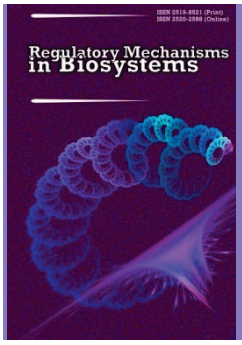

Regulatory Mechanisms in Biosystems

ISSN 2519-8521 (Print)
ISSN 2520-2588 (Online)
Regul. Mech. Biosyst.,
2023, 14(3), 415–423
doi: 10.15421/10.15421/022361

Ecological and toxicological features of the effect of stable cesium on striated muscle tissue (myocardium and skeletal muscles) of mammals

O. Yermishev

Vasyl' Stus Donetsk National University, Vinnytsia, Ukraine

Article info

Received 04.07.2023
Received in revised form 31.07.2023
Accepted 16.08.2023

Vasyl' Stus Donetsk National University, 600-richya st., 21, Vinnytsia, 21021, Ukraine.
Tel.: +38-098-400-33-33.
E-mail: o.yermishev@donnu.edu.ua

Yermishev, O. (2023). Ecological and toxicological features of the effect of stable cesium on striated muscle tissue (myocardium and skeletal muscles) of mammals. Regulatory Mechanisms in Biosystems, 14(3), 415–423. doi:10.15421/10.15421/022361

Recently, the risks of radiation danger have significantly increased. This is connected with the start of a full-scale war against Ukraine and the seizure of the Zaporizhzhya NPP by the Russian Federation, which has the second most powerful arsenal of nuclear weapons in the world. The majority of studies devoted to the effect of radioactive radiation on the human body and animals absolutely do not take into account the ecotoxic effect of the carrier and a chemical element. At the same time, the body does not distinguish between radioactive and non-radioactive isotopes of chemical elements and interacts with them during exchange processes. The aim of the work was to study the influence of stable cesium on the microscopic structure of striated muscle tissue, both skeletal and cardiac ones. The results of our research revealed that intensive accumulation of cesium for 24 days occurred in all the examined organs and tissues. In fact, the most intensive accumulative process appeared to be in the heart by 214.9 times and by 695.3 times with skeletal muscles, with a simultaneous decrease in potassium content by 19.2% and 29.1%, respectively, compared to intact rats. We can talk about the presence of two mechanisms of action of cesium on tissues, including striated muscles: as an antagonist of potassium, which concerns the transport system of the latter and as a toxic element that initiates peroxide processes with subsequent modification of membranes and their potassium channels. Functional disturbances in the work of potassium channels of excitable tissues in the repolarization phase occur in the conditions of an increase in intracellular cesium in striated muscles. These disorders can proceed according to the type of acquired "potassium" channelopathies, which in the myocardium can manifest in the form of rhythm disorders, prolonged QT syndrome, etc. This leads to the appearance of significant violations of the histological structure of the examined tissues. Cesium has pronounced damaging effects on both skeletal and cardiac striated muscle tissue, with morphological changes in skeletal and cardiac striated muscle tissue being generally similar. Dystrophic changes in the nuclei and cytoplasm of cardiomyocytes and striated muscles, signs of impaired blood circulation in the microcirculatory channel with the formation of vascular wall edema, destruction of endothelial cells, various types of hemorrhages and lymphohistiocytic infiltration of the stroma of fibers are the consequences of the toxic effect of cesium on tissues. Thus, the results of changes in the histological structure of striated muscles under the action of cesium chloride obtained by us indicate a fairly high cytocidal activity of stable cesium.

Keywords: stable cesium; myocardium; skeletal muscles; striated muscle tissue; morphological changes; histology.

Introduction

Significant achievements in the creation of radiation technologies and the mastery of nuclear energy have presented humanity with a number of new problems. In particular, this is radioactive pollution of the environment during accidents and its negative impact on the health of the population. Unfortunately, the risks of radiation danger, the protection of current and future generations of people in Ukraine from the harmful effects of ionizing radiation are constantly increasing. This is due to the full-scale invasion against Ukraine launched by the Russian Federation on February 24, 2022. In addition to the fact that the Russian Federation has the second largest arsenal of nuclear weapons in the world, it, contrary to all laws and regulations, temporarily seized the Chernobyl nuclear power plant and until now holds the Zaporizhzhia nuclear power plant, which is the largest in Europe and the third largest in the world (6 power units – 40% of all nuclear reactors in Ukraine), exposing the population of Ukraine and the European Union to a colossal radiation hazard.

In the period from 1954 to the present, about 300 accidents were registered at radiation-hazardous facilities in various countries of the world, including more than 30 large ones, which were accompanied by releases of radionuclides into the environment, and in some cases, human casualties. The history of nuclear energy has the experience of three serious accidents: at the Three Mile Island nuclear power plant, USA in 1979; Chernobyl NPP, Soviet Union in 1986; at the Fukushima-1 nuclear power plant, Japan in 2011.

On April 26, 1986, an accident occurred at the IV power unit of the Chernobyl Nuclear Power Plant, which led to the destruction of the reactor's active zone and to the radiation and environmental disaster of a global scale. The total activity of the release is estimated at 14 EBq (1 EBq = 10^{18} Bq) of radioactive materials, including 1.8 EBq of ^{131}I, 0.085 EBq of ^{137}Cs, 0.01 EBq of ^{90}Sr and 0.003 EBq of plutonium isotopes.

The Fukushima (Dai-ichi) nuclear accident was the result of a series of equipment failures caused by the aftermath of the 9.0-magnitude earthquake and tsunami on March 11, 2011, which led to the release of radioactive materials from the Fukushima-1 nuclear power plant. The total release from the Fukushima-1 reactors was estimated to be 0.16 EBq for ^{131}I and 0.015 EBq for ^{137}Cs (Saito at al., 2020).

The impact of the consequences of the Chernobyl disaster for Ukraine, despite all the measures that were taken, unfortunately, has not decreased until now and some problems have become even more relevant. There is a steady increase in morbidity and socio-psychological stress of the population living in polluted areas. Two-thirds of all radionuclides that entered the atmosphere as a result of the accident at the Chernobyl nuclear power plant fell on the territory of Ukraine. Every fifth resident of Ukraine

including more than 500,000 children were affected. The increase in morbidity is associated with a large collective dose that the population of Ukraine received both at the time of the accident and continued to receive in the post-accident period (due to the consumption of locally produced products). The main trends in the health of the population: growth rates of a number of nosologies (CVS, hematopoietic, diseases of the gastrointestinal tract, immune system) among all categories of the population; there is a high morbidity of the population that lived in the territories with soil pollution density from 1 to 5 Ki/km^2; the frequency of intrauterine fetal development disorders, which manifests itself in an increase in malformations in newborns, remains at a fairly high level (a positive correlation between the frequency of congenital malformations and the radiation dose has been established); the population is observed to receive significant doses of radiation, which is realized by chromosomal mutations and genetic damage; an atypical course of diseases is observed; there is an increase in mental disorders. Moreover, the radiation factor is at the basis of the pathology growth in the Chernobyl regions in most cases, which causes a violation of the functions of the most important body systems, making them the basis of future pathology development (Sartayev et al., 2021).

The effects caused by the incorporation of radionuclides are the most urgent radiobiological problem of the consequences of the Chernobyl accident (Cao et al., 2022). The main dose-forming radionuclide in the "post-Chernobyl" space is considered to be ^{137}Cs, which, being an analog of potassium, significantly affects many intracellular, including mitochondrial, processes in tissues and organs with a high level of metabolism. This is properly correlated with the data of clinical and epidemiological studies on a significant increase in morbidity among the population living in the areas affected by the accident at the Chernobyl nuclear power plant (Hrytsuk, 2011).

Diseases of the circulatory system occupy a special place in the general morbidity of the population that is constantly in the zone of radioecological disadvantage. For example, in the structure of morbidity of accident liquidators at the Chernobyl nuclear power plant, they make up 42%. There is an increase in the frequency of detection of coronary heart disease by 3.5 times compared to the pre-accident period, especially with severe forms of the course. Diseases of the circulatory system occupy a special place in the general morbidity of the population that is constantly in the zone of radioecological disadvantage. For example, in the structure of morbidity of accident liquidators at the Chernobyl nuclear power plant, they make up 42%. There is an increase in the frequency of detection of coronary heart disease by 3.5 times compared to the pre-accident period, especially with severe forms of the course (Avery, 1995; Saniewski et al., 2019; Saito & Tsukada, 2022).

Following the Fukushima Daichi Nuclear Power Plant (FDNPP) accidents in Japan in 2011, the number of surgeries for cryptorchidism and congenital heart disease in children increased. The number of diagnosed cases of thyroid cancer increased (from 2011 to 2016), which correlated with the radiation dose rate. Also, there was a decrease in the average birth weight of infants, violations of gestational development and pregnancy associated with the accumulation of ^{137}Cs in the body and the corresponding additional dose of radiation in Japan since 2012 (Scherb & Hayashi, 2020).

Most of the research in the field of radiobiology and radiation medicine devoted to the impact of radioactive radiation on the human body and animals absolutely does not take into account the ecotoxic effect of the carrier, a chemical element. At the same time, the body does not distinguish between radioactive and non-radioactive isotopes of chemical elements and interacts with them during exchange processes.

Unfortunately, until now there is not enough information about morphological changes in the tissues and organs of humans and animals due to excessive intake of stable cesium into the body, the effect of which has been studied much less than the effect of radioactive isotopes of this metal.

Recently, there have been quite a lot of scientific studies and publications regarding the possibilities of using stable cesium in the therapy of oncological diseases. Many of them are contradictory and information about the action of cesium at the cellular level may possibly make corrections in the general understanding of the mechanisms of the toxic action of cesium.

The aim of the work was to reveal the influence of stable cesium on the microscopic structure of striated muscle tissue, both skeletal and cardiac. It is known that the stable isotope of cesium ^{133}Cs has a tropism towards the myocardium and muscle tissue when it naturally enters the body of humans and animals. This is due to the almost complete analogy of metabolic pathways and kinetic characteristics of organ, tissue and subcellular exchange of potassium and cesium, as well as to the fact that the level of cesium accumulation in tissues is proportional to its respiratory activity.

Materials and methods

At all stages of the research, all procedures with animals were carried out in compliance with the generally recognized bioethical principles of the "three Rs", as well as the provisions of the Helsinki Declaration of the World Medical Association (2000), the relevant provisions of the WHO, the Council of Europe Convention on Human Rights and Biomedicine (1997), International Code of Medical Ethics (1983), the International Council of Medical Scientific Societies, "General Ethical Principles of Experiments on Animals", approved by the First National Congress on Bio-ethics (Kyiv, 2001) due to the provisions of the "European Convention for the Protection of Vertebrate Animals, which are used in experiments and many other educational purposes" (Strasbourg, March 18, 1986). The protocol of the experimental part of the study complies with the principles of biological ethics and was approved by the Local Ethics Committee of the Vasyl Stus Donetsk National University, Faculty of Chemistry, Biology and Biotechnology (Vinnytsia, Ukraine).

Young male white laboratory rats, weighing 180–200 g, kept in cages on a standard diet were used for research. The studies were performed in two groups of animals, in each of which 8 rats were selected; the first group – intact rats, the second – animals poisoned with cesium chloride by daily oral administration of 1.6% aqueous solution of cesium chloride (manufactured by Jinan Great Chemical Industry Co., Ltd., China) at a dose of 75 mg/kg, which is 1/20 LD_{50}. The experiment lasted 24 days.

The rats were euthanized by terminal blood sampling by cardiac puncture under anesthesia with total exsanguination of the animal on the fourth and 24th days. The content of cesium and potassium in the selected biological samples was determined using the method of atomic emission spectroscopy with inductively coupled plasma (AES-ICP) on an Ortima 2100 DV device from Perkin-Elmer (USA) on day 24. Biochemical parameters of blood, namely: the activity of enzymes: aspartate aminotransferase (AST, E.S. 2.6.1.1), alanine aminotransferase (ALT, E.S. 2.6.1.2), alkaline phosphatase (ALP, E.S. 3.1.3.1), gamma-glutamine transaminase (GGT, E.S. 2.3.2.2), α-amylase (E.S. 3.2.1.1), total protein, urea, creatinine, glucose were determined using a biochemical analyzer Roshe 9180 Electrolyte Analyser (Israel) with Vitalab Selectra "E" reagents (Netherlands).

For microscopic examination, the material was taken from pre-weighed animals. Pieces of skeletal muscle for microscopic examination were cut from the thigh muscles of rats, pieces of the heart muscles from the wall of the left ventricle. The material was fixed for 2–3 weeks in a 10% solution of neutral formalin with a three-time change of the fixative, then dehydrated in alcohols of increasing concentration, after which it was embedded in paraffin. Sections with a thickness of 10 μm were made from paraffin blocks on a sled microtome, stained with Karatsi's hematoxylin and eosin, examined and photographed under a Granium R-60 lux light-optical microscope.

Cesium (Cs) is an alkali metal of group 1 of D. I. Mendeleev's periodic system and belongs to trace elements. It is contained in extremely small amounts in all external environments. The Clark nuclide content in the Earth's crust is $3.7 \cdot 10^{-4}$%, soil – $5 \cdot 10^{-5}$%, living phytomass – $6 \cdot 10^{-6}$%. Cesium in the Earth's crust is 1.9 mg/kg and the concentration in seawater is about 0.5 μg/kg.

It is interesting that when comparing the concentration of toxic heavy metals in seawater with the concentration of cesium, it turns out that the concentration of cesium 0.3 μg/L is greater than the concentration of Pb and Hg (0.03 μg/L), Cd (0.11 μg/L), Mn (0.20), Cu (0.25) and Cr (0.30) (Egorov, 2019).

Cesium easily penetrates into the systems of plants and animals and is deposited in soft tissues (Saito at al., 2022). The total content of this intracellular form is very low, no more than 0.00131 g (Cao et al., 2022).

Cesium isotopes with mass numbers from 112 to 151 and 22 nuclear isomers (radioactive) are known. Natural cesium is a monoisotopic element consisting of one stable isotope, ^{133}Cs. The longest-lived artificial radioactive cesium nuclides are ^{135}Cs with a $T_{1/2}$ half-life of about 2.3 million years and ^{137}Cs ($T_{1/2}$ = 30.17 years). Cesium-137 is one of the culprits of radioactive contamination of the biosphere, as it is formed during nuclear fission in nuclear reactors and during nuclear weapons tests. Studies of the effects of cesium on the human body and animals intensified with the explosive development of nuclear energy and the creation of nuclear weapons (Cao et al., 2022). It is believed that ^{137}Cs can be detected in the environment for up to 300–600 years (Venturi, 2021).

In terms of basic physical and chemical characteristics, cesium is similar to potassium. Therefore, for example, most of its salts are easily soluble in water, so it is evenly distributed in the liquid environments of the body. Despite the significant difference in the relative atomic mass (respectively for potassium – 39, and for cesium 133–137), its atomic and covalent radii are only 11–12%, and the ionic radius exceeds those of potassium by 27%. However, functionally, it is not able to replace potassium in biochemical and physiological processes in the body. The important role of potassium in the body is evidenced by the increase in its concentration in animal tissues in the process of evolution from 0.9 mEq/100 g in the body of a freshly caught jellyfish to 12 mEq/100 g in the muscles of fish and 15 mEq/100 g in the muscles of mammals (Nesterov & Skulskii, 1965).

Cesium (Cs) is an alkali metal like potassium (K) and sodium (Na). The radius of the bare ion of alkali metal elements increases depending on the molecular weight (for example, 0.169 nm for Cs^+ and 0.133 nm for K^+); however, the hydrated radius of Cs^+ was determined to be the same as that of K^+ (0.33 nm). Therefore, it was assumed that Cs^+ is transported via K^+-transporters simultaneously blocking potassium channels (Gilles, 2022). Like potassium, cesium is intensively absorbed in the small intestine and excreted by the distal part of the nephron (Lyon & Mayhew, 2003). Absorption of cesium is associated with the depletion of both intracellular and extracellular potassium and is accompanied by the occurrence of cesium-associated hypokalemia (Horn et al., 2015; Kobayashi et al., 2021).

Processes of cesium displacement of potassium from cells are observed in all organisms, both plant and animal, including hydrobionts. Currently, there is a fairly large amount of data showing that the accumulation of a number of chemical elements by hydrobionts is determined not only by their content in the environment, but also by the concentration of their chemical analogues – macroelements – in water. First of all, this applies to such elements as Sr and Ca, Cs and K and to their radionuclides – ^{90}Sr and ^{137}Cs, the concentration of which by hydrobionts depends on the content of calcium and potassium, respectively. When potassium is replaced by sodium in an equivalent amount, marine macrophytes compensate for the deficiency of potassium by absorbing cesium (Egorov, 2019).

Cesium enters the human body mainly with food products. Only 0.25% enters through the respiratory system. The average content of cesium in the body of an adult is 0.0015 g with a daily intake of 10 μg (Davis et al., 1988). The concentration of cesium increased in all organs except the skin in the process of human ontogenesis after the first year of life and with age (Persigehl et al., 1977).

Little is known about the metabolism and toxicity of cesium. Cesium salts have been used in animal models to induce cardiac arrhythmias for several decades, but the consequences of cesium toxicity in humans have rarely been described. Cesium is considered a relatively safe and low-toxic (medium-toxic) metal. Signs of its mild toxicity are gastrointestinal disturbances, hypotension, syncope, numbness or tingling of the lips. As new results of studies of the effects of cesium salts on humans and animals become available, many experts are changing their minds in favour of classifying cesium as a compound with high toxicity (Cesium salts. Evaluation statement, 2021; www.industrialchemicals.gov.au).

Oral cesium chloride is widely promoted for use in alternative and integrative medicine (these are products and practices used alongside standard medical care) to treat the symptoms and side effects of cancer and its treatment despite the American Cancer Society's warnings about its use (www.cancer.org/treatment/treatmentsandsideeffects/complementaryandalternativemedicine/herbsvitaminsandminerals/cesium-chloride).

Cancer is the second leading cause of death worldwide, but current treatments are often inadequate or associated with toxicity. Initial evidence in the scientific literature appears to support a role for nonpharmacologic strategies, including hypoglycemia and controlled alkalosis in the treatment of cancer. Both hypoglycemia and controlled alkalosis in model studies can be obtained under the action of cesium drugs. The biological rationale for hypoglycemia-based cancer treatment is that cancer cells preferentially use glucose as an energy source; in particular, cancer cells have impaired regulation of glycolysis and several mitochondrial defects that demonstrate impaired oxidative phosphorylation. Preliminary data obtained as a result of preclinical and human studies confirm the role of hypoglycemia in the induction of apoptosis in cancer cells (Redaelli et al., 2019).

Cesium is also used as an alternative and complementary cancer treatment in the context of "high pH therapy". This therapy is based on the hypothetical preferential uptake of cesium cations by malignant cells in exchange for protons which should slow down the progression of the tumour cell cycle and the induction of apoptosis due to the formation of intracellular alkalosis. There is little scientific evidence to support this theory despite it being considered "alternative medicine". In addition, cells do not have clearance channels mediated by cesium (Cs^+) ions. Thus, such unstable electrochemical distributions have a serious potential to disrupt electrochemically dependent cellular processes such as glucose cotransporters. Therefore, a detailed study of the effects of changing pH and inhibiting glucose uptake is warranted as a possible cesium-induced antitumour therapy.

Cs has no known beneficial functions in humans confirmed by clinical studies; in addition, in high doses it causes toxicity and even death (Sessions et al., 2013). When ingested, cesium affects fertility and has reproductive toxicity. In males, the negative effect on the reproductive system is provided by a decrease in sperm motility and morphology at a dose of 38 mg/kg body weight/day. In women, a higher percentage of dead offspring in the postnatal days, lower average birth weight and reduced growth rates were observed (Australian Government Department of Health. Cesium salts. Evaluation statement, 2021).

Cesium chloride (CsCl) and cesium carbonate (Cs_2CO_3) have been used in the clinical setting as alternative cancer therapies, but their safety has yet to be evaluated and the efficacy of Cs in cancer therapy has never been demonstrated in controlled trials; however, relief of cancer-related pain and rapid reduction of tumour masses have been reported (Melnikov & Zanoni, 2010). Side effects of Cs include QT prolongation, hypokalemia, seizures, cardiac arrhythmia (torsades de pointes), syncope, and cardiac arrest. However, some patients treated with various doses of Cs have been reported to remain alive for 10–150 days and some others for up to one year (Kobayashi et al., 2017; Kobayashi et al., 2021).

Self-treatment of cancer with cesium chloride, despite its proven ineffectiveness, continues to cause serious side effects. Hypokalemia is among them contributing to the development of life-threatening arrhythmia (Horn et al., 2015).

Cesium consumption of 6 g per day has been found to cause severe hypokalemia, hypomagnesemia, prolongation of the QTc interval, episodes of polymorphic ventricular tachycardia and even acute cardiac arrest (Melnikov & Zanoni, 2010).

A case of cesium toxicity is described in the literature. It was manifested by syncope, polymorphic ventricular tachycardia, hypokalemia, and prolongation of the QT interval up to 650 milliseconds and which disappeared within 4 days after withdrawal of cesium at a dose of 3 g/day for 3 weeks (Lyon & Mayhew, 2003).

Thus, before using Cs as a treatment in the clinical setting, it is important to clearly define its biological effects on cells. However, Cs was found to inhibit the proliferation of human cervical cancer cells in a dose-dependent manner. Besides, it was suggested that Cs inhibits the glycolysis pathway. Interesting data were obtained in the study of the effect of cesium on cultured human HeLa cells, the growth and proliferation of which is inhibited by the addition of 10 mM CsCl to the culture medium. An increase and a decrease in the intracellular concentrations of cesium and potassium are respectively observed in cells treated with cesium, inducing an intracellular cation imbalance, and an intracellular pH shift towards alkalosis is observed. A decrease in the concentration of potassium ions leads to a decrease in the activity of the glycolytic enzyme pyruvate kinase which uses K^+ as a cofactor that leads to an energy deficit in cells (Kobayashi et al., 2017; Kobayashi et al., 2021). The study of the effect of cesium cations on

glycine receptors (GlyRs), which are one of the most widely distributed neurotransmitter receptors in the peripheral and central nervous systems, revealed an agonistic interaction with GlyRs (Fricke et al., 2023).

Also, the level of transcription and expression of hexokinase, glyceraldehyde-3-phosphate dehydrogenase, pyruvate kinase (PK), lactate dehydrogenase, and pyruvate kinase PK activity decreased under the influence of Cs. Analysis of the metabolites of the glycolysis pathway showed that under the influence of Cs there is an increase in the [NAD+]/[NADH] ratio and a decrease in the [lactate]/[pyruvate] ratio, which indicates the inhibition of aerobic glycolysis by cesium (Kobayashi et al., 2017; Kobayashi et al., 2021).

In vitro experiments with human lymphocytes cultured in a medium containing 250 and 500 μg/mL CsCl did not show an increase in the frequency of micronuclei compared to untreated controls. The same experiments, however, demonstrated a decrease in mitotic activity with an increase in the concentration of CsCl in the culture medium (Santos-Mello et al., 1999).

When studying the effect of cesium on platelet activity, plasma coagulation and fibrinolysis *in vitro* and *in vivo*, it was found that in the case of *in vitro* coagulation, CsCl had no significant effect on factor IX (FIX) activation compared to various monovalent salts; therefore, cesium does not affect FIX activity, and the only noticeable effect of cesium is the inhibition of ADP-mediated platelet activation (Nielsen et al., 2023).

Studies of the effect of nanoforms of cesium on the human body are promising for the development of new methods of treatment of tumour pathology. Thus, when comparing the effects of cesium and cesium nanoparticles (38 ± 6 nm), called NanoCs, on the human body, it was found that neither significantly changed the intracellular pH. In addition, NanoCs leads to a significant decrease in glucose uptake compared to free CsCl, suggesting that cesium inhibits glucose uptake and affects cell lifespan by initiating apoptosis instead of cytocidal action. In addition, NanoCs lead to tumor regression in vivo (Daza et al., 2016).

All the data were analyzed using Statistica 8.0 (StatSoft Inc., USA). The results in the tables are shown as x ± SE (mean ± standard error). The differences between values were considered significant at $P < 0.05$.

Results

Studying and understanding the medical and biological effects of incorporated cesium is impossible without a clear understanding of its tissue and intracellular distribution. Cesium has a fairly high coefficient of biological efficiency. It is also an analogue and antagonist of potassium which plays an important and functional role in the activity of the myocardium and muscle tissue as a whole. Being a weak Lewis acid with a low tendency to form complexes with ligands, the chemical similarity of Cs to the biologically necessary alkaline cation K^+ favours high levels of metabolism-dependent intracellular accumulation. The mechanism of the toxic effect of cesium on tissues and cells is associated not only with an increase in the concentration of the intracellular cluster of cesium, but also due to a decrease in the concentration of intracellular potassium, with displacement and blocking of absorption.

The results of our research revealed that intensive accumulation of cesium occurred in all the examined organs and tissues. In the blood of rats poisoned with cesium chloride the concentration of cesium increased by 8.09 times, in the liver by 29.5 times, in the kidneys by 383.3 times, in the heart by 214.9 times and in skeletal muscles by 695.3 times, in accordance with these indicators in the group of intact animals. But the greatest accumulation is observed in the muscles, heart and kidneys, the organs that are closely related to the exchange of potassium and which can be explained by the competitive relationship between potassium and cesium for the action of cesium chloride as a result of which cesium displaces potassium (Table 1). Also, the research results showed that under the action of cesium chloride on rats, there was a probable decrease in the content of potassium in the liver by 13.7%, in the heart by 19.2%, in the blood by 28.5%, in the muscles by 29.1% and in the kidneys - by 40.4%, compared to intact rats ($P < 0.05$, Table 2).

This is due to the fact that cesium, as an analogue/antagonist of potassium, is evenly distributed throughout the tissues when it enters the body and, like potassium, is deposited exclusively intracellularly, displacing the latter due to its higher chemical activity. Across the cell membrane, cesium is transported through potassium channels, which control potassium flux and play an important role in cell physiology. Potassium channels are grouped into four subfamilies that differ in domain structure, control mechanisms and functions, ensuring cell proliferation, migration, and apoptosis. It is capable of selectively accumulating in many organs, creating concentration gradients in the mitochondrial matrix and nucleus, which probably causes the development of mitochondrial dysfunction and genome instability.

Table 1
Cesium content in organs and tissues of rats poisoned with cesium chloride (μg/g, x ± SD, n = 8)

Organs and tissues	Intact rats	Rats poisoned with CsCl
Blood	5.45 ± 0.22	44.1 ± 1.0*
Liver	5.35 ± 0.23	157.9 ± 3.8*
Kidneys	4.91 ± 0.18	1882.1 ± 51.9*
Heart	6.86 ± 0.31	1474.0 ±46.5*
Muscles	3.32 ± 0.17	2309.5 ± 61.5*

Note: * – $P < 0.05$ compared to the control.

Table 2
Potassium content in organs and tissues of rats poisoned with cesium chloride (mg/g, x ± SD, n = 8)

Organs and tissues	Intact rats	Rats poisoned with CsCl
Blood	9517 ± 293	6808 ± 134*
Liver	10584 ± 620	9133 ± 1014*
Kidneys	10208 ± 380	5856 ± 152*
Heart	11792 ± 594	9523 ± 278*
Muscles	14985 ± 412	9743 ± 270*

Note: see Table 1.

As a result of the development of acidosis, which we have identified in cesium poisoning, various metabolic and functional disorders occur in the body of animals. These are marked by changes in protein, energy, carbohydrate and lipid metabolism and are characterized by dysproteinemia, changes in the intensity of ammonium generation, ketonemia, accumulation of free fatty acids, low molecular weight organic acids, inhibition of the Krebs cycle, and the intensity of mitochondrial oxidation. The study of the main biochemical parameters in the blood of poisoned animals revealed significant changes in their concentrations in the dynamics (Table 3).

Table 3
Biochemical parameters of the blood of rats under the influence of CsCl (x ± SD, n = 8)

Item	Control range	Rats poisoned with CsCl	
		4th day	24th day
Total protein, g/L	63.67 ± 1.23	64.08 ± 2.11	54.83 ± 1.98*
Urea, mmol/L	6.13 ± 0.54	7.01 ± 0.61*	8.05 ± 0.60*
Creatinine, μmol/L	30.10 ± 1.89	57.92 ± 2.11*	79.34 ± 3.03*
Glucose, mmol/L	3.78 ± 0.12	4.21 ± 0.18*	5.13 ± 0.27*

Note: see Table 1.

As shown in Table 3, the level of total protein in the body of poisoned rats decreased on day 24 and was 54.83 ± 1.98 g/L compared to 63.67 ± 1.23 g/L in the control group. The level of urea on day 4 of cesium chloride poisoning was 7.01 ± 0.61 mmol/L, which is 14.3% higher than in the control group. On day 24 of the study, the blood urea level increased by 31.3% compared to the control value. The results of the study of creatinine content showed that in the experimental group on day 4 of the experiment its level increased by 1.9 times, and on day 24 by 2.64 times. The results of the study of glucose levels in the blood of rats poisoned with cesium chloride indicate a violation of carbohydrate and energy metabolism. The blood glucose level in intact animals was 3.78 ± 0.12 mmol/L. In the blood of rats injected with cesium chloride, the glucose level increased to 4.21 ± 0.18 mmol/L on day 4 of the experiment and progressively increased throughout the study, as evidenced by the data obtained on day 24.

Changes in the activity of enzymes in the blood are not only an indicator of cytolysis, but also reflect adaptive mechanisms of a metabolic nature, including the effects of toxicants on the body, and each enzymo-

logical parameter of the blood (aspartate aminotransferase – AST, alanine aminotransferase – ALT, alkaline phosphatase – ALP, gamma-glutamyltransferase – GGT, α-amylase) not only supports metabolic parameters (total protein, urea, glucose), but also serves as a good indicator of the respective metabolic system. The results of our studies of AST and ALT activity in the blood of rats poisoned with cesium chloride indicate an increase in enzyme activity in the dynamics during 24 days of the study. Thus, the level of AST increased by 26.6% on day 4 and by 41.6% on day 24 of poisoning, and ALT by 14.8% and 41.5%, respectively, compared to this indicator of the intact group of animals. The analysis of the results of studies of the activity of ALP in the blood of rats poisoned with cesium chloride showed an increase by 24.9% on day 4 and 33.7% on day 24 of poisoning, compared with intact animals (Table 4).

Table 4

Concentrations of blood plasma enzymes in rats under the influence of CsCl (units/L, x ± SD, n = 8)

Enzymes	Groups of animals		
	intact rats	rats poisoned with CsCl	
		4th day	24th day
Aspartate aminotransferase	174.21 ±11.43	220.58 ± 12.71*	246.62 ± 13.10*
Alanine aminotransferase	55.88 ± 3.11	64.13 ± 2.41*	79.08 ± 4.91*
Gamma-glutamyltransferase	7.41 ± 0.61	9.11 ± 0.68*	16.21 ± 0.91*
Alkaline phosphatase	246.01 ± 16.62	307.35 ± 16.28*	328.83 ± 17.94*
α-Amylase	248.64 ± 17.02	347.28 ± 17.21*	480.74 ± 31.12*

Note: see Table 1.

There is also a dynamic increase in plasma GGT activity by 1.2 times on day 4 and by 2.3 times on day 24 of the experiment compared to intact animals. On day 4, there was an increase in α-amylase by 39.7%, and on day 24 of the experiment, an increase in α-amylase activity by 93.4% was observed compared to intact animals.

Macroscopic examination revealed severe hemorrhages of various sizes in the liver, kidneys, heart, and spleen. Microscopic examination of the skeletal striated muscle tissue of animals control group revealed that its structure did not differ from that described in the literature.

Microscopic examination of preparations of skeletal striated muscle tissue of animals of the experimental group poisoned with cesium chloride revealed that the muscle fibers were thickened, the sarcoplasm was homogeneous, transverse striations were poorly detected, the nuclei were hypochromic and poorly stained. Such changes are characteristic of dystrophic processes in muscle fibers. Bad staining of nuclei indicates the destructive effect of cesium on chromatin that in the future threatens the development of karyorrhexis, which is the complete destruction of nuclei. Microscopy of the sarcolemma did not reveal changes in the structure. The walls of the arteries were swollen, sometimes soaked in plasma. A large number of erythrocytes were contained in the vessel lumen (Fig. 1a). In some places, perivascular accumulations of free-lying erythrocytes were detected – diapedesis hemorrhages. All histological specimens showed signs of blood circulation disorders in the vessels of the microcirculatory bed, namely: uneven blood filling of vessels, paresis of individual venules, swelling and loosening of the perimysium and endomysium (Fig. 1a, 1b), infiltration of their tissue by lymphoid and histiocytic elements (Fig. 1b), the presence of perivascular extravasates.

When conducting morphometry of the hearts of animals with the introduction of cesium, we found that at the organ level, Cs caused only a slight (5% lower than control) decrease in the weight of the hearts of animals ($P < 0.05$). Morphometric analysis of histological preparations did not reveal differences with controls in the total area occupied by cardiomyocytes. The microscopic structure of cardiac muscle tissue of control group animals also did not differ from that described in the literature.

Dystrophic changes in cardiomyocytes were detected in the myocardium during microscopic examination of cardiac muscle tissue of animals poisoned with cesium chloride. Cardiomyocyte damage was manifested by alterative changes in the form of granular and focal hydropic dystrophy. The muscle fibers were branched, had unclear contours in most viewed fields, the cytoplasm of cardiomyocytes was weakly granular with vaguely expressed transverse striations (Fig. 1c). In the myocardium, there are pronounced manifestations of interfibrous and intracellular edema, most myocytes are in a state of cytolysis with nuclear destruction. Focal lysis of myofibrils with their fragmentation was observed.

Cardiomyocyte nuclei differed in polymorphism and hyperchromia, karyopyknosis and karyolysis were detected in some areas.

In the intermuscular connective tissue, arteries and arterioles were anemic, spasmodic in some places, plasmarrhagia and proliferation of vascular endothelium were noted. In the stroma, intermuscular edema and perevascular-cellular infiltration represented by cells of the lymphocytic and plasmatic series were expressed. In part of the arteries, the walls were in a state of mucoid swelling with basophilic staining. Zones of histiocytic infiltration were found around the vessels. Rather massive hemorrhages of spotted or striped form were observed in the entire thickness of the myocardium (Fig. 1d).

The following changes in the endocardium were also observed: the subendothelial layer was swollen, in some places the endothelium was exfoliated, while massive subendocardial hemorrhages were also detected in some locations (Fig. 1e, 1f).

Compared with cardiomyocytes, the remodeling of stromal components was more dynamic. An increase in volume density due to an increase in the volume density of capillaries was found. Under various stressors, an increase in sensitive structures (occupied area, number, etc.) is a compensatory and adaptive mechanism. Capillaries are the first to contact and react to the toxic effects of cesium. The increase in the area occupied by them is also a compensatory reaction to preserve the full supply of cardiomyocytes against the background of an increase in functional tension. However, a qualitative analysis shows that the rearrangements that have taken place do not eliminate the toxic effects of cesium. The death of a large number of cardiomyocytes and their hypertrophy, interstitial edema, expansion of capillaries, violations of their hemodynamics and permeability (diapedic hemorrhages, focal erythrocyte stasis), violations of the structure of the capillary wall and endothelial barrier occurring in the myocardium indicate deep, possibly irreversible structural functional changes of the myocardium.

Discussion

Total plasma protein is one of the most important biochemical parameters of blood plasma, which is an indicator of the body's amino acid reserve and provides a sufficient pool of free amino acids in the plasma. It is associated with a large number of functions and is an integrating link between all systems. A decrease in the level of total protein is often observed in various physiological and pathological conditions. Plasma contains only 30% of the body's total protein, and its decrease in the blood is possible only after all tissue depots have been exhausted, and protein itself is an indicator of the entire body's reserves. At the same time, a decrease in the level of total protein by 1 g/L in plasma means a loss of 30 g of proteins by tissues, i.e., it is not a "pseudo-variable" indicator with a wide range of fluctuations of 65–85 g/L, but an individual-constant indicator that reflects the well-being of the metabolic status of the whole organism. An essential aspect of this state is the optimal ratio of ana- and catabolism, which changes dramatically in pathology. Total protein is a link in the functioning of numerous body systems. This is the first and foremost sign of physiological normality, as well as the genetic potential of the body in various physiological and pathological conditions. The level of protein is seriously affected by the state of the body's coagulation, immune and detoxification systems, which determine the required intensity of catabolism and their condition. And the physiological basis for the normalization of immune status is normal cellular metabolism with adequate heat production (López-Otín & Kroemer, 2021).

As shown in Table 3, the level of total protein in the body of poisoned rats decreased on day 24 and amounted to 54.83 ± 1.98 g/L compared to 63.67 ± 1.23 g/L in the control group. The main role of the protein synthesizing function belongs to the liver, so the detected hypoproteinemia may be associated with impaired hepatocyte metabolism. Renal damage cannot be ruled out, given that when the glomeruli are affected, protein is filtered out and lost in the urine. It should not be forgotten that acidosis increases protein catabolism, which is directly related to gluconeogenesis. Considering that total blood protein consists of more than 300 different proteins with different functional purposes, in the body of poisoned rats,

with a decrease in total protein levels by 13.9%, one should expect a violation of blood enzymatic activity, transport and neutralization of substances, and protective properties (Ali & Kunugi, 2021).

Thus, a decrease in the level of total protein indicates significant disturbances in protein metabolism that occur in cesium chloride poisoning. Equally important plastic constants of blood plasma that characterize protein metabolism and the functional state of the body are urea and creatinine. Urea is a benchmark indicator of the "well-being" of protein metabolism, reflecting the intensity of amino group use and, possibly, a functional connection with NO, which ensures the regulation of microcirculation. In this case, two options are possible: low urea levels indicate a total deficiency of amino groups necessary for the synthesis of nucleotides and amino acids, and high levels indicate excessive catabolic activation.

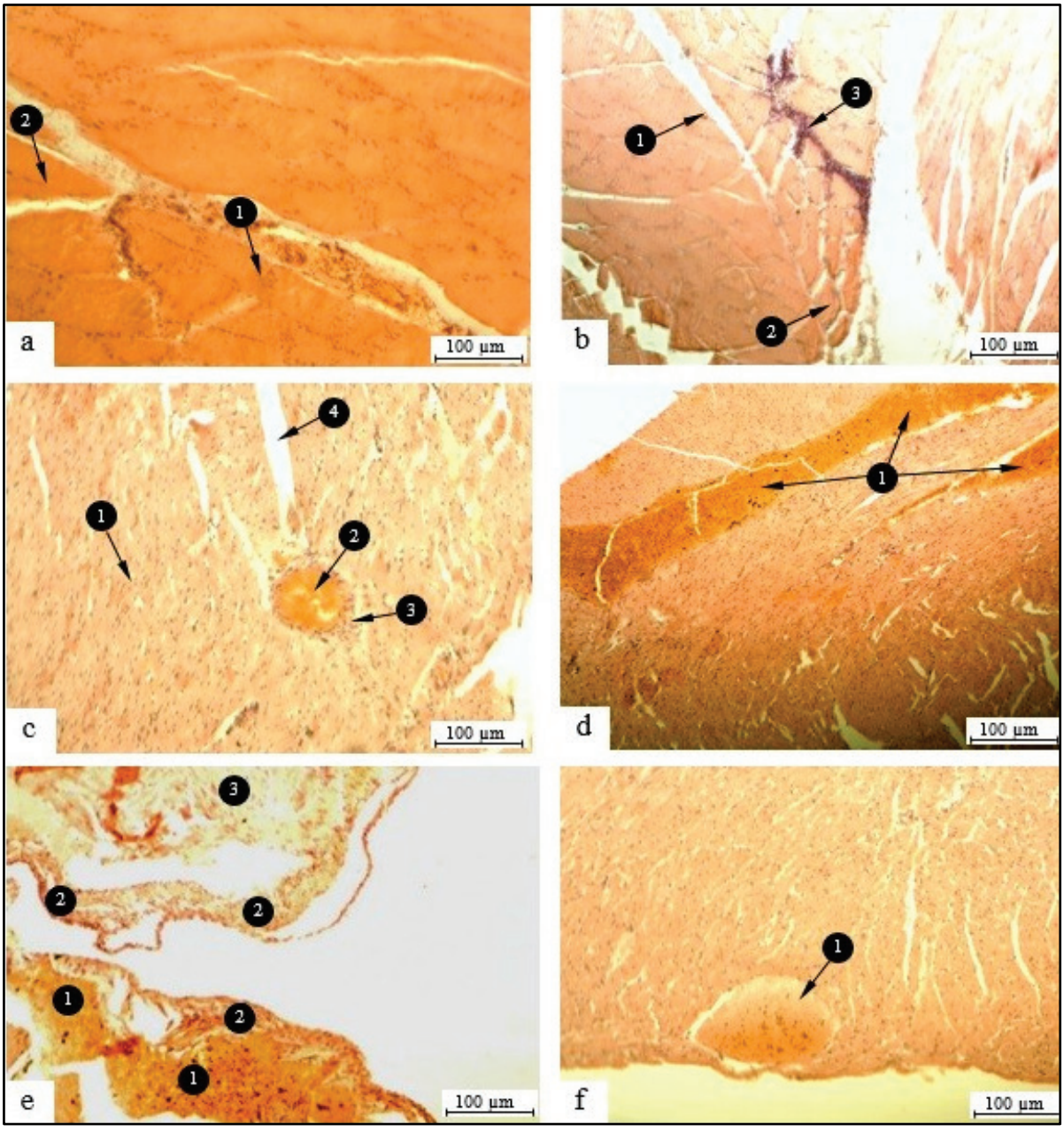

Fig. 1. Muscle tissue of animals of the experimental group: *a* – skeletal muscle, hyperemia of perimysium vessels (*1*), swelling of the perimysium (*2*); *b* – skeletal muscle, lymphohistiocytic infiltration of the endomysium (*1*), swelling of the perimysium (*2*), massive hemorrhage into the thickness of the skeletal muscle (*3*); *c* – cardiac muscle tissue, irregular staining of cardiomyocytes (*1*), vascular hyperemia (*2*), perivascular lymphoid-histiocytic infiltration (*3*), swelling of the intermuscular connective tissue (*4*); *d* – cardiac muscle tissue, striped hemorrhages in the thickness of the myocardium (*1*); *e* – endocardium of animals of the experimental group: subendocardial hemorrhage (*1*), endothelial detachment (*2*), subendocardial edema (*3*); *f* – cardiac muscle tissue, an expanded venule with blood stratification into plasma and blood-forming elements (*1*); staining with Carazzi's hematoxylin and eosin

As shown in Table 3, the urea level on day 4 of cesium chloride poisoning was 7.01 ± 0.61 mmol/L, which is 14.3% higher than in the control group. On the 24th day of the study, the blood urea level increased by 31.3% compared to the control value, which may indicate an increase in protein breakdown processes (increased thermogenesis, febrile intoxication syndrome, hepatic decompensation), as well as the development of renal failure as a result of cesium nephrotoxicity (Adeyomoye at al., 2022). The results of the study of creatinine content showed that in the experimental group on day 4 of the experiment, its level increased by 1.9 times, and on day 24 by 2.64 times. On the one hand, the increase in blood creatinine can be explained by a disruption of the final stage of creatinine synthesis in the kidneys and a disturbance in glomerular filtration rate, and on the other hand, by an increase in the blood fund of macroergic compounds (ATP, creatine phosphate). Given that creatinine is formed spontaneously from creatine entering the bloodstream, mainly from skeletal and cardiac muscles, where its concentration is high, it can be assumed that such a

rapid and significant increase in blood creatinine is due to both impaired filtration processes in the glomeruli and the destruction of these tissues (Andres-Hernando et al., 2023).

The results of the study of glucose levels in the blood of rats poisoned with cesium chloride indicate a violation of carbohydrate and energy metabolism. The blood glucose level in intact animals was 3.78 ± 0.12 mmol/L. In the blood of rats injected with cesium chloride, the glucose level increased to 4.21 ± 0.18 mmol/L on day 4 of the experiment and progressively increased throughout the study, as evidenced by the data obtained on day 24. With prolonged exposure to cesium salts, an increase in glucose levels was observed, which was 35.7% higher than the control value. Such changes can be caused by a violation of potassium metabolism, for example, when potassium is replaced by cesium in a cell, glucose transport into the cell decreases due to changes in the activity of insulin-dependent receptors (López-Otín & Kroemer, 2021). Glucose is the main substrate of energy metabolism in the cell, so as a result of its intracellular deficiency, the mechanisms of glycogenolysis and gluconeogenesis are compensatively triggered, which lead to a further increase in blood glucose levels (Furuichi & Manabe, 2021). The glucose level is ensured by the protein pool of the whole organism. The importance of gluconeogenesis and protein hormones regulating carbohydrate metabolism (insulin, glucagon, somatostatin, etc.) is determined by the priority status of protein metabolism. Thus, disorders of carbohydrate metabolism are based on disorders of protein metabolism, which is responsible for the synthesis of regulatory hormones. In the case of cesium poisoning, hypoproteinemia forces the body to "rebuild" metabolic flows. The deficiency of free amino acids leads to inhibition of insulin synthesis and the development of secondary hyperglycemia of a reversible nature (González et al., 2023).

It is well known that a deviation in one of the homeostasis indicators triggers a cascade of compensatory reactions that are implemented through enzymatic activity, and hence enzymemia, to restore it and ensure optimal functioning of various body systems.

On the other hand, a change in homeostasis indicators means the onset of homeokinesis as the most important quality of living matter. It is enzymes that play a major role in maintaining the most important physiological constants and biochemical parameters of blood in different areas and situations. The body tries to compensate for a decrease in any parameter in various ways. Total protein, along with glucose, is one of its most important indicators, but not of an urgent, but of a delayed nature. Two transaminases (AST and ALT) and GGT are involved in maintaining the level of total protein. At the cellular level, each of these enzymes plays a coordinating role in metabolism, and therefore in maintaining optimal levels of total protein.

The results of our studies of AST and ALT activity in the blood of rats poisoned with cesium chloride indicate an increase in the activity of enzymes in the dynamics during the 24 days of the study. Thus, the level of AST increased by 26.6% on day 4 and by 41.6% on day 24 of poisoning, and ALT by 14.8% and 41.5%, respectively, compared to this indicator of the intact group of animals.

AST (aspartate aminotransferase) is not only an enzyme for enzymetic diagnosis of cell and tissue damage, but also an enzyme for enzymatic characterization of the catabolic component of metabolism and an indicator of thermogenesis. Due to its subordination to a complex of physiological parameters (pressure, pulse, respiratory rate, body temperature), this transaminase is a key characteristic of catabolic/destructive processes at the final stages by intensifying the work of the tricarboxylic acid cycle (TCA) in mitochondria.

Excess of AST activity over ALT within normal limits is usually characteristic of healthy people and animals. However, an increase in AST with a simultaneous increase in the AST/ALT ratio (de Ritis coefficient greater than 2) indicates excessive energy expenditure, which leads to depletion of the body's adaptive reserve.

It should be added that morphologically, the heart is a cluster of muscles, nerve nodes and conduction pathways, i.e., an organ not designed to produce enzymes. In both the literal and figurative sense, AST is a marker of optimal adaptive combustion in various physiological and pathological conditions and the main enzyme of the entire metabolism. ALT (alanine aminotransferase), in contrast to AST, is a key characteristic of anabolic (synthetic) processes in the body and is involved in maintaining a constant blood glucose level through gluconeogenesis (GOG), the raw material of which is glycogenic amino acids, glycerol of neutral fats and phosphatides. It is generally accepted that elevated ALT levels are a sign of liver damage, but, for example, under stress, glucocorticoids dramatically increase its synthesis, which means that physiological systems are ready to pump (transaminase) alanine into pyruvate for gluconeogenesis. An increase in ALT levels in hypoproteinemia indicates compensatory activation of gluconeogenesis and pumping of proteins (alanine) into carbohydrates (glucose) (Southwell et al., 2023).

GGT (gamma-glutamyltransferase) is an indicator of the body's aminoacid reserve and the efficiency of microsomal oxidation (cell endotoxicity system). The main function of GGT in the body is adaptation to protein starvation in various normal and pathological conditions. We found a dynamic increase in the activity of GGT in rat blood plasma under the influence of cesium chloride by 1.2 times on day 4 and 2.3 times on day 24 of the experiment compared to intact animals. An increase in activity above the normal range means that the body borrows inviolable proteins from various tissues, including brain tissue, for survival (and for recovery in case of pathologies). The task of the GGT enzyme is to take amino acids from tissues and ensure that the blood has an adequate level of total protein.

During the onset and development of pathological processes in humans and animals, the qualitative and quantitative state of the body's protein pool is modulated by the activity of GGT. The source of protein in conditions of its deficiency is muscle tissue, and clinically this condition is manifested by the development of toxic myopathy with a decrease in muscle mass (Cho et al., 2023).

Increased enzymemia has two main mechanisms of formation, which are not mutually exclusive and can occur simultaneously. The traditional cytolytic mechanism is characterized by a proportional increase in the activity of enzymes (AST and ALT) and protein metabolites (urea, creatinine). At the same time, the concentration of GGT, which plays a key role in compensatory changes in the blood, does not change. In the blood of animals under the influence of cesium chloride, a 2.3-fold increase in GGT was observed, indicating a catabolic mechanism of enzymemia, which is characterized by serious changes in metabolism, mainly of a dystrophic (catabolic) nature, and not just simple cellular damage.

The analysis of the results of studies of ALP activity in the blood of rats poisoned with cesium chloride showed an increase by 24.9% on day 4 and by 33.7% on day 24 of poisoning, compared with intact animals (Table 4). ALP (alkaline phosphatase) is associated with transphosphorylation processes involving ATPases and creatine phosphokinase (CPK), as well as the functioning of the phosphate-buffer system. The high activity of ALP indicates the intensity of transmembrane processes, and thus an important role in maintaining blood glucose levels and life support systems when they are intensified. An increase in alkaline phosphatase in the blood ensures not only dephosphorylation and glucose release from the cell, but also forms a significant amount of inorganic phosphate, without which the synthesis of ATP from adenosine diphosphate (ADP) is impossible and this accordingly affects bioenergy in the cell and in the body as a whole (Liu et al., 2023).

Under these conditions, homeostasis and, above all, glucose levels are maintained by 3 major pathways: 1) combustion of substrates in mitochondria with the participation of AST; 2) maintenance of glucose levels and preservation of nitrogen deficiency with the participation of ALT; and 3) increased amino acid transport with the participation of GGT.

The detected α-amylase hyperfermentation (on day 4, an increase in α-amylase by 39.7% was observed, and on day 24, an increase in α-amylase activity by 93.4% was shown compared to intact animals) may indicate two possible mechanisms of its formation. The first is due to the cytotoxic effect of cesium, since α-amylase is found in many types of cells and tissues, and the second is due to the nephrotoxicity of cesium and reduced clearance of the enzyme in the development of renal failure (Chen et al., 2022).

Cesium ions can easily penetrate through biological membranes and are fairly evenly distributed in liquid media and tissues, which is due to their good solubility in water and significant similarity in many chemical and physical parameters with potassium ions (Omi et al., 2020). It was shown by the method of neuron activation analysis that with natural intake the stable cesium isotope $^{133}Cs^{+}$ has a tropism towards the myocardium

and muscle tissue, it is mainly localized in the A-band of muscle myofibrils (Ling, 1977) meanwhile the total content of ^{133}Cs in the human myocardium and animals is practically the same.

When perfusing an isolated turtle heart with a cesium solution, most of the intracellular potassium can be replaced by cesium. During the initial stages of perfusion, the heart accumulated Cs and lost K, the exchange rate of K for Cs was estimated to be approximately 0.6. Subsequently, perfusion leads to equi-ionic replacement of K with Cs (Guerin & Wallon, 1979).

The study of the influence of different external concentrations of cesium on the output of potassium in the Purkinje fibers of the cattle heart and the muscles of the auricle of the guinea pig in Tyrode's solution (containing different amounts of external potassium) showed that cesium ions reduce the output and input of potassium depending on the concentration, and this effect is due to the interaction of Cs ions with the outer part of the membrane (Cameliet, 1980). Muscles lose K in exchange for Cs in the presence of cesium (Younes et al., 2023).

Cesium accumulation in striated muscles also depends on their type. It was found that red muscle in general tends to accumulate cesium to a greater extent than white muscle. [K]/[Cs] ratios ranged from 1.94 for red muscle to 1.08 for white muscle (Kernan, 1969).

The vulnerability of the myocardium and red muscles to the toxic effect of cesium is due to its pronounced tropism and ability to accumulate in the matrix of mitochondria (MT), the number of which per unit cell volume of this tissue is much higher than that of white muscles (Wellard et al., 2002). The calculation of the value of the concentration gradient of stable cesium in the MT of the human myocardium, based on data on its subcellular distribution, was 1.7 which indicates an active accumulation of cesium in the MT, corresponds to the value of the gradient of potassium ions in the MT matrix and confirms the role of MT as an intracellular depot of potassium ions and identity of tissue and intracellular traffic of potassium and cesium ions (Hrytsuk, 2008).

Muscles are characterized by an extremely high level of blood supply and oxygenation, therefore, under conditions of exposure to cesium, we can talk about a local "oxygen" effect that occurs in tissues. The strength of this effect will depend on the physical properties of the cesium atom, reaching its maximum value in radioactive isotopes. Cesium activates free radical processes, initiating damage in many parts of cell membranes simultaneously, including membrane-receptor complexes. The accumulation of cesium in the MT, which is characterized by the maximum concentration of oxygen compared to other organelles of the cell (Skulachev et al., 2000) increases the probability of the formation of active oxygen species (AOS) – one of the key factors in the harmful effects of ecotoxicants on living organisms. The accumulation of AOS in muscle tissue, including the myocardium, is known to cause damage not only to the system of mitochondrial membranes but also to the entire complex of muscle fibers and cardiomyocytes, which is the most important pathogenetic mechanism in the development of pathology of the muscular apparatus and cardio vascular pathology (Lankin, 2000; Zheloba, 2000; Supinski et al., 2020).

The highly impressive effect of incorporated Cs on the MT of striated muscles can be explained from the position of Herbert Ling's association-induction hypothesis (AIH), according to which intracellular K^+ is absorbed by anionic groups of dicarboxylic amino acids (Asp, Glu) of proteins (Ling, 1977; Ling, 2001). It is known that in muscles, including cardiomyocytes, approximately 60% of all free carboxyl groups of proteins capable of binding K^+ are located in A-discs of myofibrils, represented mainly by contractile (actin, myosin) and regulatory proteins. In this regard, according to AIH by Herbert Ling, about 60% of intracellular K^+, and under the action of cesium and Cs^+, is localized in the contractile apparatus, as well as in membrane proteins (ion channels, receptors, etc.), the perimembrane space, in the matrix of MT, damaging them that leads to disruption of energy exchange, ultrastructure, electrical and contractile activity. Taking into account the ability of the nuclear compartment to deposit K^+ ions (Cs^+) and create an intracellular gradient of their concentration, the proposed pathogenetic mechanism of damage to the myocardium and skeletal muscles upon incorporation of Cs^+ should be supplemented and strengthened by the development of the phenomenon of genomic instability in them (Pelevina et al., 2009). The long half-life of Cs from the human body – about 50 days in children, up to 100 days in adults – indicates in favour of the given data on the compartmentalization of Cs^+ inside cardiomyocytes and muscle fibers. Briefly speaking, the theory of association-induction consists in the author's desire to transfer the "center of emphasis" in understanding the vital functions of the cell from the cell membrane to the cytoplasm, considering the change in electron density in macromolecules caused by external signals as the main mechanism of regulation of cell functions. These ideas are based on the close relationship of three main "players" – proteins, structured water and inorganic ions in the cytoplasm of the cell (Ling, 2001).

The obtained data on the violation of the cytological structure of the nuclei with the development of karyorrhexis are confirmed by studies of the genotoxic and clastogenic effect of cesium on cells. Thus, the frequency of chromosomal aberrations increased linearly with an increase in the concentration of cesium (CsCl) from 1/20 to 1/50 LD_{50} in mouse bone marrow cells *in vivo* after oral administration of cesium chloride. At the same time, the effect of cesium on the frequency of cell division was opposite, lower doses had a stimulating effect and high doses were mitostatic (Ghosh et al., 1990).

Similar results were obtained in human peripheral blood lymphocytes *in vitro*. The degree of chromosomal aberrations directly depended on the dose of cesium and mainly chromatid-type aberrations were detected. In addition, their frequency did not depend on the age or gender of the donor (Ghosh et al., 1993).

Conclusions

Damage to the kidneys is not excluded, given that when the glomeruli of the kidneys are damaged, the protein is filtered and lost in the urine. It should not be forgotten that acidosis increases protein catabolism, which is directly related to gluconeogenesis. Taking into account that the total protein of the blood consists of more than 300 different proteins with different functional purposes, in the body of poisoned rats, with a decrease in the level of total protein by 13.9%, we should expect a violation of the enzymatic activity of the blood, transport and neutralization of substances, protective properties.

We can talk about the presence of two mechanisms of cesium action of on tissues, including striated muscles in the following way: as an antagonist of potassium, which concerns the transport system of the latter, and as a toxic element that initiates peroxide processes with subsequent modification of membranes and their potassium channels. Under the conditions of an increase in intracellular cesium in striated muscles, there are functional disturbances in the work of potassium channels of excitable tissues in the repolarization phase. These disorders can proceed according to the type of acquired "potassium" channelopathies, which can be manifested in the form of rhythm disorders in the myocardium, prolonged QT syndrome, etc. This leads to the appearance of significant violations of the histological structure of the examined tissues. Cesium has pronounced damaging effects on both skeletal and cardiac striated muscle tissue, with morphological changes in skeletal and cardiac striated muscle tissue being generally similar. Dystrophic changes in the nuclei and cytoplasm of cardiomyocytes and striated muscles, signs of impaired blood circulation in the microcirculatory channel with the formation of vascular wall edema, destruction of endothelial cells, various types of hemorrhages, lymphohistiocytic infiltration of the stroma of fibers are consequences of the toxic effect of cesium on tissues.

It is known that any tissue consists of a heterogeneous community of cells that differ from each other in a number of morphofunctional features, which determines their different sensitivity to external and internal influences. Under the conditions of cesium accumulation in the MT of the striated muscle cells, with an increase in the degree of degeneration, which causes damage to cardiomyocytes and muscle fibers, the least stable part of their subpopulation can be eliminated by mitoptosis. The initiation of mitoptosis, which is the earliest stage of the development of apoptosis, causes a decrease in the diversity of structural elements of the tissue, aging of the cell population, depression of various functional parameters of the tissue and limits its degree of freedom.

The authors declare that they have no conflict of interest.

References

Adeyomoye, O. I., Akintayo, C. O., Omotuyi, K. P., & Adewumi, A. N. (2022). The biological roles of urea: A review of preclinical studies. Indian Journal of Nephrology, 32(6), 539–545.

Ali, A. M., & Kunugi, H. (2021). Hypoproteinemia predicts disease severity and mortality in COVID-19: A call for action. Diagnostic Pathology, 16(1), 31.

Andres-Hernando, A., Cicerchi, C., Garcia, G. E., Orlicky, D. J., Stenvinkel, P., Johnson, R. J., & Lanaspa, M. A. (2023). Phosphate depletion in insulin-insensitive skeletal muscle drives AMPD activation and sarcopenia in chronic kidney disease. iScience, 26(4), 106355.

Avery, S. V. (1995). Caesium accumulation by microorganisms: Uptake mechanisms, cation competition, compartmentalization and toxicity. Journal of Industrial Microbiology, 14(2), 76–84.

Cameliet, E. (1980). Decrease of K efflux and influx by external Cs ions in cardiac Purkinje and muscle cells. Pflugers Archiv, 383(2), 143–150.

Cao, Y., Zhou, L., Ren, H., & Zou, H. (2022). Determination, separation and application of ^{137}Cs: A review. International Journal of Environmental Research and Public Health, 19(16), 10183.

Chen, W. N., Tang, K. S., & Yeong, K. Y. (2022). Potential roles of α-amylase in Alzheimer's disease: Biomarker and drug target. Current Neuropharmacology, 20(8), 1554–1563.

Cho, E. J., Jeong, S. M., Chung, G. E., Yoo, J. J., Cho, Y., Lee, K. N., Shin, D. W., Kim, Y. J., Yoon, J. H., Han, K., & Yu, S. J. (2023). Gamma-glutamyl transferase and risk of all-cause and disease-specific mortality: A nationwide cohort study. Scientific Reports, 13(1), 1751.

Davis, D. G., Murphy, E., & London, R. E. (1988). Uptake of cesium ions by human erythrocytes and perfused rat heart: A cesium-133 NMR study. Biochemistry, 27, 3547–3551.

Daza, E. A., Misra, S. K., Schwartz-Duval, A. S., Ohoka, A., Miller, C., & Pan, D. (2016). Nano-cesium for anti-cancer properties: An investigation into cesium induced metabolic interference. ACS Applied Materials & Interfaces, 8(40), 26600-26612.

Egorov, V. N. (2021). Theory of radioisotopic and chemical homeostasis of marine ecosystems. Springer, Cham.

Fricke, S., Harnau, M., Hetsch, F., Liu, H., Leonhard, J., Eylmann, A., Knauff, P., Sun, H., Semtner, M., & Meier, J. C. (2023). Cesium activates the neurotransmitter receptor for glycine. Frontiers in Molecular Neuroscience, 16, 1018530.

Furuichi, Y., Kawabata, Y., Aoki, M., Mita, Y., Fujii, N. L., & Manabe, Y. (2021). Excess glucose impedes the proliferation of skeletal muscle satellite cells under adherent culture conditions. Frontiers in Cell and Developmental Biology, 9, 640399.

Ghosh, A., Sharma, A., & Talukder, G. (1993). Clastogenic effects of caesium chloride on human peripheral blood lymphocytes *in vitro*. Toxicology in Vitro, 7(2), 137–140.

Ghosh, A., Sharma, A., & Talukder, G. (1990). Clastogenic effects of cesium chloride on mouse bone marrow cells *in vivo*. Mutation Research Letters, 244(4), 295–298.

Gilles, O. (2022). K^+-independent Kir blockade by external Cs^+ and Ba^{2+}. Physiological Reports, 10(5), e15200.

González, P., Lozano, P., Ros, G., & Solano, F. (2023). Hyperglycemia and oxidative stress: An integral, updated and critical overview of their metabolic interconnections. International Journal of Molecular Sciences, 24(11), 9352.

Guerin, M., & Wallon, G. (1979). The reversible replacement of internal potassium by caesium in isolated turtle heart. The Journal of Physiology, 293, 525–537.

Gunko, N. V., Ivanova, O. M., Loganovsky, K. M., Korotkova, N. V., & Masiuk, S. V. (2021). Some issues of life activities of populationin the chornobyl exclusion zone in Ukraine. Problems of Radiation Medicine and Radiobiology, 26, 141–161.

Horn, S., Naidus, E., Alper, S. L., & Danziger, J. (2015). Cesium-associated hypokalemia successfully treated with amiloride. Clinical Kidney Journal, 8(3), 335–338.

Kernan, R. P. (1969). Accumulation of caesium and rubidium *in vivo* by red and white muscles of the rat. The Journal of Physiology, 204(1), 195–205.

Kobayashi, D., Kakinouchi, K., Nagae, T., Nagai, T., Shimura, K., & Hazama, A. (2017), Cesium reversibly suppresses HeLa cell proliferation by inhibiting cellular metabolism. FEBS Letters, 591, 718–727.

Kobayashi, D., Nishimura, N., & Hazama, A. (2021). Cesium treatment depresses glycolysis pathway in HeLa cell. Cellular physiology and biochemistry. International Journal of Experimental Cellular Physiology, Biochemistry, and Pharmacology, 55(4), 477–488.

Ling, G. N. (1977). Thallium and cesium in muscle cells compete for the adsorption sites normally occupied by K^+. Physiological Chemistry and Physics, 9(3), 217–225.

Ling, G. N. (2001). Life at the cell and below-cell level: The hidden history of a fundamental revolution in biology paperback. Pacific Press, New York.

Liu, K., Yu, Y., Yuan, Y., Xu, X., Lei, W., Niu, R., Shen, M., Zhou, L., Peng, R., Wang, Q., Yang, H., Guo, H., Ge, Y., Liu, G., He, M., Wu, T., & Zhang, X. (2023). Elevated levels of serum alkaline phosphatase are associated with increased risk of cardiovascular disease: A prospective cohort study. Journal of Atherosclerosis and Thrombosis, 30(7), 795–819.

López-Otín, C., & Kroemer, G. (2021). Hallmarks of health. Cell, 184(1), 33–63.

Lyon, A. W., & Mayhew, W. J. (2003). Cesium toxicity: A case of self-treatment by alternate therapy gone awry. Therapeutic Drug Monitoring, 25(1), 114–116.

Melnikov, P., & Zanoni, L. Z. (2010). Clinical effects of cesium intake. Biological Trace Element Research, 135(1–3), 1–9.

Melnikova, N. N., & Yermishev, O. V. (2013). Biokhimichni zminy v orhanizmi shchuriv za diji tseziju khlorydu [Biochemical changes in the body of rats under the influence of cesium chloride]. Ukrainskyj Biokhimichnyj Zhurnal, 85(2), 105–109 (in Ukrainian).

Nesterov, V. P., & Skulskii, I. A. (1965). Sravnitel'noe issledovanie raspredelenija Li, Na, K, Rb i Cs v myishechnoj tkani morskikh zhivotnykh [Comparative investigation of Li, Na, K, Rb, and Cs distribution in muscle tissue of marine animals]. Zhurnal Evoliutsionnoj Biokhimii i Fiziologii, 1(2), 151–157 (in Russian).

Nielsen, V. G., Goff, T., Hunsaker, B. D., & Neves, C. D. (2023). The gilded clot: Review of metal-modulated platelet activation, coagulation, and fibrinolysis. International Journal of Molecular Sciences, 24(4), 3302.

Omi, T., Nakiri, S., Nakanishi, S., Ishii, N., Uno, T., Konno, F., Inagaki, T., Sakamoto, A., Shito, M., Udagawa, C., Tada, N., Ochiai, K., Kato, T., Kawamoto, Y., Tsuchida, S., & Hayama, S. I. (2020). Concentrations of ^{137}Cs radiocaesium in the organs and tissues of low-dose-exposed wild Japanese monkeys. BMC Research Notes, 13(1), 121.

Persigehl, M., Schicha, H., Kasperek, K., & Klein, H. J. (1977). Trace element concentration in human organs in dependence of age. Beiträge zur Pathologie, 161(3), 209–220.

Prister, B. S., Kliuchnykov, O. O., Shestopalov, V. M., & Kuhar, V. P. (2016). Problemy bezopasnosti atomnoj energetiki. Uroki Chernobyilya [Nuclear power safety problems. Lessons from Chernobyl]. NPP Safety Problems Institute, Chornobyl (in Russian).

Redaelli, M. B., Zangrillo, A., Gregorc, V., Ciceri, F., Dagna, L., Tshomba, Y., Navalesi, P., & Landoni, G. (2019). How to obtain severe hypoglycemia without causing brain or cardiac damage. Medical Hypotheses, 130, 109276.

Saito, R., Kumada, R., Inami, K., Kanda, K., Kabeya, M., Tamaoki, M., & Nemoto, Y. (2022). Monitoring of radioactive cesium in wild boars captured inside the difficult-to-return zone in Fukushima Prefecture over a 5-year period. Scientific Reports, 12(1), 5667.

Saito, R., Nemoto, Y., & Tsukada, H. (2020). Relationship between radiocaesium in muscle and physicochemical fractions of radiocaesium in the stomach of wild boar. Scientific Reports, 10(1), 6796.

Saniewski, M., Zalewska, T., Suplińska, M., Falkowska, L., Grajewska, A., Nehring, I., Saniewska, D., Staniszewska, M., & Pawliczka, I. (2019). ^{137}Cs and ^{40}K in gray seals *Halichoerus grypus* in the Southern Baltic Sea. Environmental Science and Pollution Research International, 26(17), 17418–17426.

Santos-Mello, R., Schmidt, T., Neuhauss, E., & Almeida, A. (1999). Induction of micronuclei by CsCl *in vivo* and *in vitro*. Mutation Research/Genetic Toxicology and Environmental Mutagenesis, 446(2), 239–244.

Sartayev, Y., Takahashi, J., Gutevich, A., & Hayashida, N. (2021). Screening for the ^{137}Cs body burden owing to the Chernobyl accident in Zhytomyr region, Ukraine: 2009–2018. PloS One, 16(1), e0245491.

Scherb, H., & Hayashi, K. (2020). Spatiotemporal association of low birth weight with Cs-137 deposition at the prefecture level in Japan after the Fukushima nuclear power plant accidents: An analytical-ecologic epidemiological study. Environmental Health: A Global Access Science Source, 19(1), 82.

Sessions, D., Heard, K., & Kosnett, M. (2013). Fatal cesium chloride toxicity after alternative cancer treatment. The Journal of Alternative and Complementary Medicine, 19(12), 973–975.

Southwell, N., Primiano, G., Nadkarni, V., Attarwala, N., Beattie, E., Miller, D., Alam, S., Liparulo, I., Shurubor, Y. I., Valentino, M. L., Carelli, V., Servidei, S., Gross, S. S., Manfredi, G., Chen, Q., & D'Aurelio, M. (2023). A coordinated multiorgan metabolic response contributes to human mitochondrial myopathy. EMBO Molecular Medicine, 15(7), e16951.

Supinski, G. S., Schroder, E. A., & Callahan, L. A. (2020). Mitochondria and critical illness. Chest, 157(2), 310–322.

U.S. Department of Health and Human Services. Public Health Service (2004). Toxicological profile for cesium. Agency for Toxic Substances and Diseases Registry. Cesium- Health Effects, Atlanta.

Venturi, S. (2021). Cesium in biology, pancreatic cancer, and controversy in high and low radiation exposure damage-scientific, environmental, geopolitical, and economic aspects. International Journal of Environmental Research and Public Health, 18(17), 8934.

Younes, S., Mourad, N., Salla, M., Rahal, M., & Hammoudi Halat, D. (2023). Potassium ion channels in glioma: From basic knowledge into therapeutic applications. Membranes, 13(4), 434.