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Research Article
Renal Protective Effects of Coenzyme Q10 Against Chromate Induced Nephrotoxicity in Rats

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Abstract

Background and Objective: Exposure to human carcinogens as hexavalent chromate compounds is unavoidable. Chromate induces nephrotoxicity mainly due to increased cellular oxidative stress. The current study evaluates the renoprotective effects of coenzyme Q10 (CoQ10) in potassium dichromate (Chromate) induced nephrotoxicity in rats. **Materials and Methods:** Animals were divided to 3 groups, normal control group was fed distilled water, positive control group was treated by 12 mg kg^{-1} chromate once per week for 6 weeks. The third group was treated daily by CoQ10 (10 mg kg^{-1}) for 6 weeks and 12 mg kg^{-1} chromate once per week for 6 weeks. At the end, blood pressure (BP) and heart rate (HR) were measured. Kidney function tests, lipid profile, oxidative stress and inflammatory bio-markers were determined. **Results:** Chromate resulted in hypertension, worsens kidney function tests, oxidative stress and inflammatory bio-markers. The use of CoQ10 ameliorated these harmful effects. This could be attributed to its antioxidant and anti-inflammatory activity. **Conclusion:** The present results suggest that CoQ10 has a promising potential in the protection against chromate-induced nephrotoxicity.

Key words: Chromate, nephrotoxicity, CoQ10, oxidative stress

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Potassium dichromate, K2Cr2O7, a Cr (VI) compound, is the most toxic form of Cr (VI) and has been demonstrated to induce nephrotoxicity associated with oxidative stress in humans and animals. Chromium is considered as harmful human carcinogen, however exposure to it is unavoidable in developing countries. Exposure occurs in manufacturing industries as in chrome plating, pigment production, leather tanning, welding, painting[1,2]. In addition to, contaminated drinking water and food or in some drugs for weight loss[1-3]. Many previous studies have reported cardiovascular disorders, oxidative stress and several types of cancers in people who exposed to chromates[4-8]. Nephrotoxicity is a major adverse effect of chromium poisoning due to chromium excretion through the kidney, this increases its chromium content and subsequently nephropathy occurs. The toxic manifestations of chromium are considered to be due to oxidative stress leading to serious damage to the vital organs[9]. Potassium dichromate is used in the present study to induce oxidative kidney damage in rats which mimics the occupational hazard.

Chelating agents as calcium disodium ethylenediaminetetraacetic acid (Ca-EDTA) and 2,3-dimercaprol are used for treatment of heavy metal poisoning. Although, chelation may result in severe side effects[10]. The use of antioxidants or medicinal herpes have been suggested as a potential better option[11-13]. The CoQ10 is the only lipid soluble naturally-occurring, vitamin-like antioxidant that is synthesized endogenously. It is involved in the Electron Transport Chain (ETC) which is essential for aerobic respiration. CoQ10 was reported to decrease the generation of reactive oxygen species and increase the cellular antioxidant capacity[14]. Fish, meat, certain oils and nuts are rich in CoQ10[15]. CoQ10 is used as a cotherapy in cancer, cardiovascular diseases, diabetes and muscular neurodegenerative disorders[16]. Previous studies showed different effects of CoQ10 on kidney function tests indifferent animal models[17-20]. However, its effect on chromate induced nephrotoxicity has not been investigated yet. So, the present study was designed to evaluate the renal protective effects of coenzyme Q10 (CoQ10) against chromate induced nephrotoxicity in rats.

MATERIALS AND METHODS

Chemical reagents: Potassium chromate was obtained from Sigma-Aldrich company. The CoQ10 powder was a generous gift from Mepaco (Egypt). All other chemicals and kits used were of analytical grade. Kits were purchased from Bio-diagnostic, Egypt.

Animals: Adult female Wistar rats (180-200 g) obtained from National Scientific Research Center (Giza, Egypt). Rats were housed under controlled temperature (25±2°C) and constant light cycle (12 h light/dark) and allowed free access to a standard rodent chow diet and water *ad libitum*. The investigation complies with the Guide for Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 2011).

Experimental design: Animals were divided into 3 groups. First, normal (control) group received 2% Tween 80 once daily for 6 weeks. Second, positive control group received chromate (12 mg kg^{-1} IP) once per week for 6 weeks. Third group received CoQ10 (10 mg kg^{-1}) in addition to chromate for 6 weeks. Doses were selected according to previous studies[21,22].

Tissue collection: At the end of the experiment, blood pressure and heart rate were measured. After scarification under light ether anesthesia, blood and kidneys were collected. Blood was allowed to stand for 30 min, then centrifuged at 1000 rpm for 15 min to separate serum and stored at -80°C. Kidneys were harvested and kept at -80°C for measurements of biochemical parameters.

Hemodynamic parameters measurement: Heart rate and blood pressure were measured by CODA™ monitor (Kent Scientific, Torrington, CT, USA). Rats were restrained on a heated platform. A volume pressure recording cuff was placed close to the tail. Systolic and diastolic blood pressures and heart rate were recorded according to Kurtz *et al.*[23].

Lipid profile: Total cholesterol, triglycerides (TG) and high density lipoprotein (HDL) were quantified in serum using commercial kits. Low density lipoprotein (LDL) level in serum was calculated using Friedewald equation:

$$LDL = TC\left(HDL - c + \frac{TG}{5}\right)$$

as mentioned previously in Elhemely *et al.*[24].

Kidney function tests: Blood urea nitrogen (BUN), creatinine and albumin were determined in serum according to methods described previously[25,26].

Oxidative stress and inflammatory bio-markers: The GSH content was determined spectrophotometery in kidney at 405 nm using Ellman's reagent according to method described before by Beutler *et al.*[27]. The MDA in the kidney was determined at 534 nm according to method of Satoh [28]. Nitric oxide (NO) was determined at 450 nm using Griess reagent by reduction of nitrate to nitrite using vanadium trichloride[29]. Kidney Tumor necrosis factor-alpha (TNF-α) level was measured using rat ELISA kit (BD Biosciences, San Diego, USA) according to Petrovas *et al.*[30].

Statistical analysis: Data were presented as mean±SD. Analysis was done using one-way ANOVA followed by Tukey-Kramer multiple comparison test. The SPSS software, version 16 was used for all the statistical tests. The level of significance was fixed[31] at $p<0.05$.

RESULTS

MAP and HR: Chromate resulted in hypertension and tachycardia. Treatment with CoQ10 resulted in a significant decrease in systolic (143±2.5 vs. 160±1.9) and diastolic pressure (116±1.8 vs. 125±2.1) by 10.6 and 7.2% as compared to the toxic control group (Table 1).

Lipid profile: Chromate resulted in hypocholesteremia manifested by significant increase in TG (100.3±0.5 vs. 58.9±0.5), LDL (107.4±0.9 vs. 90.2±1.5), Chlo (150.1±0.4 vs. 122.3±0.4) and significant decrease in HDL as compared to normal control group (40.1±0.7 vs. 60.3±0.4). Treatment with CoQ10 resulted in a significant decrease in TG (80.6±0.6 vs. 100.3±0.5), LDL (92.7±1.1 vs. 107.4±0.9), Chlo (135.5±0.5 vs. 150.1±0.4) by 19.6, 13.7 and 9.7% and significant increase in HDL (80.1±0.4 vs. 40.1±0.7) by 99.8% as compared to the toxic control group (Table 2).

Kidney function tests: Chromate resulted in a significant increase in BUN (13.7±0.5 vs. 12.1±0.5) and serum creatinine (1.3±0.9 vs. 0.9±1.5). CoQ10 treatment resulted in a significant decrease in BUN (11.8±0.6 vs. 13.7±0.5) by 13.9% and serum creatinine (0.75±1.1 vs. 1.3±0.9) by 42.3% (Table 3).

Oxidative stress and inflammatory bio-markers: Chromate resulted in a state of oxidative stress as shown by a significant decrease in serum NO (20.1±0.5 vs. 25.3±0.5) and kidney GSH (16.2±0.7 vs. 25.1±0.4), a significant increase in kidney TNF α (2.5±0.9 vs. 1.85±1.5) and MDA (14.3±0.4 vs. 11.4±0.4). The CoQ10 treatment resulted in a significant increase in NO (35.4±0.6 vs. 20.1±0.5), GSH (33.4±0.4 vs. 16.2±0.7) by 76.1 and 106.2% and significant decrease in TNF α (2.1±1.1 vs. 2.5±0.9) and MDA (10.1±0.5 vs. 14.3±0.4) by 16 and 29.4% (Table 4).

Table 1: Effects of 6 weeks treatment with CoQ10 on hemodynamic parameters in chromate-induced toxicity in female rats

	Treatments		
Parameters	CN	Chromate	CoQ10
Systolic BP (mm Hg)	140±0.7	160±1.9[a]	143±2.5[b]
Diastolic BP (mm Hg)	118±0.8	125±2.1	116±1.8[b]
Heart rate (bpm)	375±0.6	400±1.7[a]	395±2.2[a]

Values are the Means±SD from ten animals in each group, [a]p<0.05 vs. normal control group, [b]p<0.05 vs. positive control group

Table 2: Effects of 6 weeks treatment with CoQ10 on lipid profile in chromate-induced toxicity in female rats

	Treatments		
Parameters	CN	Chromate	CoQ10
TG (mg dL^{-1})	58.9±0.5	100.3±0.5[a]	80.6±0.6[a,b]
LDL (mg dL^{-1})	90.2±1.5	107.4±0.9[a]	92.7±1.1[a,b]
HDL (mg dL^{-1})	60.3±0.4	40.1±0.7[a]	80.1±0.4[a,b]
Chlo (mg dL^{-1})	122.3±0.4	150.1±0.4[a]	135.5±0.5[a,b]

Values are the Means±SD from ten animals in each group, [a]p<0.05 vs. normal control group, [b]p<0.05 vs. positive control group

Table 3: Effects of 6 weeks treatment with CoQ10 on kidney function tests in chromate-induced toxicity in female rats

	Treatments		
Parameters	CN	Chromate	CoQ10
BUN (mg dL^{-1})	12.10±0.5	13.70±0.5[a]	11.80±0.6[a,b]
Cr (mg dL^{-1})	0.90±1.5	1.30±0.9[a]	0.75±1.1[a,b]
Albumin (mg dL^{-1})	0.41±0.4	0.47±0.7	0.40±0.4

Values are the Means±SD from ten animals in each group, [a]p<0.05 vs. normal control group, [b]p<0.05 vs. positive control group

Table 4: Effects of 6 weeks treatment with CoQ10 on oxidative stress parameters in chromate-induced toxicity in female rats

	Treatments		
Parameters	CN	Chromate	CoQ10
NO (μmol μL^{-1})	25.30±0.5	20.1±0.5[a]	35.4±0.6[a,b]
TNFα (μg mL^{-1})	1.85±1.5	2.5±0.9[a]	2.1±1.1[a,b]
GSH (mg g^{-1} kidney)	25.10±0.4	16.2±0.7[a]	33.4±0.4[a,b]
MDA (mg g^{-1} kidney)	11.40±0.4	14.3±0.4[a]	10.1±0.5[a,b]

Values are the Means±SD from ten animals in each group, [a]p<0.05 vs. normal control group, [b]p<0.05 vs. positive control group

DISCUSSION

Antioxidant status is a potential biomarker to determine the physiological state of a cell, tissue or organ. It has been reported that some toxicants including certain drugs[32,33] and chemicals including potassium dichromate[1], exert their toxic effects by inducing the generation of reactive oxygen species (ROS). Increased production of ROS has been suggested to

induced nephrotoxicity and kidney tissue injury which is mediated inpart by disturbance in the balance of antioxidant defense system[34]. These antioxidant enzymes protect the cell against cytotoxic ROS. In the present study chromate has been shown to generate oxidative kidney damage. Increase of ROS and inhibition of antioxidant enzymes were demonstrated in renal tissues after chromate exposure. Chromate resulted in sate of oxidative stress manifested by GSH and NO depletion, this is involved in the pathogenesis of chromate nephrotoxicity. In addition, chromate increased lipid peroxidation (LPO). Chromate nephrotoxicity may be due to combination of cellular peroxidation, mitochondrial dysfunction, protein synthesis inhibition and damage of DNA[35-37]. In addition apoptosis may be involved in chromate induced nephrotoxicity[38,39]. The present findings are in agreement with these previous studies. Increased oxidative stress and lipid peroxidation, in addition to, antioxidant defenses mediators depletion are implicated in chromate-induced acute renal injury[9].

The present comparative study demonstrated that CoQ10 which are powerful antioxidant significantly enhanced antioxidant defense mechanism and protect against chromate induced alterations in oxidative stress parameters. This can be supported by a marked increase in NO and GSH level associated with lowering of MDA and TNF-α. This is associated with lowered lipid peroxidation which may be due to the decrease oxidative stress. Improved kidney function with CoQ10 treatment was manifested by reductions in serum creatinine and BUN.

Previous studies have reported that CoQ10 has the ability to improve diabetes and blood pressure by multiple mechanisms, including the ability to lower oxidative stress[40,41]. In previous study CoQ10 pretreatment inhibited mitochondrial damage, expression of cytochrome c, cell apoptosis, reduce thiobarbituric acid reactive substances and MDA[42,43].

CONCLUSION

The use of CoQ10 was associated with beneficial effects in protection against chromate induced nephrotoxicities in rats. The appreciable beneficial effects are mediated through its antioxidant and anti-inflammatory capabilities.

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