UDC 577
Original scientific papers

EFFECT OF OLIVE OIL ON ANTIOXIDATIVE DEFENSE COMPONENTS IN LIVER OF CADMIUM INTOXICATED RATS

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Ognjanović I. Branka, Snežana D. Maletić, Sladjan Z. Pavlović, Radoslav V. Žikić, Andraš Š. Štajn, Ratko M. Radojičić and Zorica S. Saičić (2002): *Effect of olive oil on antioxidative defense components in liver of cadmium intoxicated rats.* - Iugoslav. Physiol. Pharmacol. Acta, Vol. 38, No. 3, 101-110, Beograd.

The present study investigated the possible protective role of olive oil on antioxidative defense components in liver of cadmium (Cd) intoxicated animals. Male, *Wistar albino* 3 months old rats were injected with a single dose of: 1) $CdCl_2$ (0.4 mg Cd/kg i.p. and sacrificed after 24^h), 2) olive oil (0.4 ml olive oil/kg b.m., i.m., 48^h before the sacrificing) and 3) olive oil + Cd (in above mentioned amounts). Treatment with Cd increased lipid peroxidation (LP) in blood and activities of alanine and aspartate transaminase (ALT and AST) in plasma. Concentrations of non

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enzymatic components of antioxidative defense system (AOS): vitamin C (Vit C) and vitamin E (Vit E) were significantly decreased in liver tissue of Cd treated rats. Pretreatment with olive oil reversed Cd induced alterations in LP content and transaminases activities, as well as on endogenous antioxidive defense components.

Key words: antioxidative defense components, olive oil, cadmium, liver, rat

INTRODUCTION

Environmental pollutants including a variety of industrial and domestic chemicals, pesticides, fertilizers, heavy metals and ionizing radiation are the major factors responsible for oxidative stress. Intoxication by heavy metals, particularly lead, cadmium, arsenic and mercury constitute serious threats to human health (HU, 2000).

Cadmium (Cd) is a known toxicant in humans and living organisms (SHUKLA and SINGHAL, 1984; STOHS and BAGCHI, 1995). With increasing production and utilization of Cd, not only industrial workers but the general population is also exposed to the toxic effects. Cd produce a various pathological conditions, like hepatic and renal dysfunctions, testicular damage, respiratory and nervous system disorders (STOHS and BAGCHI, 1995). The deleterious effects of Cd have been shown to be due to oxidative damage by enhancing the peroxidation of membrane lipids in different tissues and in erythrocytes (KOSTIĆ *et al.*, 1993a; SARKAR *et al.*, 1997).

To preserve the integrity of biological membranes from detrimental oxidative processes caused by free radicals, both enzymatic and non enzymatic components of antioxidative defense system (AOS) are present in the cell (PAPAS, 1996). Components of AOS can be divided into two main groups: antioxidant defense enzymes (FRIDOVICH, 1978; MATES, 2000) and antioxidant defense components such as glutathione (GSH), (GRIFFITH, 1999), coenzyme Q (CRANE, 2001) and urate (SEVANIAN *et al.*, 1991). Other exogenous antioxidative defense components, such as tocopherols, ascorbate, vitamin A and carotenoids and some metals essential for the function of antioxidant defense enzymes are of dietary origin (PAPAS, 1996).

FARISS (1991) has shown, that the scavengers of free radicals and antioxidants may be used in the protection against Cd toxicity. Some antioxidants, such as vitamin E (Vit E), ascorbic acid (AsA), GSH and selenium (Se) exert protective effects against oxidative damages in different tissues (SHUKLA and CHANDRA, 1989; BEYER, 1994; NIKI *et al.*, 1995). Constituents of some dietary plant products, such as flavonoids and phenolics are powerful antioxidants and may play a protective role in several human pathologies (CROFT, 1998).

Mediterranean food is rich in vegetables, cereals, fruits and oil (mostly olive oil), so that the problem of coronary and cardiovascular diseases and arteriosclerosis are diminished in the population of Mediterranean countries.

On the basis of many literature data, it is established that population of Mediterranean countries which use olive oil in nutrition in comparison to the countries where the sunflower oil is used, suffer from sicknesses caused by reactive oxygen species. Olive oil is composed of polyphenol oxidants and squalen which decrease induced production of free radicals and prevent some diseases (cardiovascular). High content of monounsaturated fatty acids present in olive oil may also protect organism from the appearance of coronary diseases (MANCINI *et al.*, 1995; MANNA *et al.*, 1997). Olive oil contains lipid antioxidants (Vit E and b-carotene) which inhibit the oxidation of lipoproteins of low density and prevent chain reactions of lipid peroxidation (GERBER, 1997).

In this study, a possible protective effect of olive oil pretreatment on cadmium induced oxidative stress and metabolic values, as well as on antioxidative defense components (Vit C and Vit E) in liver tissue in rats was investigated.

MATERIAL AND METHODS

In our experiments 90 days old male *Wistar* rats, weighing 250-280 g kept on 12-h light - dark cycles with controlled temperature (20-22°C) were used. All rats were housed in individual cages and given a standard diet and tap water ad libitum. The animals were injected with: 1) $CdCl_2$ (0.4 mg Cd/kg b.m., i.p., 24^h before the sacrificing), 2) olive oil (0.4 ml/kg b.m., i.m., 48^h before the sacrificing) and 3) olive oil + Cd (in above mentioned amounts). Control animals received the equivalent volume of saline. 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. Blood was collected in heparinized test tubes and prepared for further analysis. Concentration of lipid peroxidation (LP) was assayed as thiobarbituric acid reactive substances (TBARS) in the blood according to OHKAWA *et al.*, (1979). Aliquots of blood for the determination of transaminases were centrifuged to separate plasma and red blood cells. Plasma specimens were used for determination of activities of transaminases (alanin transaminase - ALT and aspartat transaminase - AST) by spectrophotometric method (WOOTTON *et al.*, 1964). All chemicals were SIGMA (St. Louis, MO, USA) products.

The liver tissue was dissected thoroughly washed with ice-cold saline, weighed, minced and homogenized with a Janke and Kunkel IKa-Werk Ultra-Turrax homogenizer at 0-4°C (10% w/v) using 0.25 M sucrose, 1 mM EDTA and 0.05 M Tris-HCl solution, pH 7.4.The homogenates were sonicated and then used to determine the concentrations of vitamin C (Vit C) and vitamin E (vit E). Vit C concentration was determined spectrophotometrically by dinitrophenyl-hydrazine method (OMAYE *et al.*, 1979) and expressed as mg%. Vit E concentration was measured by the method of DESAI (1984) and expressed as μg/g tissues. Protein content was determined by the method of LOWRY *et al.*, 1951 using bovine serum albumin as a reference. Concentration of cadmium (Cd) in the liver

was determined by atomic absorption spectrophotometer using a Perkin-Elmer Model 5000 after digestion with concentrated nitric (17 vol) and perchloric acid (1vol) mixture (SHIRLEY *et al.*, 1949) and expressed as mg Cd /g whole mass.

Data are given as means ± S.D. Statistical analysis of results was based on Student's paired t-test considering the significance at a level of $p < 0.05$ (HOEL 1966).

RESULTS

Results presented in Table 1. show that intraperitoneally administration of Cd induces a significant increase of LP concentration ($p<0.05$). In rats exposed to olive oil concentration of LP was not significantly changed in comparison to controls. In rat pretreated with olive oil before injection of Cd (olive oil + Cd) concentration of LP was significantly decreased in comparison to animals receiving Cd.

Table 1. - Concentration of lipid peroxide (LP) in the blood of controls and experimental groups. The values are means ± S.E from seven animals

Groups	LP (nmol/ml)
Control	1.21 ± 0.04
Cd	2.35 ± 0.09 *
Olive oil	1.17 ± 0.06 #
Olive oil + Cd	1.52 ± 0.05 #

* $p < 0.05$ compared to the corresponding value of control group

# $p < 0.05$ compared to the corresponding value of Cd group

Significant increase ($p<0.05$) of transaminases activity (ALT and AST) in the plasma of Cd exposed rats was shown in our experiments (Table 2). In rats receiving only olive oil and in rats pretreated with olive oil (olive oil + Cd) the activities of ALT and AST in the plasma were similar to control values, but were significantly decreased in comparison to animals which receiving Cd.

Table 2. - Activity of transaminases: alanin amino transaminase (ALT) and aspartat amino transaminase (AST) in the plasma of controls and experimental groups. The values are means ± S.E from seven animals

Groups	ALT (U/L)	AST (U/L)
Control	14.84 ± 0.34	66.31 ± 1.86
Cd	19.91 ± 0.27 *	94.93 ± 1.78*
Olive oil	14.20 ± 0.94	68.34 ± 3.88
Olive oil + Cd	15.02 ± 0.90#	69.83 ± 2.33#

* $p < 0.05$ compared to the corresponding value of control group

# $p < 0.05$ compared to the corresponding value of Cd group

The results of our experiments show that concentrations of Vit C and Vit E in the liver were significantly decreased ($p<0.05$) in Cd treated rats in respect to the controls animals (Table 3). Pretreatment with olive oil reversed concentrations of Vit C and Vit E to the control levels.

Table 3. - Antioxidative defense components: vitamine C (Vit C) and vitamine E (Vit E) in the liver of controls and experimental groups. The values are means ± S.E from seven animals

Groups	Vit C (mg%)	Vit E (μg/g tissues)
Control	28.95 ± 0.46	17.45 ± 0.62
Cd	21.16 ± 1.04*	12.98 ± 0.57*
Olive oil	25.62 ± 1.14#	16.79 ± 0.42#
Olive oil + Cd	26.43 ± 0.74 *	16.48 ± 0.36#

* $p < 0.05$ compared to the corresponding value of control group
# $p < 0.05$ compared to the corresponding value of Cd group

Our results show that Cd caused an increase accumulation of Cd in the liver ($p<0.05$), as well as decrease of protein concentration ($p<0.05$),(Table 4). Concentrations of Cd and protein were significantly increased ($p<0.05$) in the liver of rats pretreatment with olive oil in comparison to both Cd treated rats.

Table 4. - Concentrations of cadmium (Cd) and protein in the liver of controls and experimental groups. The values are means ± S.E from seven animals

Groups	Cd (μg/g)	Protein (mg/ml)
Control	N.D.	15.09 ± 0.14
Cd	8.61 ± 0.08*	10.13 ± 0.41*
Olive oil	N.D.	15.94 ± 0.28#
Olive oil + Cd	4.16 ± 0.14*#	14.85 ± 0.31#

* $p < 0.05$ compared to the corresponding value of control group
# $p < 0.05$ compared to the corresponding value of Cd

DISCUSSION

Cd is a ubiquitous toxic metal that may induce oxidative damage by disturbing the prooxidant-antioxidant balance in tissues. Cd toxicity is associated with increased lipid peroxidation, enzyme inactivation and several specific cell membrane lesions (CASALINO *et al.*, 2000a; STOHS *et al.*, 2000).

Our previous investigations showed that chronic treatment with Cd induced oxidative damage in erythrocytes of rats and goldfish causing destruction of cell membrane and increase lipid peroxidation, as well as alteration of AOS, energy metabolism and the appearance of anemia (KOSTIĆ *et al.*, 1993b; PAVLOVIĆ *et al.*, 2001; ŽIKIĆ *et al.*, 2001).

Treatment with Cd increased LP concentration in the blood suggesting that the Cd induced oxidative stress, while olive oil pretreatment reversed this change to control values (Table 1). Several studies have reported that lipid peroxidation resulting from oxidative damage is the primary mediator of Cd toxicity (SARKAR *et al.*, 1997; SHAIKH *et al.*, 1999; CASALINO *et al.*, 2002b).

Intoxication with Cd was also followed by significantly increased of transaminases activities (ALT and AST) in the plasma (Table 2). These results are in accordance with results obtained in our previous investigations and point to the damage of liver and disturbed carbohydrate and protein metabolism (RAJANNA *et al.*, 1984; SHAIKH *et al.*, 1999). Similar results were obtained in our previous study with rats after chronic treatment with Cd (ŠTAJN *et al.*, 1993).

In our previous research it was also shown, that Cd increased the activity of transaminase enzymes (ALT and AST) in serum of rabbits (PISCATOR and AXELSSON, 1970) and in the plasma of rats (RAJANNA *et al.*, 1984; SHAIKH *et al.*, 1999). These enzymes have an important role in the processes of amino acid and protein metabolism. It is known that ALT and AST enzymes are widely spread in tissues and in normal conditions they show very low activity in serum (plasma). However, in stress condition and also due to the influence of different pollutants when the damages of tissues occur, particularly in liver and heart, causing the liberation of transaminases into circulation, increasing their concentration and activity (HWANG and WANG, 2001). The activities of ALT and AST in rats receiving olive oil and olive oil + Cd were not changed in comparison to controls, whereas they were significantly decreased in comparison to values in rats which received Cd (Table 2). Our results show, that olive oil pretreatment diminished the harmful effects of Cd on the activities of ALT and AST enzyme.

The results of our experiments show that concentrations of Vit C and Vit E in the liver were significantly decreased ($p<0.05$) in Cd treated rats in respect to the controls (Table 3). Oxidative stress induced by acute Cd administration was reduced by olive oil pretreatment.

It is known that increased accumulation of Cd in the liver induces lipid peroxidation and increases the production of malondialdehyde (MDA) which consequently inhibits the enzyme L-gulonolactone oxidase (SHUKLA and CHANDRA, 1989; HUDECOVA and GINTER, 1992) necessary for the synthesis of Vit C. Vitamine C is a potent scavenger of free oxygen radicals and it has been shown that marginal Vit C deficiency results in intracellular oxidative damage in the guinea-pig (HUDECOVA and GINTER, 1992).

Our previous results showed that chronic treatment with Cd induces a decrease of Vit C concentration in the liver (OGNJANOVIĆ *et al.*, 1995) and kidneys (ŠTAJN *et al.*, 1997) of young and adult rats, while Cd increases the concentration of Vit E in rat liver (OGNJANOVIĆ *et al.*, 1995), kidneys (ŠTAJN *et al.*, 1997) and in the plasma (KOSTIĆ *et al.*, 1993b; OGNJANOVIĆ *et al.*, 2000; PAVLOVIĆ *et al.*, 2001).

It has been shown, that pretreatment of laboratory animals with Mn salts and hydroxytyrosol (CASALINO *et al.*, 2002a), Vit E (CHEN and TAPPEL, 1995; SHAIKH *et al.*, 1999; OGNJANOVIĆ *et al.*, 2000), as well as AsA (GUPTA and KAR,

1998) and N-acetylcysteine decreases Cd induced toxicity (SHAIKH *et al.*, 1999). Some antioxidants present in olive oil can exert protective role against Cd induced oxidative damage in liver tissue. (SHAIKH *et al.*, 1999; CASALINO *et al.*, 2002a).

Asa is the major water-soluble and no enzymatic primary preventive antioxidant in the cells and body fluids, scavenges the free radicals produced by Cd and serves as a metabolic marker of Cd toxicity (HUDECOVA and GINTER, 1992; NIKI *et al.*, 1995). In addition, AsA may have an important role in the regeneration of reduced form of Vit E (BEYER, 1994, CHEN and TAPPEL, 1995) and interacts with the tocopheroxyl radical, resulting in the formation of dehydroascorbic acids and ?-tocopherol (BEYER, 1994, SHAIKH *et al.*, 1999). GSH is required for the reduction of dehydroascorbate back to ascorbate (GRIFFITH, 1999). When there is a reduction in the level of GSH, this conversion is affected and hence the AsA concentration is lowered (RANA and VERMA, 1996).

A significantly increased accumulation of Cd in liver tissue was observed in animals treated with Cd, as well as decrease($p<0.05$) of protein concentration (Table 4). Concentration of protein was significantly increased ($p<0.05$) in the liver of rats exposed to olive oil, as well as in rats pretreatment with olive oil compared to Cd group.

Cd intoxication is responsible for alterations in various metabolic processes and the inhibition of protein synthesis (DUDLEY *et al.*, 1984; TANDON *et al.*, 1992). Liver, kidney, lung, testis and heart are the target organs following Cd exposure with the severity of their intoxication dependent on the route, dose, and duration of the exposure (OGNJANOVIĆ *et al.*, 1995; ŠTAJN *et al.*, 1997; CASALINO *et al.*, 2002b).

Our previous data showed that per oral intake of Cd induces great accumulation of Cd in the liver (OGNJANOVI? *et al.*, 1995), kidneys (ŠTAJN *et al.*, 1997) and in the heart (ŽIKIĆ *et al.*, 1998) of rats which is accompanied with marked alterations of enzymatic and no enzymatic components of AOS.

CONCLUSIONS

Our results suggest that the treatment with Cd increased concentration of lipid peroxide (LP) in the blood and activities of transaminase (ALT and AST) in the plasma, suggesting that Cd induced oxidative stress. Cd causes alterations in carbohydrate and protein metabolism and decrease protein concentration, as well as Vit C and Vit E concentrations in the liver. A possible protective role of olive oil pretreatment (and the role of antioxidants present in oil) in the prevention of toxic effects of Cd on the concentration of LP, the activities of transaminases, as well as on endogenous antioxidative defense components was pointed out in this study.

Acknowledgements.- This research was supported by the Ministry of Science and Technology of Serbia, Grant No 1669.

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Recieved July 15, 2004
Accepted September 1, 2004

EFEKAT MASLINOVOG ULJA NA ANTIOKSIDACIONE ZAŠTITNE KOMPONENTE U JETRI PACOVA POSLE INTOKSIKACIJE KADMIJUMOM

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Izvod

U ovom radu ispitivana je moguća zaštitna uloga maslinovog ulja na antioksidacione zaštitne komponente u jetri pacova intoksiciranim kadmijumom (Cd). Mužjaci pacova *Wistar albino*, starosti tri meseca akutno su tretirani sa: 1) CdCl (0.4 mg Cd/kg t.m., i.p., 24[h] pre žrtvovanja), 2) maslinovim uljem (0.4 ml maslinovog ulja/kg t.m., i.m., 48[h] pre žrtvovanja) i 3) maslinovim uljem + Cd (u navedenim količinama). Posle tretmana kadmijumom značajno se povećava koncentracija lipidnih peroksida (LP) u krvi, kao i aktivnost alanin i aspartat transaninaza (ALT i AST) u plazmi. Koncentracije neenzimskih komponenti antioksidacionog zaštitnog sistema (AOS): vitamin C (Vit C) i vitamin E (Vit E) su značajno smanjene u jetri kod pacova tretiranih kadmijumom. Eksperimenti sa pacovima koji su u predtretmanu dobijali maslinovo ulje pokazuju da maslinovo ulje sprečava ili ublažava kadmijumom izazvane promene u koncentraciji LP, aktivnosti, kao i koncentraciji endogenih antioksidacionih zaštitnih komponenti.

Primljeno 15. jula 2004.
Odobreno 1. septembra 2004.