХ НЕСПРИЯТНИХ ФАКТОРІВ НА ГІСТОЛОГІЧНУ СТРУКТУРУ КОМПОНЕНТІВ КІСТКОВОЇ ТКАНИНИ ЩУРІВ**

**Анотація.** Забруднення навколишнього середовища з кожним роком стає все більш серйозною проблемою для людства. Одними з найбільш небезпечних, довго діючих і стійких забруднювачів є важкі метали, найпоширенішими техногенними асоціаціями яких є солі ртуті, кадмію і свинцю. Кадмій і його сполуки потрапляють в організм переважно через дихальні шляхи (10-40%). У районах забрудненими кадмієм ґрунтами пил є потенційно важливим джерелом надходження токсиканту в організм. Природний вміст кадмію в найважливіших продуктах харчування невеликий і

знаходиться в межах 0,001 - 1,5 мг/кг (виняток становлять нирки тварин: до 40 мг/кг), але може бути значно вищим за рахунок антропогенне забруднення. Хронічна інтоксикація кадмієм, опосередкована зазначеними вище Cd-індукованими механізмами цитотоксичності, може спричинити розвиток астеновегетативного, астеноневротичного та неврастенічного синдромів із вегетативними розладами, кадмієвого паркінсонізму, прогресуючого пневмосклерозу та емфіземи легень, шлунково-кишкових розладів, дисфункції нирок та печінки., ураженню яєчок, надниркових залоз, гіпохромної анемії та ураженню кістково-хрящової тканини. Нині використання сукцинатів (препаратів на основі бурштинової кислоти) є одним із пріоритетних напрямків сучасної фундаментальної та практичної медицини. Препарати, що містять бурштинову кислоту (сукцинати металів, мексидол, реамберин та ін.), — це препарати метаботропного типу дії, фармакотерапевтична дія яких спрямована на відновлення порушених патологічними процесами біохімічних реакцій обміну речовин. Бурштинова кислота є внутрішньоклітинним метаболітом, який бере участь в метаболічних процесах в організмі і виступає субстратом для окисного фосфорилування в мітохондріальному циклі трикарбонових кислот, виконуючи каталітичну функцію, знижує концентрацію лактату, пірувату і цитрату, рівень яких підвищує енергію, необхідні для нормального функціонування клітин. Цей проміжний продукт відноситься до малотоксичних сполук і не має мутагенної або тератогенної дії. Сукцинати, відновлюючи баланс активності про- та антиоксидантної систем, пригнічуючи надмірне утворення активних форм кисню та послаблюючи процеси перекисного окиснення ліпідів, можуть потенційно усунути або значно зменшити прояви Cd-індукованої токсичності, провідний механізм якої вважається окисненням. Враховуючи вищезазначене, актуальним є експериментальне вивчення морфологічних Cd-індукованих патологічних змін у кістках щурів та оцінка можливості корекції кадмій-асоційованої остеотоксичності за допомогою препаратів бурштинової кислоти, зокрема сукцинатів заліза та цинку як потенційних біологічних антагоністів кадмію.

**Ключові слова:** остеотоксичність, кісткова тканина, щури, експеримент, гістологічні зміни, морфологія, кістки різного типу, стегнова кістка, нижня щелепа, забруднення навколишнього середовища, сукцинати, кадмій.

**Introduction.** Environmental protection in the interests of public health, in particular, reducing the risk of adverse effects of pollution of various natural objects on humans, is a fundamental task of state environmental policy [1]. Prevention of environmental degradation and danger to the population due to anthropogenic or natural factors is currently considered the basis of environmental security of the state, which is an important component of national security [2].

Contamination of the environment, which is becoming an increasingly serious problem for mankind every year, does not contribute to the harmonious



relationship between the world's population and the natural environment. [1, 2]. According to the Lancet Commission of the Global Alliance on Health and Pollution (Global Alliance for Health and Pollution, GAHP), Ukraine is included in the anti-rating of European countries by the number of fatalities related to environmental pollution. This factor is considered by scientists to be the cause of the annual death of more than 57,000 Ukrainians – this is the fourth indicator in Europe. The same "honorable" fourth place Ukraine ranks in the number of deaths per 100 thousand population - 128 cases [3].

**Literature Review.** One of the most dangerous, long-acting and stable pollutants are heavy metals, the most common man-made associations of which are salts of mercury, cadmium and lead, which when entering the body of mammals stimulate oxidative stress and compete with biogenic metals (zinc, copper, calcium, etc.) binding to the active center of many proteins and enzymes, causing disruption of their functions [5].

Cadmium (Cd) is a natural element with a relatively low content in the earth's crust (0.1-0.5 parts per million). In the free state in the environment does not occur, but is present mainly in the form of free hydrate ions and complex compounds with inorganic (chloride, carbonate, sulfide and hydroxide complexes) and organic ligands (amino, fulvic and nucleic acids) [5, 6].

Cadmium contamination of the environment (air, water and soil) is carried out from natural or man-made (anthropogenic) sources. According to Z. Rahman et al. (2019) та G. Genchi et al. (2020), the share of anthropogenic sources in environmental pollution is 3-10 times greater than natural, and ranges from 54% to 95% [5, 6].

**Materials and Methods.** Cadmium and its compounds enter the body mainly through the respiratory tract (10-40%), as well as the diet: the average "consumption" of the element with food, typically ranges from 8 to 25 mcg per day, of which approximately 0.5-1.0 mcg is actually stored in the body. "Inorganic" cadmium accumulates primarily in the liver, to a lesser extent - in the male genitals. The main part of the total cadmium in the form of a thiol complex is still absorbed by the kidneys: a violation of their functioning occurs when the concentration of the toxicant in the cortical layer of the body is about 200 mg / kg. The biological half-life of cadmium ranges from 40 days in the blood to 20 years or more - in the kidneys and liver. The FAO / WHO provisionally acceptable limit for "safe" cadmium intake is 7 µg / week / kg body weight or 25 µg / kg body weight per month, and the maximum dose is 60-70 µg per day [6, 7].

A set of studies conducted in the first twenty years of the XXI century showed that one of the important "targets" of the negative effects of cadmium is cartilage: prolonged exposure to the toxicant leads to increased fragility of the skeleton and reduced bone mineral density [8].

The key role in understanding the processes of regulation of bone reconstruction belongs to the cytokine system of the receptor activator of nuclear

factor kappa- $\beta$  (Receptor Activator of Nuclear factor kappa-B, RANK), its ligand (Receptor Activator of Nuclear factor kappa-B Ligand, RANKteger) and osteo , OPG), responsible for osteoclastogenesis, resorption and remodeling of bone tissue. Regulation of bone remodeling occurs under the influence of systemic and local factors with hormonal activity. PTH, calcitriol, somatotrophic hormone, insulin, thyroid and sex hormones affect bone remodeling by maintaining a constant metabolism of calcium, phosphorus, magnesium from bone to extracellular fluid and vice versa. Local factors (insulin-like growth factor, osteoclast-activating factor, platelet-derived growth factor, fibroblast growth factor, prostaglandin E2) are mediators of the response to mechanical stress and changes in systemic hormone levels. Imbalance between the processes of bone remodeling is a central link in the pathogenesis of osteoporosis, including cadmium induced [8-9].

In this aspect, the "indicative" victims of cadmium are patients with endemic disease itai-itai ("it hurts – it hurts disease"), which was first discovered in the Jinzu River Basin in Toyama Prefecture (Japan) in the 1920s [9]. The level of urinary excretion of cadmium in itai-itai patients ranged from 10-30  $\mu\text{g}$  / g creatinine, and the results of radiological examinations of their bones showed the presence of Loozer zones - areas with abnormal radiolucency, which crossed one or both cortical edges of the bone and was an obvious indicator of osteoporosis. [9].

In 2000 M. Kasuya substantiated the mechanism of osteomalacia in patients with itai-itai, explaining it by the development of Cd-induced renal tubular insufficiency, which led to increased bone resorption and, finally, to bone damage [10]. However, this mechanism of osteoporosis in patients with itai-itai did not explain all the phenomena observed in other people who were exposed to cadmium. Thus, R. Honda et al. (2003) found reduced bone mineral density in Japanese women without signs of renal impairment [11], which demonstrated the complexity of the mechanisms of Cd-induced osteotoxicity.

Currently, two mechanisms of cadmium effect on bone tissue are assumed - direct and indirect. The direct mechanism involves the direct effect of the toxicant, which causes dysfunction of bone cells and causes increased bone resorption and weakening of its calcification. The indirect mechanism is mediated by the development of Cd-induced renal failure, associated with increased renal excretion of calcium and phosphorus, inhibition of the production of active metabolites of vitamin D, and impaired absorption of calcium in the digestive tract [12].

It is now believed that the main cause of bone damage in chronic cadmium intoxication is renal dysfunction. At the same time deterioration of a condition of microarchitectonics of bone tissue with the subsequent strengthening of fragility of bones and risks of fractures increases in proportion to degree of defeat of the tubular device of kidneys. Dysfunction of the enzymatic system that metabolizes vitamin D causes a decrease in the production of its active metabolite –  $1\alpha$ , 25-dihydrooxycalciferol ( $1\alpha$ , 25 (OH) 2D) in the proximal tubules. A number of studies of  $1\alpha$ , 25 (OH) 2D and parathyroid hormone (PTH) in residents with Cd-induced

renal impairment showed that decreased levels of this active metabolite were closely correlated with increased PTH and  $\beta$ 2-microglobulin. Once the accumulation of cadmium in the kidneys reaches the critical level required to induce proximal tubular dysfunction, the content of the active metabolite of vitamin D in the serum decreases significantly, and calcium loss - on the contrary, increases. Decreased serum production of 1,25-dihydroxycalciferol causes impaired reabsorption of calcium from the gastrointestinal tract, which in turn increases the secretion of PTH, which activates osteoclasts to "resorb" bones and release calcium into the systemic circulation and osteoporosis [12].

The direct effect of cadmium on bone metabolism has been demonstrated by studies of levels of biomarkers of bone remodeling. Thus, abnormal bone synthesis was accompanied by an increase in the concentration of osteocalcin in the serum and alkaline phosphatase in the bones. Acceleration of bone resorption, which did not depend on renal dysfunction and was manifested by an increase in deoxypyridioline, as well as N- and C-terminal telopeptide of type I collagen (NTx and CTx), was found even in people with low cadmium levels [2, 11].

In vivo studies in experimental animals have shown that chronic exposure to cadmium reduces the mineralization of vertebral bodies, changing their biomechanical properties and making them more susceptible to deformation and destruction. [29]. The results of studies by J. Rodríguez et al. (2016) and D. García-Mendoza et al. (2019) provided evidence that chronic exposure to cadmium reduces bone volume and increases the activity of Tartrate-Resistant Acid Phosphatase (TRAP) in the subchondral layer of the tibia [8, 14], indicating the induction of osteopenia by increased bone resorption. There was an increase in the percentage of adipose bone marrow, which indicated cadmium deprivation of differentiation of mesenchymal cells to osteoblasts by stimulating adipogenesis [14].

In vitro studies have shown that cadmium increases RANKL expression, TRAP activity and TRAP-positive cell formation in the presence of RANKL, and stimulates osteoclast formation in osteoblast and osteoclast progenitor subculture. In addition, cadmium has been shown to induce osteoblast apoptosis by disrupting their cytoskeleton, as well as causing DNA fragmentation, an increase in the number of micronuclei and nuclear bridges, and an increase in reactive oxygen species [10, 12].

Another potential "target" of the negative effects of cadmium on the musculoskeletal system is articular cartilage. An adequate cell model for studying the mechanisms of Cd-induced toxicity was provided by the culture of primary chondrocytes in vitro, obtained by stepwise digestion with trypsin and collagenase IV cartilage of the knee joint of 15-day-old chicken embryos. The study showed that cadmium inhibited the expression of COL2A1 macromolecules and acid mucopolysaccharides in the extracellular cartilage matrix and promoted the expression of MMP-9 protein [15].

Due to the fact that the leading mechanism underlying Cd-induced cytotoxicity is oxidative stress [6, 15, 16], it can be assumed that restoring the



balance of activity of pro- and antioxidant systems, inhibition of excessive generation of reactive oxygen species (ROS), weakening of lipid peroxidation processes against the background of increasing the energy potential of the cell will potentially contribute to leveling or significantly weakening.

Traditionally, the main sources of ROS in mitochondria were considered to be the respiratory complex I (NADH: ubiquinone oxidoreductase, CI) and complex III (ubiquinol: cytochrome oxidoreductase c, CIII), while the contribution of complex II (succinate dehydrogenase, LDH, CII) in this process was practically not taken into account [17]. However, it soon became known that mitochondrial complex II is indeed able to generate high concentrations of reactive oxygen species under conditions of low levels of succinate when the flow of electrons to the respiratory chain is blocked. [18]. It was shown that the main site of production of reactive oxygen species in the respiratory complex II is FAD, covalently linked to the subunit A of succinate dehydrogenase, provided that the binding site of dicarboxylate is free. Fully reduced FAD can transfer either one electron to oxygen, causing the formation of superoxide under aerobic conditions (which is characteristic of succinate: ubiquinone oxidoreductase), or two electrons, generating H<sub>2</sub>O<sub>2</sub> (which is typical of fumarate: ubiquinone reductase, which functions in the environment) [19].

In 2015, K. Kluckova and a team demonstrated that the ability of the succinate dehydrogenase complex to generate ROS links it with the process of cellular apoptosis. Thus, studies of complex II integrity have shown that induction of cell apoptosis is associated with specific enzyme degradation, resulting in SDGA and SDHV subunits being released from the membrane domain into the mitochondrial matrix, then remaining enzymatically active and can effectively remove electrons from succinate. Due to the absence of electron acceptors as a result of separation from SDGS and SDGD, the flow of electrons is blocked, they are transferred to molecular oxygen, generating excessive amounts of ROS, which induce cellular apoptosis [20].

The results of studies of the 70-80s of the last century showed that succinates have an inhibitory effect on lipid peroxidation in mitochondria / mitoplasts / submethochondrial particles formed by NADPH / ADP / Fe<sup>3+</sup> + complexes or organic hydropero. These prooxidants significantly stimulated the formation of malonic dialdehyde (the final product of LPO), and lipid peroxidation of membranes dissipated mitochondrial membrane potential due to the appearance of physical "holes" in the lipid bilayer. In a study by P. Sharmila et al. (2017) showed the accumulation of proline in mitochondria and a decrease in the ability of mitochondria to oxidize nicotinamide-adenine-dinucleotide by 35% under the action of cadmium. The protective role of succinate as a mitochondrial respiratory substrate was mainly due to a decrease in the CoQ pool. NAD<sup>+</sup> -dependent substrates were less effective in inhibiting lipid peroxidation because strong peroxide stimuli permeate the membranes, releasing NAD<sup>+</sup>. Therefore, with decreasing coenzyme

concentration, the oxidation of substrates slowed down and the formation of the antioxidant CoQH<sub>2</sub> decreased. However, succinate was oxidized by membrane-bound succinate dehydrogenase, and the activity of the enzyme was only moderately sensitive to oxidants. Therefore, succinate was more effective in maintaining the pool of CoQH<sub>2</sub>, thus ensuring the integrity of cell membranes [21].

So:

- succinates have an inhibitory effect on lipid peroxidation in mitochondria / mitoplasts / submethochondrial particles formed by NADPH / ADP / Fe<sup>3+</sup> + complexes or organic hydroperoxides [17];
- the protective role of succinates as a mitochondrial respiratory substrate is mainly due to the support of the CoQH<sub>2</sub> pool, which ensures the integrity of cell membranes [5, 16];
- succinates inhibit FAD-induced electron transfer to oxygen in mitochondrial respiratory complex II, which significantly reduces the production of superoxide and H<sub>2</sub>O<sub>2</sub> [10];
- succinates inhibit the generation of reactive oxygen species, disrupting the transfer of electrons through complex II to the pool of ubiquinones [15].

Currently, the use of succinates (preparations based on succinic acid) is one of the priorities of modern fundamental and practical medicine. Drugs containing succinic acid (metal succinates, mexidol, reamberin, etc.) are drugs of metabotropic type of action, the pharmacotherapeutic effects of which are aimed at restoring biochemical metabolic reactions disrupted by pathological processes. Succinic acid is an intracellular metabolite that is involved in metabolic processes in the body and acts as a substrate for oxidative phosphorylation in the mitochondrial cycle of tricarboxylic acids, performing a catalytic function, reduces the concentration of lactate, pyruvate and citrate, the level of which increases energy. required for normal cell function. This intermediate refers to low-toxic compounds and has no mutagenic or teratogenic effects [22].

**Conclusion.** Succinates, by restoring the balance of activity of pro- and antioxidant systems, inhibiting the excessive generation of reactive oxygen species and weakening the processes of lipid peroxidation, can potentially eliminate or significantly reduce the manifestations of Cd-induced toxicity, the leading mechanism of which is considered to be oxidation.

Given the above, experimental study of morphological Cd-induced pathological changes in rat bones and evaluation of the possibility of correction of cadmium-associated osteotoxicity by using succinic acid preparations, in particular, iron and zinc succinates as potential biological antagonists of cadmium, is urgent and urgent.

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