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Cadmium – influence on biochemical processes of the human organism

Heavy metals belong to well-known environmental pollutants of particularly serious hazard to human health, because the effects of their action are not immediate but they come out after many years in consecutive generations. Food contamination by heavy elements is very hard to avoid and it is a reflection of the air, water and soils contamination by dusts, industrial gasses, sewage, waste and coal burning processes. Heavy metals content in the environment is quite diverse and their action depends on the absorbed dose, the type of element, the chemical form that they appear in and the state of organism nutrition.

One of the most harmful heavy metals is cadmium, which is widely spread in nature. Cadmium is used to metal surfaces coating instead of zinc, as a component of alloys and solders and to cadmium lamps and dyes. It gets to the atmosphere with industrial emissions. Environment contamination by cadmium is particularly big nearby non-ferrous metals steel mills. Big amounts of this element are brought into soils together with phosphorous fertilizers. The biggest source of human population exposition to cadmium is cigarettes smoke. One cigarette contains 1–2 μg of cadmium, while over 70% together with inhaled smoke comes into lungs and then into the circulation system (28). Plants exceptionally easily absorb cadmium, and its huge mobility in all sorts of soils causes its very quick joining in food chains (7).

Cadmium constitutes a big danger for living organisms because of its huge easiness of absorption and relatively long time of its arrest in tissues and bioaccumulation in organs that fulfil important functions in organism (kidneys, liver and testicles, which are critical organs in cadmium poisonings) (7). Its biological half-life amounts to 10–30 years depending on the intake form and individual features of the organism. Cadmium daily intake with food by adults amounts on average to 20–120 μg. In smokers that element occurs in amounts much higher than in non-smokers. Exposure index of cadmium is its blood concentration, which in human is 0.1-1.7 μg/l. Limit values of safe concentration equals to 10 μg/l (7). Cadmium intake takes place mainly by the alimentary canal and respiratory system (28). It creates complexes with blood plasma proteins (albumins) and thanks to that it is easily transported and then deprotoned in kidneys and liver (in these organs 50% of total cadmium content in the organism is present).

Chronic cadmium poisonings develop slowly. According to many researches chronic exposition evokes kidneys damages, leads to anaemia, bones diseases and cancers and it holds some shares in development of hypertension and cardiovascular diseases (5). Longer exposition leads to development of chronic cadmialism. It is characterized by general weakness, xerostomia, metallic taste, lack of appetite, cadmium gingival margin, periodical stomach aches and headaches, OB increase, and other symptoms. After about 5 years insomnia, nervous excitability, vertigo, epistaxis, muscular and joint pains and decalcification bone changes occur. Moreover, after a dozen years or so of exposure incessant myalgia, weakness, insomnia, breathlessness, pulmonary emphysema, kidneys and medulla damage and lungs fibromal changes begin.

The most dramatic example of high cadmium concentration poisonings was "Itai – Itay byo" diseases group, which occurred in 1912 in Toyma district in Japan upon the Jintsu River. The source of such high amounts of cadmium in the environment was water and rice contaminations by functioning nearby zinc mine Kamioka Mining Co., Ltd. Daily cadmium intake varied in the range of 500–800μg while in non-contaminant regions it amounted to 30–50 μg (13). That group of diseases was characterized by myalgia and back pains, bone tissue atrophy (softening and fragility of bones) (26) and serious kidneys damage (27). During those 15-30 years over 150 persons died because of chronic cadmium poisoning.

Toxic cadmium action involves free oxygen generation and inactivation of protein that contain cysteine residues with –SH groups (5). This element is an inhibitor of phosphatases and enzymes containing sulfhydryl groups, it makes disorders in protein metabolism and causes appearance of their excretion with urine (8). That metal induces a cascade of events leading in consequence to protooncogens expression in cell (7). In tissues cadmium is selectively bounded by metallothioneins. Zinc given to animals before cadmium intoxication had protective action, diminishing tissues damages made up by cadmium (21). Metallothioneins show beneficial action in acute cadmium poisonings and they prevent cadmium interactions with –SH groups of enzymatic proteins. In chronic cadmium poisoning critical organs are kidneys while in acute poisoning – liver and testicles (7).

Liver picks out cadmium in form of complexes with albumins, then it is bounded with metallothionein (12) and systematically liberated into blood plasma. Cd-thionein easily crosses renal glomerules and inside renal tubules it can be demoted to free cadmium and amino acids or is entirely resorbed by proximal tubule cells and then, inside these cells, demoted. Cadmium disturbs renal tubules and renal glomerules functions, which leads to changes in renal glomerules permeability and renal tubules resorption. The result of that are proteins, increased amount of calcium and phosphoric ions and even zinc and copper appearance in urine (8).

For a long time multimensional influence of cadmium on the circulation system and metabolic transformations was intriguing for scientists. Many researches showed accumulation of that metal in heart muscle and also quite big increase of myocardium mass in animals exposed to cadmium action, especially in case of simultaneous low-selenium diet (2). Higher blood cadmium concentrations were stated in patients with dilated cardiomyopathy. In animals chronic exposure to cadmium decreased contractility of heart muscle. One of the reasons of incorrect myocardium contractility can be disturbing by cadmium metabolism highly-energetic phosphates and cadmium and calcium ions competition for binding sites in cell membrane and intercellular structures connected with contractility system (2, 13). In living organisms cells there are many places where cadmium ions can emulate calcium ions, compete with them or in some other way disturb processes controlled by calcium ions (5). Because of their similarity to each other, cadmium is able to open calcium canals in cell membrane and cross them very slowly; it can inhibit calcium influx contributing to smooth muscular coat relaxation (2). Additionally cadmium exposition caused decreased coronary influx evoked by direct interaction of that metal on vessels wall, and also on the development of arteriosclerotic changes of heart and aorta coronary vessels (2, 17). For the sake of similar ionic radius, cadmium as well as lead and mercury, can substitute for calcium in molecule of calmodulin, contributing to activation of many calmodulin dependent enzymes like myosin light chains kinase, which plays some role in contracile-relaxation cycle of smooth muscles (2).

Oral cadmium intoxication and also chronic occupational exposure lead to anaemia that is characterized by hypoferremia, significant reticulocytosis, poikilocytosis and anisocytosis (5). The main reason of cadmium-induced anaemia is deprivation of ferrous intestinal absorption and cadmium competition in kinship to proteins participating in iron transport: serum transferring and ferritin (5). Additionally cadmium shortens erythrocytes lifetime and influences erythropoesis. Cadmium disturbs calcium and phosphate ions homeostasis in the organism (it increases their excretion as a result of kidneys damage). Additionally it disturbs production of an active form of vitamin D_3 by slowing down

hydroxylases by binding with –SH groups present in catalytic centres of the enzymes that participate in cholekalcyferol activation (biologically inactive form of vitamin D_3). Osseous tissue mineralization disorders by cadmium lead to osteomalacia and osteoporosis (1), whose symptoms are bones decalcification, pains and compression sensitivity and consequences are bones softening, vertebrae flattening, ribs fracture, pelvis deformity, motor functions disturbance and even making the latter impossible (7, 13).

Cancerogenic properties of cadmium have been repeatedly confirmed in experiments on animals. They showed that cadmium might initiate new growth tumour formation as well as emphasize the process of cancerous cells metastases (15). In laboratory researches administration of cadmium to animals caused formation of diverse neoplastic changes like sarcoma in injection place (23), pulmonary carcinoma (15), tuberculosis of prostate and testicles (22) and tumours of haematopoietic system (7,13). Epidemiological studies suggest connections between cadmium exposition and pulmonary (19), prostate (25), nose and nasal sinuses (11) cancers occurring in humans. For these reasons in 1993 cadmium was regarded as a human cancerogenic factor of the first category by International Agency for Research on Cancer (IARC) (15, 24).

Mechanism of cadmium cancerogenic action is quite well known. That metal, being zinc antagonist, can stimulate orphan receptors causing a series of biochemical consequences, which lead to introduction of numerous protooncogens transcription (4, 14, 15, 18, 24). Cadmium can also interact directly with DNA (16) although it is thought to be a very weak mutagen and clastogen (24). At noncytotoxic doses Cd interferes with DNA repair processes (9), which can be the direct source of mutations leading to cancerogenic properties of cadmium (3). The inhibition of repair and detoxifying enzymes by this metal (10) may partially explain the observed weak genotoxic properties of this metal. Nongenotoxic mechanisms upregulating intracellular signalling pathways leading to increased mitogenesis are discussed as major mechanisms for the interpretation of the carcinogenic activity by chronic cadmium exposure (4).

It is worth to stress that zinc is a very important factor able to decrease or totally inhibit cancerogenic action of cadmium, in dependence on the type of tissue and general conditions. It appears mainly because of competition of these two metal ions to active cellular sites responsible for enzymes and genes regulation (24), and the ability of zinc to metallothionein synthesis induction. Metallothionein binding cadmium reduces many of its harmful actions (12).

Cadmium, as well as other heavy metals, is considered to be a potential immunotoxic factor, which can reveal direct toxicity on immune system cells or modulate immunological answer to antigens and mitogens. It can also affect contact allergy and immunologic diseases (29). Based on numerous studies it was stated that cadmium may deprivate antigen presentation and it can stimulate macrophages to increased oncogen degradation. Cd significantly decreases immunity of the examined to bacterial, viral and parasitic infections and malignant diseases. Chronic cadmium poisoning can cause dysfunctions in B-lymphocytes differentiation process and immunoglobulin production impairment (6). Effects of cadmium toxic action to a large degree depend on that metal influence on metabolism and functions of many elements like calcium, zinc, iron, copper and selenium.

For the sake of similar chemical properties of cadmium and zinc (these both elements belong to IIB group of periodic table) their metabolism and kinetics in the organism, although not identical, in both cases are regulated by metallothionein. It takes part in detoxification of such heavy metals as cadmium or mercury and in maintaining homeostasis of some important microelements like zinc or copper (20, 23).

Many researches have shown competitive interactions between cadmium and zinc resulting mainly from the affinity of these both elements to metallothionein. Zinc administered to animals before cadmium intoxication has protective action by decreasing or levelling cadmium induced tissues damage (7, 8,

24). Some of cadmium toxic actions are accompanied by disturbed zinc metabolism (for instance in cadmium induced kidney dysfunctions an increased zinc excretion with urine is observed) (17). Due to great toxicity of cadmium constant supervision of its concentration in the environment is essential and very important.

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SUMMARY

Heavy metals are too well-known environmental pollutants of particularly dangerous effect to human health. Because of their wide usage in many industrial branches they are present everywhere in the air, water and soils. Food contamination by heavy elements is hard to avoid and it is a result of environmental contamination by dusts, industrial gases, sewage, waste and coal burning processes. One of the most harmful heavy metals, widely spread in nature is cadmium. Toxic cadmium action involves free oxygen generation and inactivation of protein containing cysteine residues with –SH groups. It influences many metabolic processes causing great damage in many organs. Cadmium can also interact with some essential elements leading to their homeostasis disorders.

Kadm – wpływ na procesy biochemiczne organizmu ludzkiego

Metale ciężkie należą do tych zanieczyszczeń środowiska, które są szczególne groźne dla zdrowia człowieka. Ze względu na dość szerokie zastosowanie w wielu gałęziach przemysłu są one obecne w powietrzu, wodzie oraz w glebie. Zanieczyszczenie żywności pierwiastkami ciężkimi jest trudne do uniknięcia i jest odzwierciedleniem skażenia powietrza, wody, gleby przez pyły, gazy przemysłowe, ścieki, odpady, a także procesy spalania węgla. Jednym z najgroźniejszych metali ciężkich, szeroko rozpowszechnionych w środowisku, jest kadm. Toksyczne działanie kadmu polega na wytwarzaniu wolnych rodników oraz inaktywacji białek zawierających w swojej budowie reszty cysteinylowe z grupami tiolowymi –SH. Wpływa on na wiele przemian metabolicznych, powodując uszkodzenia różnych organów. Kadm może również oddziaływać na niektóre ważne bioelementy, prowadząc do zaburzenia ich homeostazy.