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Effects of Heavy Metal Salts in Biochemical Processes, Rat Liver Mitochondria

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Abstract: *In vitro experiments have shown that heavy metals Cu2+ and Cd2+ effectively affect respiration and the system of oxidative phosphorylation of mitochondria. Ca2+ ions inhibit mitochondrial respiration in the V3 and V4 states, uncoupling oxidative phosphorylation. The effect of Cd2+ on respiration and oxidative phosphorylation of mitochondria differs from the effect of Co2+ and other heavy metals. At the same time, Cd2+ increases mitochondrial respiration in low concentrations, and inhibits it in high concentrations. The results obtained in this work expand the traditional understanding of the various mechanisms of action of heavy metals on the bioenergetic metabolism of the cell.*

Keywords: *Heavy metal salts, hepatosomatic, toxic, cadmium, intoxication.*

Introduction. Heavy metal salts are present in the environment and are the cause of many chronic diseases of humans and animals [1]. The toxic effect of heavy metals on a living organism is based on damage to cells and their organelles, accompanied by their functional or structural and functional changes. Among heavy metals, cadmium, cobalt, lead, zinc, aluminum, chromium are dangerous to life and health.

Cadmium can have mutagenic and teratogenic effects on the body, which lead to minor destruction of the cellular apparatus of the placenta and embryonic tissues in the early stages of organogenesis [2]. An increase in the hepatosomatic index and the presence of pronounced necrotic changes in the liver is the main manifestation of the influence of high doses of cadmium [3]. In the work [4], it was explained that the hepatotoxic effect of cadmium leads to the formation of significant changes in the biochemical parameters of human blood. In conditions of chronic poisoning, cadmium leads to liver destruction and kidney damage, as it has a pronounced hepatoxic and nephrotoxic effect [5].

Toxic effects of cadmium, leading to the development of mitochondrial dysfunction. The growth of ischemic phenomena arising from damage to the endothelial cells of the liver vessels, leading to the formation of hepatocellular trauma [6]. In an experimental study [7], it was found that mitochondria and the endoplasmic network of hepatocytes have the greatest sensitivity to the toxic effects of cadmium. Chronic exposure to xenobiotics leads to the formation of structural changes in liver tissue cells, which manifests itself in the form of swelling and changes in the shape of mitochondria, as well as in the appearance of signs of their biodegradation. The toxic effect of cadmium contributes to the development of total hydropic dystrophy of hepatocytes, sometimes turning into balloon dystrophy. Acute intoxication with cobalt salts revealed: leukocytosis, erythrocytosis, increased hemoglobin concentration in the blood; chronic: leukopenia, erythrocytosis, increased hemoglobin concentration. During intoxication with metal salts, the destruction of the membranes of rat erythrocytes was revealed [8]. In connection with the above, it becomes relevant to study the specific mechanisms of the effect of STM on the energy-transforming functions of biomembranes.

The aim of the work was to study the effect of STM – cobalt chloride and cadmium chloride ions on respiration and oxidative phosphorylation (OF) of rat liver mitochondria in in vitro experiments.

Materials and methods. Mitochondria were isolated from the liver of rats weighing 150-200 g. by differential Schneider centrifugation in an isolation medium containing 250 mM sucrose, 10 mM tris chloride, 1 mM EDTA, pH 7.4. The protein content of mitochondria was determined colorimetrically by the biuret method.

The respiration rate of mitochondria in the V3 and V4 states was measured using a polarograph OH - 102 (Hungary, Radelkis) with an open platinum electrode. The values of DC and DF/O were determined by the Chance method [5], based on the fact that the amount of oxygen in 0.5 ml of the incubation medium at 26 °C is 250 ng - oxygen atom. The incubation medium (SI) was used in the experiments: sucrose - 125 mM, KCI - 60 mM, KH2PO4 - 2.5 mM, succinate - 5 mM, tris-HCI - 5 mM, pH -7.4; ADP additives up to a final concentration of 0.2 mM; protein concentration Mx 3 mg/ml. Rotenone was introduced into the incubation medium to prevent the accumulation of oxalic acid, a competitive inhibitor of succinate oxidation.

Results. When studying the effect of cobalt ions on respiration and mitochondria in in vitro experiments (Table 1), it was shown that Ca2+ ions inhibit respiration in the metabolic states V3 and V4. At the same time, respiratory control (DC) and ADP/O indicators decrease. However, complete separation of oxidative phosphorylation is not observed. Significant inhibition of respiration and dissociation of mitochondria is also observed when exposed to higher concentrations of Co2+ (10-5M - 10-4M).

It is known that, unlike Zn2+, low concentrations of Co2+ do not affect the respiratory chain, then one of the reasons for respiratory depression and disconnection of oxidative phosphorylation by Co2+ ions may be a decrease in the membrane potential as a result of an increase in passive permeability to charged membrane particles or a change in the state of the CA-sensitive pore.

Table 1. The effect of cobalt ions on respiration and oxidative phosphorylation of rat liver mitochondria.

Experience conditions	The rate of consumption of O2, ng-atom O/ min. mg. protein		DK	ADF/O
	V_3	V_4		
Control	74,0±1,22	19,6±0,24	3,78	2,00±0,03
Co^{2+} $1 \cdot 10^{-5}$M	65,8±1,82 P<0,02	19,0±0,31 P>0,05	3,46	1,85±0,05 P<0,05
Co^{2+} $2 \cdot 10^{-5}$M	58,6±2,82 P<0,01	18,4±0,24 P<0,02	3,19	1,74±0,04 P<0,01
Co^{2+} $5 \cdot 10^{-5}$M	52,4±3,55 P<0,01	16,4±0,81 P<0,02	3,16	1,70±0,08 P<0,03
Co^{2+} $1 \cdot 10^{-4}$M	48,0±5,18 P<0,01	14,4±1,96 P<0,05	3,3	1,62±0,03 P<0,001

Note*. SI: Sucrose - 125 mM, KCI - 60 mM, KH2PO4 - 2.5 mM, succinate - 5 mM, tris-HCI - 5 mM, pH - 7.4; ADP additives up to a final concentration of 200 microns, protein concentration of 3 mg/ml.

According to researchers [9] Cu2+ ions are activators of cytochrome c oxidase and rotenone insensitive NADPH oxidase system of mitochondrial membranes. These authors have shown that the increase in the activity of these enzymes depends on the concentration of Cacl2. Co2+ ions also activate the succinate oxidase system of the mitochondrial respiratory chain. The authors conclude that the presence of Ca2+ ions in the medium leads to significant changes in the electron transport chain of mitochondria [10,11].

S.M.Korotkov et al. [12] revealed that the effect of Cd2+ ions on respiration and mitochondrial function is peculiar: relatively low concentrations stimulate respiration in the V3 and V4 states, while the DC and ADP/O coefficients are slightly reduced.

Under these conditions, high concentrations of this cation inhibit respiration in both states and lead to complete separation of OF with the removal of the DC mechanism. In in vitro experiments, we studied the effect of Cd2+ on respiration and mitochondria of rat liver.

Cd2+ ions in relatively low concentrations increased the V3 and V4 indices, however, the DC and ADP/O coefficients decreased slightly. The addition of Cd2+ to the suspension of mitochondria to a final concentration of 10-5 M also caused simultaneous stimulation of respiration in the V3 and V4 states, while the values of DC and ADP/O were slightly below the control level. A further increase in the concentration of Cd2+ in the medium led to respiratory depression. With an increase in the concentration of Cd2+ to 210-5 M, mitochondrial respiration in the V3 state was inhibited by 67%. Respiratory suppression was also observed in the V4 state. Due to the noted oppression, the value of the DC coefficient decreased to 1.61; ADP/O-1.3. At a concentration of Cd2+10-5 M, the DC coefficient decreased to 1, i.e. there was a complete disconnection of the OF with the removal of the DC mechanism.

In our experiments, dithiotreitol (DTT) removes the effect of Cd2+ on respiration and the AF system. It is known that DT protects the thiol groups of mitochondrial membranes. It can be assumed that the effect of Cd2+ on the function of mitochondrial membranes is mediated through thiol groups of membranes.

The mechanisms of action of Cd2+ on respiration and mitochondria are quite complex and attract many researchers. Back in the 80s, it was shown that Cd2+ increases the permeability of mitochondrial membranes for cations and activates respiration. Higher concentrations of Cd2+ inhibit respiration in the presence of OF disconnectors.

The effect of Cd2+ on mitochondrial function depends on its concentration. Apparently, in the presence of high concentrations, the activities of succinate dehydrogenase, cytochrome C oxidase, and other enzymes are inhibited, as a result of which respiration is suppressed.

The effect of Cd2+ on respiration is partially removed by heavy metal ions and the classical inhibitor of Ca2+ transport in Mx - ruthenium red [13], however, the mechanisms of action of these agents have not been definitively elucidated.

It should be noted that the effects of Cd2+ on respiration and OF Mx differ from the effects of Co2+. At higher concentrations, Co2+ does not completely dissociate OF, while Cd2+ completely dissociates OF mitochondria.

Our research in this paper has established that the Co2+ and Co2+ ions separate OF. However, the mechanisms of separation of OF by heavy metals have not been definitively established. To date, the mechanisms of action of the disconnectors of have been established. All mechanisms and postulates of the action of disconnectors of OP believe that they facilitate the transition of protons (H+) or other charged particles directly through the mitochondrial membrane.

The engine of the formation of ATP from ADP and inorganic phosphate is precisely the proton gradient on both sides of the Mx membrane, which is not permeable to H+, supported by biological oxidation reactions. However, molecules of disconnectors - protonophores can bind H+, and ionophores can bind a cation and transfer them through the inner membrane, as a result of which there is a decrease in the MP of the membranes and the separation of OF.

It is possible that in our experiments heavy metal ions interact with mitochondrial membranes and induce their passive permeability. As a result, there is a decrease in the membrane potential and separation of the mitochondria.

Thus, in vitro experiments have established that the heavy metals Cu2+ and Cd2+ studied by us effectively affect respiration and the mitochondrial system. Ca2+ ions inhibit mitochondrial

respiration in the V3 and V4 states, separating OF. The effect of Cd2+ on respiration and mitochondria differs from the effect of Co2+ and other heavy metals. At the same time, Cd2+ increases mitochondrial respiration in low concentrations, and inhibits it in high concentrations. The results obtained in this work expand the traditional understanding of the various mechanisms of action of heavy metals on the bioenergetic metabolism of the cell.

Literature

1. Hodgson E., Levi P.E. Pesticides: An important but underused model for the environmental health sciences // Environ. Health Persp. – 1996. – Vol. 104. – № 1. – P. 97-106.
2. Chen, K.L. Mercuric compounds induce pancreatic islets dysfunction and apoptosis in vivo / K.L. Chen, S.H. Liu, C.C. Su // International Journal of Molecular Sciences. — 2012. — Vol. 13. — № 10. – P.12349—12366.
3. Mazzei, V. Bioaccumulation of cadmium and lead and its effects on hepatopancreas morphology in three terrestrial isopod crustacean species / V. Mazzei, G. Longo, M.V. Brundo, F. Sinatra, C. Copat, C.G. Oliveri, M. Ferrante // Ecotoxicology and Environmental Safety. — 2014. — Vol. 30. № 110. – P. 269—279.
4. Adams, S.V. Cadmium exposure and cancer mortality in the Third National Health and Nutrition Examination Survey cohort // S.V. Adams, M.N. Passarelli, P.A. Newcomb // Occupational and Environmental Medicine. — 2012. — Vol. 69. — № 2. – P. 153—156.
5. Chen, K.L. Mercuric compounds induce pancreatic islets dysfunction and apoptosis in vivo / K.L. Chen, S.H. Liu, C.C. Su // International Journal of Molecular Sciences. — 2012. — Vol. 13. — № 10. – P.12349—12366.
6. Blum J. L. Short-term inhalation of cadmium oxide nanoparticles alters pulmonary dynamics associated with lung injury, inflammation, and repair in a mouse model / J.L. Blum, L.K. Rosenblum, G. Grunig, M.B. Beasley, J.Q. Xiong // Inhalation Toxicology. — 2014. — Vol. 26. — № 1. – P. 48—58.
7. Gutnikova, A.R. The possibility of restoring the structure of the liver during intoxication with heavy metal salts / A.R. Gutnikova, I.M. Baibekov, D.D. Ashurova, B.A. Saidkhanov, K.O. Makhmudov // Occupational medicine and industrial ecology, -2012. — No. 6. – pp. 32-35.
8. Comparative effect of cobalt salts on the balance of proteins and fluids in the body of G.R. Khalturin rats // Modern high-tech technologies: Mat. inter. conf. ((Egypt, 2011) // The international magazine butt. And the foundation. research.- 2011.- No. 5.- pp. 61-62.
9. Almatov K.T., Saidkhodzhaev G.M., Klemesheva L.S., Irgashev M.S. Protective effect of cobalt during inactivation of succinate oxidase and NAD.N-oxidases of the respiratory chain of mitochondria by phospholipase A2 // Uzbek biol.journal – Tashkent, 1998. No. 2. – pp. 32-35.
10. Ibragimova K.M., K.T.Almatov. The effect of cobalt ions on the respiratory function of mitochondria // Science, education, technology. International Scientific Journal. – Ministry of Education and Culture of the Kyrgyz Republic, 2003. – No. 1-2. – pp. 104-109.
11. Saidkhodjaev G.M., Irgashev M.S., Klemesheva L.S., Almatov K.T. The effect of cobalt ions on the activity of the polyphermatic systems of the respiratory chain of rat liver mitochondria // Uzbek. biol. journal. – 1996. № 1-2. – pp. 17-20.
12. Korotkov S.M., Glazunov V.V., Rosengart E.V., Suvorov A.A., Nesterov I.P., Khovanskikh A.E. The effect of the hydrophilic complex of cadmium with anabazine on energized rat liver mitochondria // Reports of the Academy of Sciences of Russia. –Russia, 1996. – Vol. 346. – No. 4. – C.552-554 .
13. Korotkov S.M., Skulsky I.A. Change in the effect of Cd2+ on respiration of isolated rat liver mitochondria after their preincubation with Ca2+, Sr2+, Ba2+, Mn2+ and ruthenium red // Cytology. - 1996. – Vol. 38. – No. 4-5. – pp. 500-509.