

SOME HEMATOLOGICAL VALUES AND TRANSAMINASE ACTIVITIES IN THE PLASMA OF RATS TREATED WITH CADMIUM AND COENZYME Q₁₀

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ABSTRACT. In our experiments the red blood cells (RBC) count, hematocrite value (Ht), hemoglobin (Hb) and glucose concentrations in the blood, as well as, the plasma cholesterol concentration and activities of aspartat aminotransaminase (AST) and alanin aminotransaminase (ALT) of male *Wistar albino* rats were determined. Besides the controls (C), experimental animals were treated with: cadmium (Cd, 17 mg/day/kg body mass in drinking water + 100 µL olive oil, i.m., every fifth day), coenzyme Q₁₀ (CoQ₁₀, 16 mg/kg, dissolved in olive oil, i.m., every fifth day), concomitantly treated with Cd and CoQ₁₀ (Cd+CoQ₁₀, 17 mg Cd/day kg body mass in drinking water + 16 mg/kg CoQ₁₀, dissolved in olive oil, i.m., every fifth day) and olive oil (o. oil, 100 µL, i.m., every fifth day) during 30 days.

The obtained results show that Cd induces a significant decrease of RBC count, Hb and cholesterol concentrations and Ht value. At the same time Cd induces a statistically significant increase of plasma transaminase activities. In animals treated with CoQ₁₀ statistically significant decrease of glucose concentration was observed. In rats concomitantly exposed to Cd+CoQ₁₀ we found a significant decrease of RBC count and glucose concentration, while in the same group of animals plasma AST and ALT activities were significantly increased. In the same group of animals Hb concentration was normalized in respect to the rats treated only with Cd.

INTRODUCTION

It is well known that cadmium (Cd) produces many deleterious effects in various tissues of humans and different species of laboratory animals [1]. Major routes of Cd intake into the organism are respiratory and gastrointestinal tract [2,3]. After being taken into the organism, cadmium penetrate in the blood and bound to the serum albumines and erythrocyte membranes [4]. In the blood and tissues Cd stimulates formation of metallothioneins which represent the complexes of Cd and low-molecular mass proteins [5]. Cadmium exerts its toxic effects only if it is present as a free or non-protein bound [6]. Recent studies on mammals have shown that Cd stimulates formation of reactive oxygen species, such as superoxide anion radical [7], hydrogen peroxide [8] and hydroxyl radical [9]. As a consequence, enhanced lipid peroxidation, DNA damage, altered calcium and sulfhydryl homeostasis, as well as marked disturbances of antioxidant

defence system occur [10]. Cadmium disturbs many metabolic processes, especially energy metabolism [11], membrane transport [12] and protein synthesis [13]. Marked alterations of carbohydrate, protein and fat metabolism were observed in cadmium exposed animals [14]. Cadmium also induces onset of anemia [15], decreased hemoglobin (Hb) concentration, decreased hematocrite (Ht) value, as well as decreased blood iron level [15]. Treatment with Cd induces hyperglycemia [16] and increased plasma transaminase activities [17].

Cadmium accumulates mostly in the liver and kidneys and other tissues and organs, such as the heart and testes causing many metabolic and histological changes [1,18,19], nephrotoxicity [20], cardiotoxicity [21,22], increased lipid peroxidation, hemorrhagic lesions of seminal tubules [23] and decreased growth of the body mass of laboratory animals [24].

Elimination of cadmium from the organism is mostly linked to the intestinal mucosa, while elimination by the kidneys is very small in healthy kidneys [25].

Coenzyme Q (CoQ) is present in almost all living organisms and it is the constituent of most biomembranes [26] and the component of mitochondrial respiratory chain [27]. CoQ also exhibits antioxidant properties and the first reports of antioxidant capability of CoQ [28] demonstrate the superior antioxidant capacity of reduced form of CoQ (CoQH₂) over the oxidized form. Coenzyme Q has many protective effects in organism. The loss of the respiratory capability with age has been shown to be partially reversed by CoQ treatment [29]. Oxidative damage resulting from carbon tetrachloride administration is decreased by CoQ [30], as well as the damage of liver caused by endotoxin administration [31]. The administration of CoQ inhibits lipid peroxidation induced by carbon tetrachloride and ethanol as shown using urinary malondialdehyde as an assay for free radical damage *in vivo* [32]. Coenzyme Q has a large number of clinical applications, especially in the treatment of congestive heart failure [32] and certain neurologic disorders, such as Kearns-Sayre syndrom (mitochondrial encephalopathy) [33]. It is well known that CoQ may react with lipid free radicals or lipid peroxide radicals and thus prevent propagation reaction of lipid peroxidation [34]. Another mechanism is that superoxide dismutase interacts with hydroquinones and together with the two electron quinone reductase (DT-diaphorase), inhibits autooxidation of hydroquinones [35]. Lipid peroxide radicals may react with vitamin E (Vit. E) to produce Vit. E radical and the antioxidant reduced form of Vit E would then be regenerated by CoQH₂ [36]. Depending on number of isoprenoid side units, in living organisms there are CoQ molecules named from Q₀ to Q₁₀. In the blood and tissues of rats both CoQ₉ and CoQ₁₀ were discovered, while in humans exists only CoQ₁₀ [34].

We examined the red blood cells (RBC) count, hematocrite value (Ht), hemoglobin (Hb), glucose and cholesterol concentrations, as well as the activities of plasma aspartat aminotransaminase (AST) and alanin aminotransaminase (ALT) in rats chronically exposed to cadmium and Coenzyme Q₁₀.

MATERIAL AND METHODS

Male *Wistar albino* rats 60 days old, weighing 190 ± 20 g were used. The animals were housed in individual cages at $21 \pm 1^\circ\text{C}$ and exposed to 12hr light - 12 hr dark cycle and were fed chow pellets (Veterinarski Zavod, Zemun, Yugoslavia) and drank water *ad libitum*. The animals were divided into five 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 CdCl₂ x 5H₂O in drinking water+100 μL of olive oil, i.m., every fifth day). Third group was treated with Coenzyme Q₁₀ (CoQ₁₀, 20 mg CoQ₁₀ dissolved in olive oil, i.m., every fifth day, drinking tap water). Fourth group was treated with cadmium and CoQ₁₀ (Cd+CoQ₁₀, 200 mg CdCl₂ x 5H₂O in drinking water+20 mg CoQ₁₀, 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 Cd was 17 mg/day kg body mass, and CoQ₁₀ 16 mg/kg body mass every fifth day. Every experimental group consisted of 7 animals. All animals were sacrificed by decapitation always between 8 and 10 A.M.

Fresh blood was immediately collected using heparin (1000 U/mL) as anticoagulant. Blood samples for the counting of RBC, as well as for the determination of Hb concentration and Ht value were taken immediately after exsanguination of animals (e.g. without heparin). Aliquots of blood for the determination of cholesterol concentration and plasma transaminase activities were taken immediately after sacrificing and then centrifuged for separation of the plasma and red blood cells. RBC count and Ht value were determined by the standard hematological techniques [37]. Hb concentration was determined by cyanmethemoglobin method [38]. The concentration of glucose in the blood was measured by Hultman colorimetric method [39],

while the plasma cholesterol concentration was examined spectrophotometrically by the method of Watson [40] and Richterich and Lauber [41] using test reagents for cholesterol ("Serbolab", Kragujevac). The activities of plasma AST and ALT were measured spectrophotometrically using test reagents ("Serbolab", Kragujevac) [42].

Statistical analysis of the results was based on the Student's *t* test considering the significance at a level of $p < 0.05$.

RESULTS AND DISCUSSION

The obtained results show (Table 1) that RBC count in cadmium treated animals was significantly decreased in comparison to the controls ($p < 0.02$). At the same time, cotreatment with Cd+CoQ₁₀ also induced a significant decrease of RBC count ($p < 0.01$). It is well known that anemia is one of the most sensitive parameters of Cd toxicity [43]. Recent data show that Cd may cause anemia in rats by accelerating red cell sequestration presumably in the spleen [44]. Some other authors have shown, using the methods of electronic microscopy, marked destructions of RBC membrane skeleton after the Cd treatment [45]. In Cd treated rats iron deficiency also contributes to the development of anemia [15]. Littarru and coworkers have shown that previous enrichment of erythrocyte membranes with CoQ₁₀ significantly increased the resistance of these membranes from hemolysis induced by free-radicals generating agents [46]. Same authors have shown that CoQ₁₀ was not effective in preventing metal-catalyzed oxidation of the erythrocyte membrane enzymes, and this effect is likely to be due to lack of interaction of CoQ₁₀ with the metal target. However, in our experiments CoQ₁₀ did not diminish the negative effects of cadmium on onset of anemia. In animals exposed to cadmium a significant decrease of Hb concentration (Table 1), ($p < 0.005$) was observed. These data support the fact that Cd treatment induced anemia in the rats as a consequence of destruction of RBC [15]. In rats exposed concomitantly to Cd+CoQ₁₀ the concentration of Hb was normalized in respect to the rats treated only with cadmium. We also found a significant decrease of Ht value in Cd treated rats (Table 1), ($p < 0.005$). This result are in accordance with a significant decrease of RBC count in the blood.

Table 1. Red blood cells (RBC) count ($\times 10^{12}/L$ blood), hemoglobin (Hb) concentration (mmol/L blood) and hematocrite (Ht) value (L/L blood) in control animals (C), treated with cadmium (Cd), with coenzyme Q₁₀ (CoQ₁₀), treated concomitantly with Cd and CoQ₁₀ (Cd+CoQ₁₀) and animals treated with olive oil (o. oil).

	RBC ($\times 10^{12}/L$)	Hb (mmol/L)	Ht (L/L)
C	7.18 ± 0.33	7.54 ± 0.11	0.43 ± 0.049
Cd	5.94 ± 0.14^B	6.05 ± 0.36^D	0.33 ± 0.130^D
CoQ ₁₀	8.20 ± 0.33	7.76 ± 0.16	0.44 ± 0.047
Cd+CoQ ₁₀	6.03 ± 0.06^C	7.45 ± 0.08	0.42 ± 0.064
o. oil	7.89 ± 0.42	7.67 ± 0.10	0.45 ± 0.055

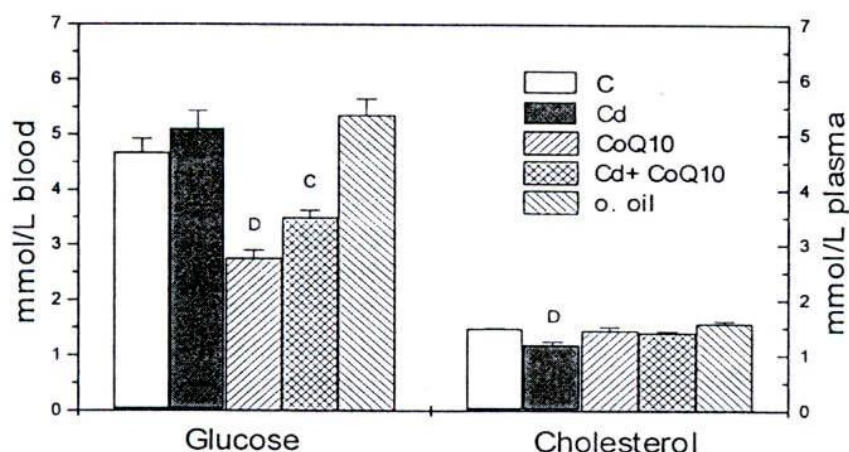
The values are means \pm SE from 7 animals.

Significantly different from controls (C): ^B $p < 0.02$; ^C $p < 0.01$; ^D $p < 0.005$.

Previous investigations of some authors showed that Cd influences the metabolism of carbohydrates causing hyperglycemia [47]. The stress caused by cadmium increases glucose concentration in the blood because of intensive glycogenolysis on one hand, and because of glucose synthesis from the tissue extrahepatic proteins and amino acids on the other [48]. Our result shows (Figure 1) that Cd caused increased blood glucose concentration, but this increase was not statistically significant. Other authors have shown that long-term exposure to cadmium of some species, such as fishes did not influenced, or even lowered plasma

glucose concentration [49]. In our experiments treatment with CoQ₁₀ and with Cd+CoQ₁₀ as well, (Figure 1) induces a significant decrease of blood glucose concentration in rats ($p<0.005$ and $p<0.01$, respectively) in comparison to control animals. It is well known that CoQ₁₀ affect the metabolism of carbohydrates in organism, such as the processes of glucose exchange between plasma and erythrocytes, and this could be explanation for the hypoglycemic effects of CoQ₁₀ [50].

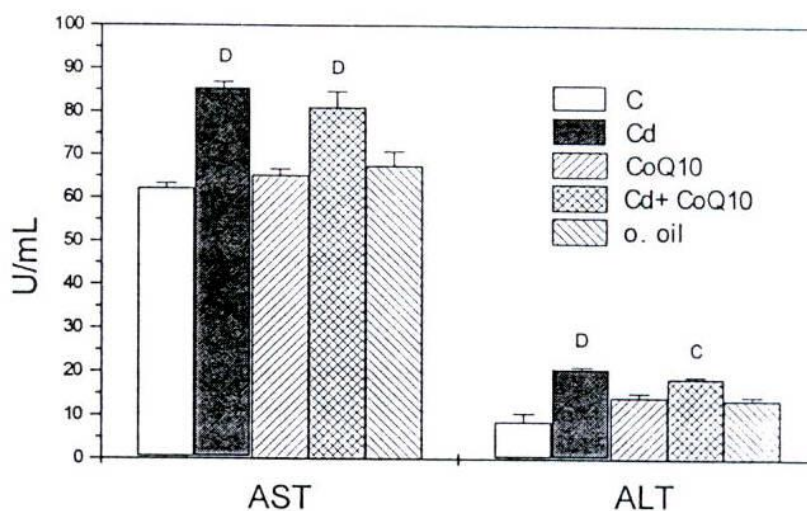
Figure 1. Blood glucose (mmol/L blood) and plasma cholesterol concentrations (mmol/L plasma) in control animals (C), treated with cadmium (Cd), with coenzyme Q₁₀ (CoQ₁₀), treated concomitantly with Cd and CoQ₁₀ (Cd+CoQ₁₀) and animals treated with olive oil (o. oil).



The values are means \pm SE from 7 animals.
Significantly different from controls (C): ^C $p<0.01$; ^D $p<0.005$.

Acute exposure to Cd in rats induced a statistically significant decrease of total, non-bound, as well as, HDL-cholesterol in the serum [51]. Similar results were obtained on *Macacrus rhesus* monkeys in the long-term experiments [52]. Our results are in accordance with the results of other authors showing a significant decrease of plasma cholesterol concentration in rats treated with cadmium ($p<0.005$) in the respect to the controls. Experiments on humans have shown that CoQ₁₀ induces a significant decrease of cholesterol concentration and that CoQ₁₀ is a potent agent in prevention of essential hypertension [53]. We didn't observe any changes in plasma cholesterol concentration in animals treated with CoQ₁₀, as well as, in animals treated with Cd+CoQ₁₀. Lin and Boylau have shown that higher levels of Vit E in the plasma may elevate the cholesterol concentration [54].

Figure 2. The activities of plasma aspartat aminotransaminase (AST) and alanin aminotransaminase (ALT) expressed in U/mL in control animals (C), treated with cadmium (Cd), with coenzyme Q₁₀ (CoQ₁₀), treated concomitantly with Cd and CoQ₁₀ (Cd+CoQ₁₀) and animals treated with olive oil (o. oil).



The values are means \pm SE from 7 animals.
Significantly different from controls (C): ^C $p < 0.01$; ^D $p < 0.005$.

In Figure 2 our results show that cadmium significantly enhances the activity of AST and ALT in the plasma of rats ($p < 0.005$) in comparison to the control rats. This is in accordance with the results of other investigators [55,56,57]. Under the influence of Cd the damage of liver, kidneys, heart and other organs may be associated with concomitant liberation of transaminases into the plasma. Similar results were obtained by other researchers using Cd as a toxicant [14,47]. In rats chronically cotreated with Cd+CoQ₁₀, a significant increase of plasma AST and ALT activities were also observed (Figure 2), ($p < 0.005$ and $p < 0.01$, respectively). Coenzyme Q₁₀ in the dosage administered did not diminish the toxic effects of cadmium on the activities of AST and ALT in the plasma.

CONCLUSIONS

Cadmium given through drinking water (17 mg/day/kg body mass) in the course of 30 days causes onset of anemia as a result of increased RBC destruction in the spleen. We also found the decreased concentration of Hb and Ht value. In Cd+CoQ₁₀ cotreated rats (17 mg Cd/day kg body mass in drinking water + 16 mg/kg CoQ₁₀, dissolved in olive oil, i.m., every fifth day) CoQ₁₀ did not diminish the toxic effects of Cd on the RBC count, but normalized the Hb concentration in respect to the animals treated only with cadmium.

Glucose concentration was significantly decreased under the influence of exogenous CoQ₁₀ (16 mg/kg CoQ₁₀, dissolved in olive oil, i.m., every fifth day) which acts as a potent hypoglycemic agent.

Cadmium induced a significant decline of cholesterol concentration, while CoQ₁₀ in our experiments did not influence the concentration of plasma cholesterol.

The plasma AST and ALT activities were significantly increased in rats treated with Cd and in rats treated concomitantly with Cd+CoQ₁₀ which indicate a marked tissue damage. At the same time CoQ₁₀ in the dosage administered did not diminish the toxic effects of Cd on the AST and ALT activities in the plasma.

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