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THE EFFECTS OF CADMIUM AND COENZYME Q_{10} ON ANTIOXIDANT DEFENCE ENZYME ACTIVITIES IN THE BLOOD OF RATS

SLADJAN Z. PAVLOVIĆ[1*], BRANKA I. OGNJANOVIĆ[2], ANDRAŠ Š. ŠTAJN[2], RADOSLAV V. ŽIKIĆ[2], ZORICA S. SAIČIĆ[1], VOJISLAV M. PETROVIĆ[1]

[1]Institute for Biological Research "Siniša Stanković", Department of Physiology, Belgrade, Serbia, Yugoslavia
[2]Faculty of Sciences, Institute of Biology, University of Kragujevac, Kragujevac, Serbia, Yugoslavia

The purpose of our study was to investigate the effects of cadmium (Cd) and coenzyme Q_{10} (CoQ_{10}) on the activities of copper, zinc-containing superoxide dismutase (CuZn SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) in red blood cells (RBC) as well as glutathione S-transferase (GST) in the plasma of male two months old *Wistar albino* rats. The animals were divided in five experimental groups as follows: (1) control (C), (2) Cd (17 mg/day/kg body mass + 100 µl olive oil, every fifth day), (3) CoQ_{10} (16/mg/kg body mass, dissolved in olive oil, every fifth day), (4) Cd+CoQ_{10} (in the above mentioned amounts) and (5) olive oil (o. oil, 100 µl i.m., every fifth day) and treated in the course of 30 days. After the treatment, the animals were sacrificed and blood samples were prepared for the analysis. Our results show that Cd administered with olive oil did not exhibit toxic effects on CuZn SOD, CAT and GSH-Px activities in RBC as well as GST activity in the plasma of rats. At the same time, CoQ_{10} by quenching the free oxygen radicals and by inhibiting lipid peroxidation may improve the antioxidant defence enzyme activities in the blood of rats. Our investigations also show that olive oil exhibit some protective effects on CuZn SOD, CAT and GSH-Px activities in RBC and GST activity in the plasma of rats treated with Cd.

INTRODUCTION

Cadmium (Cd) has been recognized as one of the most toxic environmental and industrial pollutants (Yiin, Chern, Sheu, Tseng & Lin, 1999). Major routes of Cd intake into the organism are respiratory and gastrointestinal tract (Gupta, Murthy, Thauur, Dudley & Chandra, 1990). After absorption, Cd penetrate in the bloodstream and binds to the erythrocyte membranes and plasma albumin (Waalkes & Oberdorster, 1990). In the blood and tissues Cd induces formation of metallothioneins which represent the complexes of Cd and low-molecular mass proteins (Simpkins, Lloyd & Balderman, 1998). Cd stimulates formation of reactive oxygen species and influences oxidative damage in erythrocytes resulting in loss of membrane function (Sarkar, Yadav & Bhatnagar, 1997). Cadmium induces also onset of anemia, decreases hemoglobin concentration, lowers the hematocrit value as well as decreases blood iron level (Kostić, Ognjanović, Dimitrijević, Žikić, Štajn, Rosić & Živković, 1993). A variety of accompanying changes in antioxidant defence enzymes were reported (Shukla & Chandra, 1989).

Coenzyme Q (CoQ) is the only lipid-soluble antioxidant which is normally synthesized by the organism (Lenaz, Bovina, Formiggini & Parenti-Castelli, 1999). CoQ is present in almost all living organisms where it exhibits antioxidant properties and also represents an obligatory component of the mitochondrial respiratory chain (Ernster & Dallner, 1995). Many investigations demonstrate the antioxidant capacity of reduced form of CoQ_{10} ($CoQ_{10}H_2$) over the oxidized form (Mellors & Tappel, 1966). CoQ_{10} inhibits the process of lipid peroxidation (Ernster & Dallner, 1995), regenerates the active form of vitamin E from the vitamin E radical (Kozlov, Gille, Staniek & Nohl, 1999) and stabilizes the extracellular ascorbate in the organism (Gomez-Diaz, Rodtiguez-Aguilera, Barroso, Villalba, Navarro, Crane & Navas, 1997). CoQ_{10} can protect organism from oxidative stress induced by various toxic agents (Beyer, 1988).

*Correspondence to: Sladjan Z. Pavlović, M. Sc., Research Assistant, Institute for Biological Research "Siniša Stanković" Department of Physiology, 29. Novembra 142, 11060 Belgrade, Serbia, Yugoslavia; phone: (+381) 11 764 422, ext. 141; fax: (+381) 11 761 433, e-mail: sladjan@ibiss.bg.ac.yu

Oxidative damage induced by carbon tetrachloride was decreased by CoQ_{10} administration (Bertelli, Giovannini, Bertelli, Maltinti, Scalori & Romano, 1986). Coenzyme Q_{10} inhibits also lipid peroxidation induced by carbon tetrachloride and ethanol (Beyer, 1988). CoQ_{10} has a large number of clinical applications, especially in the treatment of cardiovascular and neurologic diseases (Mortensen, Bouchelouche, Maratsu & Folkers, 1986; Zierz, Jahns & Jerusalem, 1989).

The aim of this study was to evaluate the blood antioxidant defence enzyme activities in rats chronically treated with Cd, CoQ_{10}, concomitantly treated with Cd+CoQ_{10} and olive oil. After 30 days of exposure the activities of copper, zinc- containing superoxide dismutase (CuZn SOD, EC 1.15.1.1), catalase (CAT, EC 1.11.1.6) and glutathione peroxidase (GSH-Px, EC 1.11.1.9) in red blood cells (RBC) as well as glutathione-S-transferase (GST, EC 2.5.1.18) in the plasma of rats were estimated.

MATERIALS AND METHODS

The experiments were carried out with male, 60 days old *Wistar albino* rats, weighing 190 ± 20 g at the beginning of experiments. The animals were haused in individual cages at 21 ± 1°C and exposed to 12hr light-12hr dark cycle. The rats were fed chow pellets (Veterinarski Zavod, Zemun, Yugoslavia) and drank tap water *ad libitum*. The animals were divided in five experimental groups and treated in the course of 30 days. First group of animals was control (C, drinking tap water). Second group was treated with cadmium (Cd, 200 mg $CdCl_2 \times 5H_2O$ in drinking water during 30 days + 100 µl of olive oil, i.m., every fifth day). 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). Fourth group was treated concomitantly with cadmium and Coenzyme Q_{10} (Cd+CoQ_{10}, 200 mg $CdCl_2 \times 5H_2O$ in drinking water during 30 days + 20 mg CoQ_{10}, i.m. every fifth day). Fifth group was treated with olive oil (o. oil, 100 µl), i.m., every fifth day (drinking tap water). 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. Every group consisted of 7 animals. After the treatment the animals were sacrificed by decapitation between 8 and 10 am in order to avoid any possible circadian changes in antioxidant defence enzyme activities.

Aliquots of fresh blood were taken immediately after exsanguination, collected in heparinized test tubes (1000 IU of heparin) and centrifuged (5000 rpm) for the separation of plasma and blood cells. RBC was washed three times with 3 vol. of cold 155 mmol/l NaCl. Haemolysates containing about 50 g Hb/l were prepared according to McCord and Fridovich (1969) and used for the determination of CAT and GSH-Px activities. Measurement of CuZn SOD activity was conducted in the haemolysates of washed RBC, in which Hb was previously removed by the method of Tsuchihashi (1923). CuZn SOD activity was measured by the epinephrine method (Misra & Fridovich, 1972) based on the capacity of SOD to inhibit autooxidation of adrenaline to adrenochrome. One unit of SOD activity was defined as the amount of the enzyme causing 50% inhibition of the autooxidation of adrenaline. CAT activity was assayed as suggested by Beutler (1982) and expressed as µmol H_2O_2/(min × g Hb). The activity of GSH-Px was evaluated by the method of Maral, Puget and Michelson (1977) based on the measurement of nicotine amide dinucleotide phosphate (NADPH) consumption, and expressed as nmol NADPH/(min × g Hb). For the determination of GST activity in the plasma 1-chloro-2,4-dinitrobenzene (CDNB) was used as a substrate (Habig, Pubst & Jakoby, 1974). The method is based on the reaction of CDNB with –SH groups of glutathione catalyzed by GST contained in the samples, and one unit of GST activity was defined as nmol GSH/(min × ml) of plasma.

Data are given as means ± SE. All obtained results were compared with respect to control animals (C) as well as to the animals treated with olive oil (o. oil) in order to diffentiate the effects of CoQ_{10} from the effects of o. oil. Statistical analysis of the results was based on the Student's paired "t" test considering the significance at a level of $P < 0.05$ (Hoel, 1966).

RESULTS

In comparison to the control animals the activity of CuZn SOD in RBC was significantly decreased (A: $P < 0.05$) only in rats treated with olive oil (Fig. 1). At the same time in relation to the animals treated with olive oil, CuZn SOD activity was significantly increased in rats treated with Cd and CoQ_{10} (a: $P < 0.05$) as well as in animals concomitantly treated with Cd + CoQ_{10} (c: $P < 0.01$).

The activity of CAT in RBC is presented in Fig. 2. The obtained results show that, with respect to

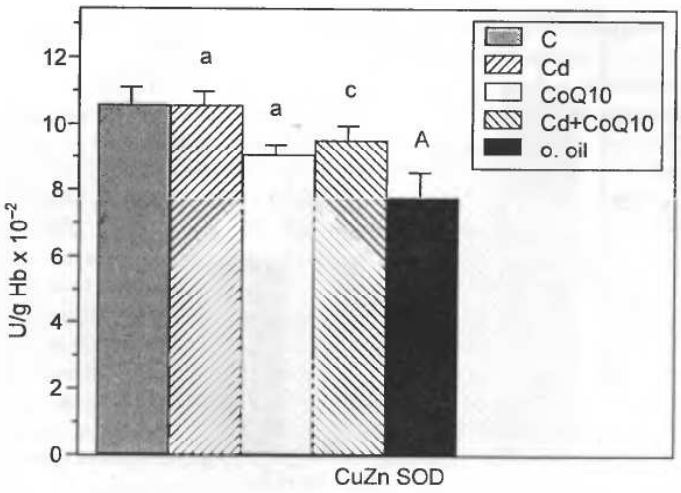

Fig. 1. The activity of copper zinc containing superoxide dismutase (CuZn SOD) expressed in U/g Hb in red blood cells (RBC) of control animals (C), treated with cadmium (Cd, 17 mg/(day × kg body mass) in drinking water + 100 µl olive oil, every fifth day, i.m.), treated with coenzyme Q_{10} (CoQ_{10}, 16 mg/(kg × every fifth day), i.m., dissolved in olive oil), concomitantly treated with cadmium and coenzyme Q_{10} (Cd + CoQ_{10}, 17 mg/(day × kg body mass) in drinking water + 16 mg/(kg × every fifth day), i.m., dissolved in olive oil) and animals treated with olive oil (o. oil, 100 µl every fifth day, i.m.). The values are means ± SE from seven animals in each group. The results were compared in respect to the control animals (C) as well as to the animals treated with olive oil (o. oil). Significance from C: $^{A}P < 0.05$. Significance from o. oil: $^{a}P < 0.05$; $^{c}P < 0.01$

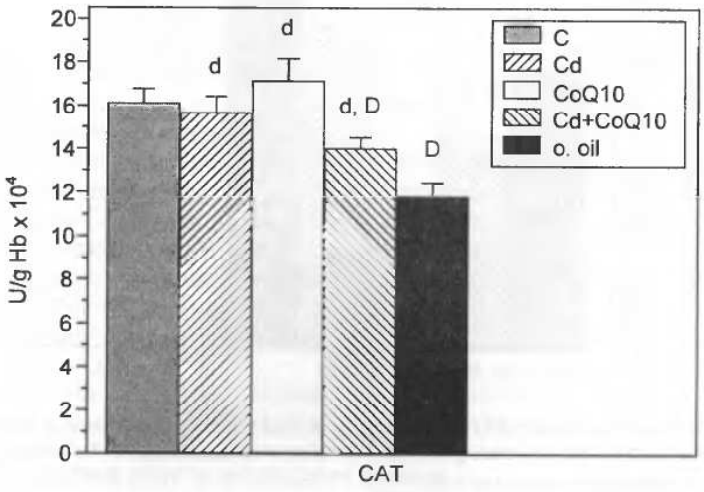

Fig. 2. Catalase (CAT) activity expressed in U/g Hb in RBC of animals. The same experimental groups as in Fig. 1. The values are means ± SE from seven animals in each group. The results were compared in respect to the control animals (C), as well as to the animals treated with olive oil (o. oil). Significance from C: $^{D}P < 0.005$. Significance from o. oil: $^{d}P < 0.005$

the control rats, CAT activity was significantly decreased in animals concomitantly treated with Cd + CoQ_{10} and in animals treated with olive oil (D: $P < 0.005$). In relation to the animals treated with olive oil, CAT activity was significantly increased in all experimental groups of animals: those treated with Cd, CoQ_{10} and those treated concomitantly with Cd + CoQ_{10} (d: $P < 0.005$).

The GSH-Px activity in RBC of rats is depicted in Fig. 3 with respect to the control animals GSH-Px activity was significantly decreased in animals treated with CoQ_{10} and olive oil (A: $P < 0.05$). On

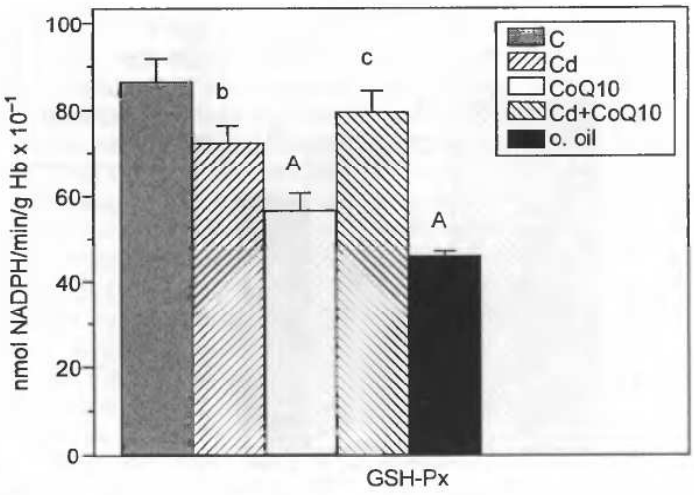

Fig. 3. The activity of glutathione peroxidase (GSH-Px) expressed in nmol NADPH/(min × g Hb) in RBC of animals. The same experimental groups as in preceeding Figs. The values are means ± SE from seven animals in each group. The results were compared in respect to the control animals (C), as well as to the animals treated with olive oil (o. oil). Significance from C: $^{A}P < 0.05$. Significance from o. oil: $^{b}P < 0.02$; $^{c}P < 0.01$

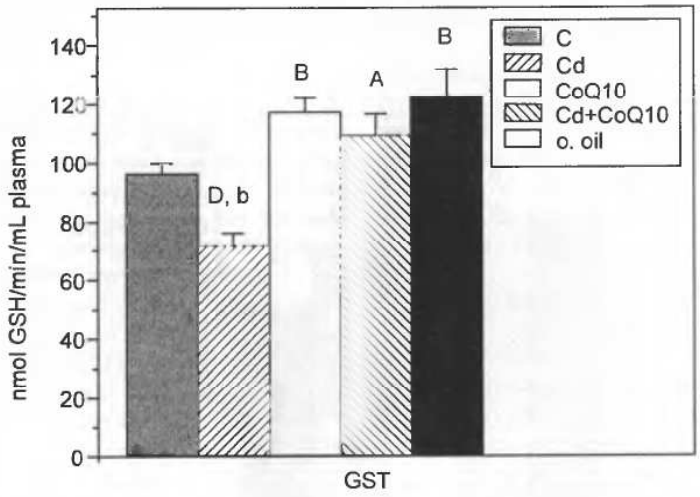

Fig. 4. Plasma glutathione-S-transferase (GST) activity expressed in nmol GSH/(min × ml plasma). The same experimental groups as in preceeding Figs. The values are means ± SE from seven animals in each group. The results were compared in respect to the control animals (C), as well as to the animals treated with olive oil (o. oil). Significance from C: $^{A}P < 0.05$; $^{B}P < 0.02$; $^{D}P < 0.005$. Significance from o. oil: $^{b}P < 0.02$

the other hand RBC GSH-Px activity was significantly increased in animals treated with Cd (b: $P < 0.02$) and concomitantly treated with Cd + CoQ_{10} (c: $P < 0.01$) in comparison to the rats treated with olive oil.

The activity of GST in the plasma was presented in Fig. 4 with respect to the controls the plasma GST activity was significantly decreased in rats treated with Cd (D: $P < 0.005$) and significantly increased in animals treated with CoQ_{10} (B: $P < 0.02$), concomitantly treated with Cd + CoQ_{10} (A: $P < 0.05$) and treated with olive oil (B: $P < 0.02$). The activity of plasma GST was significantly decreased only in animals treated with Cd (b: $P < 0.02$) in relation to the rats treated with olive oil.

DISCUSSION

During the evolution mammalian cells have developed protective mechanisms to minimize injurious events that result from normal oxidative products of cellular metabolism and toxic chemicals. The antioxidant defence system is species- and organ-specific (Petrović, Saičić, Spasić, Radojičić & Buzadžić, 1991). The extent of the oxidant damage to the erythrocytes could be used as a suitable biomarker for the estimation of general oxidant damage in the organisms (Saičić, Simović, Korać, Blagojević, Buzadžić, Spasić & Petrović, 1993).

Many authors have reported that Cd administered alone leads to an increased production of superoxide anion radicals in RBC of rats (Singhal, Anderson & Meister, 1987; Kostić *et al.*, 1993). It is reasonable to expect an increased activity of CuZn SOD in RBC of Cd treated animals as a biological response. However, in our experiments perorally administered Cd was combined with i.m. injections of olive oil every fifth day. As a consequence, the activity of CuZn SOD in RBC of animals was not changed in comparison to the control value. We propose that olive oil administered together with Cd diminished the toxic effects provoked by Cd when it was administered alone. Namely, olive oil contains many antioxidants, such as vitamin E, coenzyme Q and polyphenols, which have many beneficial effects against oxidative injuries caused by various toxicants (Quiles, Ramirez-Tortosa, Huertas, Ibanez, Gomez, Battino & Mataix, 1999). At the same time, in animals treated with olive oil the activity of CuZn SOD was even significantly lowered in comparison to the controls. Consequently, when compared to the animals treated with olive oil, the activity of this enzyme was significantly increased in animals treated with Cd and Cd + CoQ_{10}.

Superoxide dimutase has a function to eliminate the toxic superoxide anion radicals forming hydrogen peroxide (H_2O_2) which represents a substrate for CAT and GSH-Px (McCord & Fridovich, 1969). It is well known that the activity of CAT is directly proportional to the substrate level assumed to be produced by SOD (Aebi, 1974). This could be an explanation for the unchanged activity of CAT in RBC of Cd-treated animals in relation to the control value. On the other hand, CAT activity was significantly decreased in RBC of animals concomitantly treated with Cd + CoQ_{10}, as well as in animals treated with olive oil. Decreased activity of CAT in RBC of Cd + CoQ_{10} treated animals was accompanied by an unchanged activity of GSH-Px in relation to the controls. GSH-Px destroys H_2O_2 in erythrocytes more efficiently than CAT. Decreased acitvity of CAT in RBC of rats treated with olive oil is accompanied by decreased activity of SOD and smaller production of H_2O_2.

The main antioxidant function of CoQ_{10} is to prevent the formation of lipid peroxyl radicals ($LOO^{\cdot}$) and to prevent both initiation and propagation of lipid peroxidation (Ernster & Dallner, 1995). At the same time, GSH-Px has a crucial role in detoxification of H_2O_2 and organic hydroperoxides (Halliwell & Gutteridge, 1999). By quenching organic oxygen-derived free radicals, CoQ_{10} protects GSH-Px and activity of this enzyme molecule in RBC of rats treated with CoQ_{10} was significantly decreased with respect to the control value. A decreased activity of GSH-Px was also obtained in RBC of rats treated with olive oil. Earlier investigations have shown that olive oil contains polyphenolic antioxidants such as (3,4-dihydroxyphenyl)-ethanol and (p-hydroxyphenyl)-ethanol which by quenching free oxygen radicals may lower risk of reactive oxygen species-mediated injuries (Manna, Galletti, Cucciolla, Moltedo, Leone & Zappia, 1997). Our earlier investigations have shown that other antioxidants such as selenium significantly increased activity of GSH-Px in tissues of rats (Žikić, Štajn, Ognjanović, Saičić, Kostić, Pavlović & Petrović, 1998) and thus protected tissues from Cd toxicity. Obviously, this mechanism of protection is different from the mechanism by which CoQ_{10} protects tissues from oxidative damage, because Se is the constituent of the active site of GSH-Px (Stadtman, 1980).

The results of our investigations show that Cd induced a significant decrease of GST activity in the plasma of rats. Similar results were obtained in livers of rats treated by carbon tetrachloride (Takahashi, Sugimoto, Takahata, Okamoto & Kishi, 1996). After the treatment of rats with CoQ_{10} the activity of GST was significantly elevated in respect to the controls as well as to the rats treated with Cd. Same authors (Takahashi *et al.*, 1996) were also found that CoQ_{10} elevates the activity of GST and thus improve defence against oxidant injuries caused by carbon tetrachloride. Various antioxidants contained in olive oil also influence the elevation of GST activity in the plasma of rats.

CONCLUSIONS

From the presented results it may be concluded that Cd administered with olive oil did not exhibit toxic effects on CuZn SOD, CAT and GSH-Px activities in RBC as well as GST activity in the

plasma of rats. At the same time, CoQ_{10} by quenching the free oxygen radicals and by inhibiting the lipid peroxidation may improve the antioxidant defence enzyme activities in the blood of rats. Our investigations also show that olive oil exhibits some protective effects on CuZn SOD, CAT and GSH-Px activities in RBC and GST activity in the plasma of rats treated with Cd.

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