UDC 577
Preliminary reports

CHRONIC TREATEMENT WITH $CdCl_2$ AND ACCUMULATION OF CADMIUM IN THE LIVER, KIDNEYS, TESTES AND SKELETAL MUSCLE OF RATS

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Pavlović Z. Slađan, Branka I. Ognjanović, Andraš Š. Štajn, Radoslav V. Žikić, and Zorica S. Saičić (2005): *Chronic treatement with cdcl2 and accumulation of cadmium in the liver, kidneys, testes and skeletal muscle of rats.* - Iugoslav. Physiol. Pharmacol. Acta, Vol. 41, No. 3, 113-118, Belgrade.

INTRODUCTION

Cadmium (Cd) is a commonly occurring environmental pollutant which is present in soils, sediments, air and water. Unlike most metals, Cd use began fairly recently with its large-scale application dating from 1940s (STOEPPLER, 1991). Today its main uses are for Ni-Cd battery manufacture, pigments, and plastic stabilizers, whereas applications in alloys, solders and electroplating show a decreasing trend. Anthropogenic sources of Cd to the environment are: refining and use, Cu and Ni smelting and fossil fuel combustion. Natural sources of Cd to the atmosphere are: volcanic activity, forest fires and windblown transport of soil

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particles (IRWIN *et al.*, 1997). Major occupational exposure occurs in non-ferrous metal smelters, in the production and processing of Cd, its alloys and compounds and, increasingly, in the recycling of electronic waste. Non-occupational exposure is mainly from cigarette smoke which contains relatively high concentrations of this element. For non-smokers who are not occupationally exposed, diet is the main route of exposure to Cd (WHO, 1992). Cd is listed by the US Environmental Protection Agency as one of 126 priority pollutants. In most studies, the half-life in humans is estimated to be between 15 and 20 years (JIN *et al.*, 1998). After penetration into the organism, mostly through respiratory and gastrointestinal tract, Cd accumulates in the liver and the kidneys, as well as in other tissues and organs causing many metabolic, histological and pathological changes, such as nephrotoxicity, cardiotoxicity, increased lipid peroxidation and hemorrhagic lesions of seminal tubules. In tissues, Cd bounds to proteins of low molecular mass producing metallothioneins by the induction of metallothionein mRNA synthesis (GEORGE *et al.*, 1996; OGNJANOVIĆ *et al.*, 2005). Cd also depletes glutathione and protein-bound sulfhydryl groups resulting in enhanced production of reactive oxygen species (ROS), such as superoxide anion radicals, hydroxyl radicals and hydrogen peroxide. These ROS result in increased lipid peroxidation, enhanced excretion of urinary lipid metabolites, modulation of intracellular oxidized states, DNA damage, membrane damage, altered gene expression and apoptosis (KIM *et al.*, 2003). From totally accumulated Cd in the organism, about 75% is deposited in the liver and kidneys (OGNJANOVIĆ *et al.*, 1995; PAVLOVIĆ *et al.*, 2005). However, Cd accumulated in most of other tissues and organs, such as pancreas, salivary glands, testes, heart, muscles, brain or brown adipose tissue (SWIERGOSZ *et al.*, 1998).

The objective of our experiment was to determine the rate of Cd accumulation in the liver, kidneys, skeletal muscle (*m. gastrocnemius*) and testes of two months old male *Wistar albino* rats.

MATERIALS AND METHODS

The animals were divided into 2 experimental groups consisting 7 rats and treated in 30 days courses. The first group of animals was control (C). The second group was treated with 200 mg $CdCl_2$ x $5H_2O$ in drinking water during 30 days (Cd). The average intake of 17 mg Cd/mg b.m. was calculated from the water consumed.

Cd concentration was determined by atomic absorption spectrophotometry in destroyed material in the mixture of nitric and perchloric acid (17:3) at the wavelength of 228.8 nm, slit 0.1 nm and lamp current 4 mA in the mixture of air and acetylene (SHIRLEY *et al.*, 1949). Cd concentration was expressed in mg/g tissue. Data are given as mean ± SE. All obtained results were compared with respect to the control animals. Data were analyzed using Student's *t* test and differences at $p<0.05$ were considered as significant.

RESULTS AND DISCUSSION

The obtained results show a significant accumulation of Cd in examined tissues of rats (liver, kidneys, testes and skeletal muscle), (Figs. 1-4) in respect to the controls ($p<0.005$).

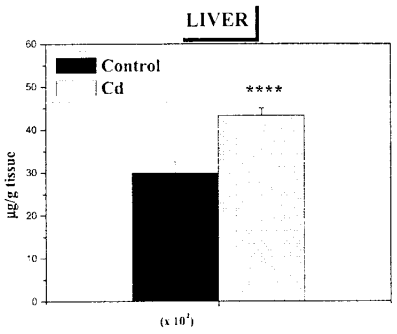

Fig. 1. - The concentration of cadmium (Cd) expressed in mg/g wet mass in the liver of control (Control), (real concentration was 10^2 times lower than presented) and cadmium-treated rats (Cd). Significantly different in respect to the control animals: **** $p<0.005$

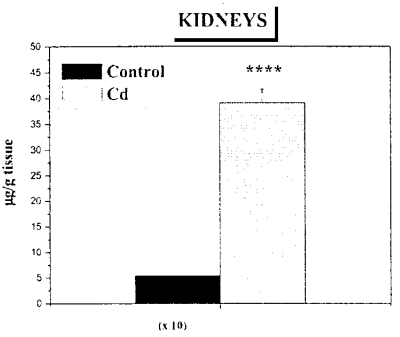

Fig. 2. - The concentration of cadmium (Cd) expressed in mg/g wet mass in the kidneys of control (Control), (real concentration was 10 times lower than presented) and cadmium-treated rats (Cd). Significantly different in respect to the control animals: **** $p<0.005$

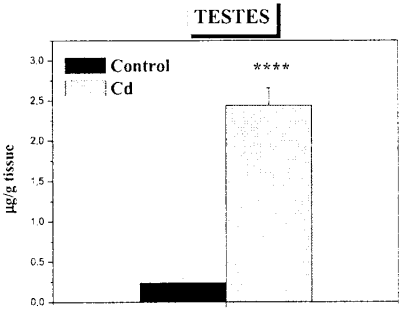

Fig. 3. - The concentration of cadmium (Cd) expressed in mg/g wet mass in the testes of control (Control) and cadmium-treated rats (Cd). Significantly different in respect to the control animals: **** $p<0.005$

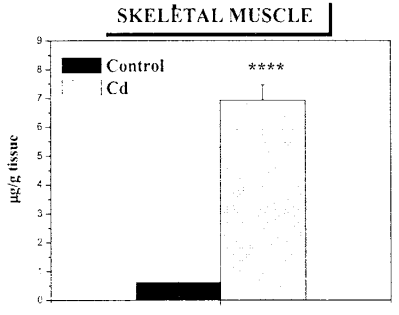

Fig. 4. - The concentration of cadmium (Cd) expressed in mg/g wet mass in the skeletal muscle (*musculus gastrocnaemius*) of control (Control) and cadmium-treated rats (Cd). Significantly different in respect to the control animals: **** $p<0.005$

This is in accordance with the fact that Cd in the organism is not metabolized and due to a very long biological half-life mostly accumulates in cells and tissues. Most of Cd accumulates in the cytosol where it induces many structural and metabolic changes. Cd decreases protein synthesis and inactivates enzymes by binding to their sulfhydryl groups.

Absorbed Cd is deposited mostly in the kidneys and the liver, whereas the kidneys, lungs, and bones are target organs for this metal (SHORE and RATTNER, 2001). Cd intoxication leads to renal, hepatic, testicular, and prostate dysfunction, osteomalacia, hypertension, as well as growth retardation and renal "Itai-itai" disease (VENUGOPAL and LUCKEY, 1978). It also causes a disturbance of the central nervous system, poor lactation and reductions in hematological parameters. The high accumulation of Cd in the liver and kidneys entails an increase of the concentration of zinc in these organs. In addition, the presence of Cd in the diet reduces the intestinal absorption of iron causing anemia (FRIBERG *et al.*, 1986). The total Cd intake over a lifetime that produced an adverse health effect in humans is 2000 mg (KLAASSEN, 2001). Cd in spite of not being a Fenton metal, causes the generation of ROS, which are capable of influencing the expression of genes. For example, the AP-1 element, consisting of the proteins coded by c-*fos* and c-*jun*, is a redox-sensitive transcription factor, and the involvement of ROS in the Cd-induced transcriptional activation of AP-1 is well known (ISHIKAWA *et al.*, 1999). Cd like other stress-related agents can stimulate intracellular networks of signaling cascades in large part by modulation of transcription factors resulting in deregulation of target gene expression. Various transcription factors, such as AP-1, MTF1, HIF-1a, NF-kB, USF and NRF2 are found to be involved in the Cd-induced deregulation of gene expression. ISHIKAWA *et al.* (1999) have reported the overexpression of several unidentified Cd-responsive nuclear proteins capable of transcriptional activation of c-*fos* gene due to their binding with the heat-shock element present in its promoter.

From the presented results, it can be concluded that dietary intake of Cd leads to its significant accumulation in liver, kidneys, testes and skeletal muscle (*m.gastrocnaemius*). At the same time, Cd in grater extent accumulates in tissues with high metabolic activity, such as liver and kidneys causing structural, biochemical and metabolic alterations.

Acknowledgements. - This work was funded by the Ministry for Science and Environmental Protection of Republic of Serbia.

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Received October 17, 2005
Accepted December 12, 2005