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A POSSIBLE PROTECTIVE ROLE OF COENZYME Q_{10} ON ANTIOXIDANT DEFENSE ENZYME ACTIVITIES IN KIDNEYS OF RATS TREATED WITH CADMIUM

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The aim of this study is to establish the effects of cadmium (Cd), coenzyme Q_{10} (CoQ_{10}) and Cd + CoQ_{10} on the activities of: superoxide dismutases (total SOD, manganese containing, Mn SOD, copper zinc containing, CuZn SOD), catalase (CAT), glutathione peroxidase (GSH-Px), glutathione-S-transferase (GST), as well as glutathione reductase (GR) in the kidneys of male *Wistar albino* rats in comparison with control animals. Significantly increased activities of Tot SOD and CuZn SOD in the kidneys of Cd-treated animals were observed. At the same time, the activity of Mn SOD was significantly decreased in the kidneys of animals treated with Cd, as well as with

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CoQ_{10}. The activity of CAT was significantly lower in rats exposed to CoQ_{10} and Cd+CoQ_{10} in respect to the control animals. GSH-Px and GST activities were significantly decreased in all treated groups of animals (Cd, CoQ_{10} and Cd+CoQ_{10}), while GR activity was not changed. Presented results reveal, that CoQ_{10} only partially reversed Cd-induced changes of antioxidant defense enzyme activities in kidney by reversing the effect of Cd on Tot SOD and CuZn SOD activities.

Key words: cadmium, coenzyme Q_{10}, kidnys, antioxidant defense enzymes, rats

INTRODUCTION

Cadmium (Cd) is a commonly occurring environmental pollutant. 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 (YIIN *et al.*, 1999). In tissues Cd bounds to proteins of low molecular mass producing metallothioneins by the induction of metallothionein mRNA synthesis (GEORGE *et al.*, 1996). Cadmium 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 (STOCHS *et al.* 2000; KIM *et al.* 2003). Kidneys are one of the most critical organs for the toxicity of Cd (ŠTAJN *et al.* 1997; HORIGUCHI *et al*, 2005). In humans the accumulation of Cd in these organs causes alterations of tubular cells, as well as the secondary nephropathy of the cortex and "Itai-itai" disease (IID) which is characterized mainly by osteomalacia and renal tubular disorder (HIRATSUKA *et al.* 1997). In addition, IID patients often have anemia (NOGAWA *et al.* 1984). This anemia was normocytic, normochromic and the blood levels of erythropoietin were not elevated despite severe anemia, suggesting that the anemia in IID patients was nephrogenous. In experiments with animals, exposure to Cd also induced anemia, but it was iron deficiency anemia due to the competition of Cd with iron in the iron transfer system of the intestinal mucosa (SAKATA *et al.* 1988).

Coenzyme Q_{10} (CoQ_{10}) is a lipid-soluble molecule and an integral part of most biomembranes. It is also a mobile constituent of mitochondrial respiratory chain. Reduced form of CoQ_{10} ($CoQ_{10}H_2$) exhibits powerful antioxidant properties which include its reaction with lipid free radicals or lipid peroxide radicals and subsequent inhibition both of initiation and propagation of lipid peroxidation (ERNSTER and DALLNER 1995). Another mechanism is that superoxide dismutase (SOD) interacts with hydroquinones and together with the two-electron quinone reductase (DT-diaphorase) inhibits autooxidation of hydroquinones. CoQ_{10} can regenerate the active form of vitamine E (Vit E) from Vit E radical and stabilize

extracellular ascorbate into the organism (KOZLOV *et al.* 1999). However, CoQ_{10} also protects DNA from oxidation caused by lipid peroxidation, protects organism from oxidative stress induced by various toxic agents, such as carbon tetrachloride or ethanol and protects cells against apoptosis by inhibition of ceramide release and caspase-3 activation (FERNANDEZ-AYALA *et al.* 2000). CoQ_{10} has a large number of clinical applications, especially in the treatment of congestive heart failure and certain neurological disorders, such as Kearns-Sayre's syndrome (mitochondrial encephalopathy), (BEAL 1999).

The main objective of this research was to evaluate the effects of Cd, CoQ_{10} and Cd+CoQ_{10} on antioxidant defense enzyme activities in kidneys of rats. After 30 days of treatment the activities of: superoxide dismutases (total SOD, manganese containing ,Mn SOD and copper zinc containing, CuZn SOD, EC 1.15.1.1), catalase (CAT, EC 1.11.1.6), glutathione peroxidase (GSH-Px, EC 1.11.1.9), glutathione-S-tranferase (GST, 2.5.1.18), as well as glutathione reductase (GR, EC 1.6.4.2) were estimated.

MATERIALS AND METHODS

In our experiments 60 days old male *Wistar albino* rats, weighing 190 ± 20 g at the beginning of experiments were used. The animals were housed in individual cages at 21 ± 1 °C and exposed to 12 h light - 12 h dark cycles. The rats were fed chow pellets (Veterinarski Zavod, Zemun, Serbia) and drank tap water *ad libitum*. The animals were divided in four experimental groups and treated during the course of 30 days. The first group of animals was control group (C, drinking tap water). The second group was treated with cadmium (Cd, 200 mg $CdCl_2$ x 5 H_2O in drinking water during 30 days + 100 μL of olive oil, i.m., every fifth day). The third group was treated with coenzyme Q_{10} (CoQ_{10}, 20 mg CoQ_{10} dissolved in olive oil, i.m., every fifth day, drinking tap water). The fourth group was treated concomitantly with cadmium and coenzyme Q_{10} (Cd+CoQ_{10}, 200 mg $CdCl_2$ x $5H_2O$ in drinking water during 30 days + 20 mg CoQ_{10}, i.m. every fifth day). The average intake of 17 mg Cd/day/kg body mass was calculated from the water consumed during the 30 days of treatment. The average intake of CoQ_{10} was 16 mg/kg body mass every fifth day. Each group consisted of 7 animals. After the treatment the animals were sacrificed by decapitation between 8 and 10 a.m. in order to avoid any possible cyclic changes in metabolic and antioxidant levels. All animal experiments were carried in such a manner that all unnecessary animal discomfort and pain were avoided.

The kidneys of rats were isolated and dissected out within 3 minutes, placed in ice-cold 155 mmol NaCl and washed with the same solution. The kidneys tissue was minced and homogenized in 10 volumes of 25 mmol/L sucrose containing 10 mmol/L Tris-HCl, pH 7.5 at 1500 rpm using Thomas Sci Co. glass homogenizer (Teflon pestle). Homogenates were then centrifuged at 4 °C at 100 000 x g for 90 minutes. All chemicals were SIGMA (St. Louis, MO, USA) products.

Total SOD activity was measured in the supernatant by the epinephrine method (MISRA and FRIDOVICH 1972) based on the capacity of SOD to inhibit

autooxidation of adrenaline to adrenochrome. For the determination of Mn SOD activity the assay was performed after the preincubation with 8 mmol/L KCN. CuZn SOD activity calculated as a difference between total SOD and Mn SOD activities. SOD activities were expressed as U/g wet mass. CAT activity was determined as suggested by BEUTLER (1982) and expressed as mmol H_2O_2/min/g wet mass. The activity of GSH-Px was measured following the oxidation of nicotinamide adenine dinucleotide phosphate (NADPH) as a substrate at 340 nm with t-butyl hydroperoxide (TAMURA *et al* 1982) and expressed in nmol NADPH/min/g wet mass. GST activity toward 1-chloro-2,4-dinitro benzene (CDNB) as a substrate was assayed according to HABIG *et al* (1974) and expressed in nmol GSH/min/g wet mass. The activity of GR was evaluated as suggested by GLATZLE *et al* (1974) and expressed in nmol NADPH/min/g wet mass.

Data are given as means ± SE. All obtained results were compared with respect to control animals (C), as well as with respect to the Cd treated animals (Cd). Statistical analysis of results was based on Student's paired t-test considering the significance at the level of $p<0.05$ (HOEL 1966).

RESULTS

Results presented in Fig. 1. showed the activities of antioxidant defense enzymes: Tot SOD, Mn SOD and CuZn SOD in kidneys of rats treated with Cd, CoQ_{10} and concomitantly treated with Cd+CoQ_{10}.

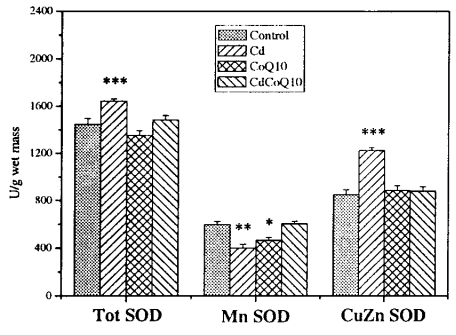

Fig. 1. - Activities of superoxide dismutases (total SOD, manganese containing, Mn SOD and copper zinc containing ,CuZn SOD) expressed in U/g wet mass in the kidneys of: control rats (C), rats treated with cadmium (Cd), rats treated with coenzyme Q_{10} (CoQ_{10}) and concomitantly treated rats with cadmium and coenzyme Q_{10} (Cd+CoQ_{10}) during 30 days. The values are means ± SE from seven animals.
Significantly different from controls (C):
* $p<0.05$ ** $p<0.01$ *** $p<0.005$

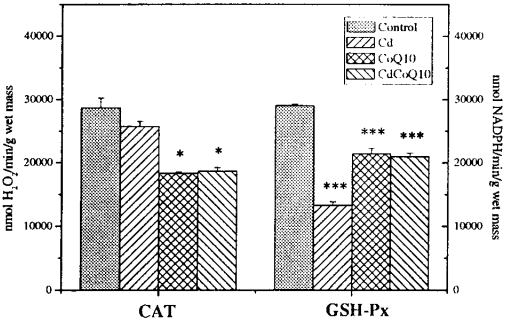

Fig. 2. - Activities of catalase (CAT) and glutathione peroxidase (GSH-Px) expressed in U/g wet mass in the kidneys of: control rats (C), rats treated with cadmium (Cd), rats treated with coenzyme Q_{10} (CoQ_{10}) and concomitantly treated rats with cadmium and coenzyme Q_{10} (Cd+CoQ_{10}) during 30 days. The values are means ± SE from seven animals.
Significantly different from controls (C):
* $p<0.05$ *** $p<0.005$

The obtained data showed that Cd induces a significant increase of Tot SOD and CuZn SOD activities in kidneys of rats ($p<0.005$). At the same time Cd influenced a significant decrease of Mn SOD activity ($p<0.01$). In kidneys of rats treated with CoQ_{10}, the activity of Mn SOD was also significantly decreased ($p<0.05$). Our results showed that activity of CAT in kidneys of rats treated with CoQ_{10} and concomitantly treated with Cd+CoQ_{10} was significantly decreased ($p<0.05$), (Fig. 2.).

The activities of GSH-Px (Fig. 2.) and GST (Fig. 3.) were significantly lower in all investigated groups of animals (Cd, CoQ_{10} and Cd+CoQ_{10}) in respect with control animals ($p<0.005$). At the same time, the activity of GR was not significantly changed in any of investigated groups of animals in comparison to the control animals (Fig. 3.).

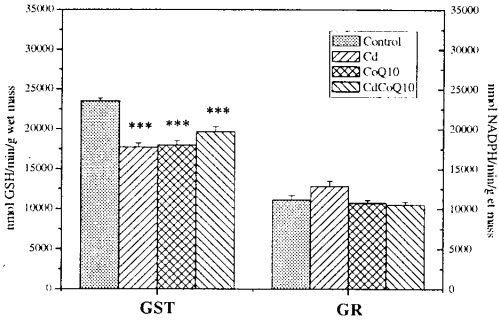

Fig. 3. - Activities of glutathione-S-transferase (GST) and glutathione reductase (GR) expressed in U/g wet mass in the kidneys of: control rats (C), rats treated with cadmium (Cd), rats treated with coenzyme Q_{10} (CoQ_{10}) and concomitantly treated rats with cadmium and coenzyme Q_{10} (Cd+CoQ_{10}) during 30 days. The values are means ± SE from seven animals.
Significantly different from controls (C):
*** $p<0.005$

DISCUSSION

The results presented in this research indicate that chronic Cd administration induced elevated activities of total SOD and CuZn SOD ($p<0.005$) in kidneys of rats (Fig. 1.). After being introduced into the organism Cd enters the blood and tissues and induces an increased production of reactive oxygen species, including superoxide anion radicals and hydrogen peroxide (KOSTIĆ *et al.* 1993). As a biological response, it is reasonable to expect an increased activity of SOD in kidneys, since in physiological conditions SOD is an important intracellular antioxidant, because it eliminates superoxide anion radicals when it is formed in excess. In contrast, the activity of Mn SOD in Cd treated animals was significantly decreased ($p<0.01$), (Fig. 1.). Studies of other authors have shown, that Cd can inhibit the activity of most enzymes of antioxidant defense system (SHUKLA *et al.* 1987). This probably is the consequence of the intracellular accumulation of ROS with subsequent development of kidney injury. We presume that Cd also, enters the mitochondria and inhibits the activities of many enzyme by binding to their sulfhydryl groups or by inhibiting the protein synthesis (STOHS *et al.* 2000). Similar results on the influence of Cd on SOD activity we obtained in skeletal muscle of rats (PAVLOVIĆ *et al.* 2001a). CoQ_{10} diminished the toxic effect of Cd on Tot SOD and CuZn SOD activities in both CoQ_{10} and Cd+CoQ_{10} treated animals. It is known that CoQ_{10} induces an elevation of Vit E concentration in tissues of rats and it is known,

that the rate of superoxide anion radicals elimination is directly related to the Vit E concentration indicating the role of Vit E in this elimination of radicals (KOZLOV *et al.* 1999). Thus, CoQ_{10} indirectly protects the total SOD activity in the cell. In contrast, we detected a significant decrease of Mn SOD activity in kidneys of rats treated with CoQ_{10} ($p<0.05$). Of the three main antioxidant defense enzymes (SOD, CAT, and GSH-Px), only CAT remained unaltered (Fig. 2.) indicating that this enzyme does not play a critical role in preventing Cd-induced oxidative injury. This is in accordance with our earlier investigations in kidneys of rats (ŠTAJN *et al.* 1997; JIN *et al.* 2004). Contrary to that, in kidneys of animals treated with CoQ_{10} and concomitantly treated with Cd+CoQ_{10} we obtained a significantly decreased activity of CAT. In respect to the control values the activity of GSH-Px was significantly decreased in all investigated groups of animals: Cd, CoQ_{10} and Cd+ CoQ_{10}. It is well established that Cd induces a decrease activity of GSH-Px (ŠTAJN *et al.* 1997). Its reduced activity contributes greatly to peroxidative damage and development of kidney injury (SUGIYAMA 1994). Application of CoQ_{10} only partly diminishes the toxic effect of Cd on GSH-Px activity, but these values are significantly lower in comparison with control animals. According to our data, the activity of GST, which catalyzes the conjugation of GSH to heavy metals and detoxicates lipid peroxides is decreased in kidneys of Cd-treated, CoQ_{10}-treated and Cd+CoQ_{10}-cotreated rats (Fig. 3). Many authors (SHUKLA *et al.* 1987) demonstrates that Cd can inhibit the activity of most antioxidant defense enzymes, which can explain decreased activity of GST in the kidneys of rats. Treatment of rats with CoQ_{10} decreased activity of GST in the kidneys. CoQ_{10} by quenching ROS can be indirectly involved in the regulation of gene expression and in modulation the activities of most enzyme. At the same time, CoQ_{10} has an important role in the prevention of lipid peroxidation and oxidative damage of tissues and thus can induce a decreased activity of GST (LINNANE *et al.* 2002). The concentration of low-molecular mass antioxidants, such as vitamins C and E also can influenced the balance of antioxidant defense enzyme activities. Our previous findings showed (PAVLOVIĆ *et al.* 2001b) that in kidneys of rats treated with CoQ_{10} the concentrations of Vit C and Vit E were significantly elevated. Increased concentration of AsA in the kidneys of CoQ_{10} treated animals fits well with increased concentration of Vit E in these organs. These vitamins, especially Vit E contributes mostly on the quenching of ROS and lipide peroxides concentration and this can exert sparing effect on GST activity in the kidneys. According to data obtained in this experiment, the only enzyme which did not influenced with treatments used was GR.

CONCLUSIONS

On the basis of obtained data presented in this study, we can conclude that used treatment and dosages of administered Cd disturbs antioxidant defense enzyme activities in the kidneys of *Wistar albino* rats. At the same time, our results reveal that CoQ_{10} only partially reversed Cd-induced changes in kidney antioxidant defense enzyme activities by reversing the effect of Cd on Tot SOD and CuZn SOD activities.

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MOGUĆA ZAŠTITNA ULOGA KOENZIMA Q_{10} NA AKTIVNOST ANTIOKSIDACIONIH ZAŠTITNIH ENZIMA U BUBREZIMA PACOVA TRETIRANIH KADMIJUMOM

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I z v o d

Cilj ovog rada bio je da se objasni efekat kadmijuma (Cd), koenzima Q_{10} (CoQ_{10}) i Cd + CoQ_{10} na aktivnost: superoksid dismutaza (ukupne, Uk SOD, mangan sadržavajuće, Mn SOD, bakar cink sadržavajuće, CuZn SOD, katalaze (CAT), glutation peroksidaze (GSH-Px), glutation-S-transferaze (GST) kao i glutation reduktaze (GR) u bubrezima mužjaka *Wistar albino* pacova u poređenju sa kontrolnom grupom životinja. Dobijeni rezultati pokazuju značajno povećanje aktivnosti Uk SOD i CuZn SOD u bubrezima pacova tretiranih sa Cd. U isto vreme aktivnost Mn SOD je bila značajno smanjena u bubrezima pacova tretiranih sa Cd, kao i tretiranih sa Cd+CoQ_{10}. U poređenju sa kontrolnim životinjama, aktivnost CAT je bila značajno smanjena u bubrezima pacova tretiranih sa CoQ_{10}, kao i tretiranih kombinacijom Cd+CoQ_{10}. Aktivnosti GSH-Px i GST su bile značajno smanjene u bubrezima svih tretiranih grupa životinja (Cd, CoQ_{10} i Cd+CoQ_{10}), dok se aktivnost GR nije statistički značajno menjala. Iz prikazanih rezultata može se zaključiti, da CoQ_{10} samo delimično utiče na promene aktivnosti antioksidacionih zaštitnih enzima nastale pod uticajem Cd, kao i da vraća aktivnosti Uk SOD i CuZn SOD na normalne vrednosti.

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