EFFECTS OF CISPLATIN ON LIPID PEROXIDATION AND THE GLUTATHIONE REDOX STATUS IN THE LIVER OF MALE RATS: THE PROTECTIVE ROLE OF SELENIUM

IVANA S. TRBOJEVIĆ[1], BRANKA I. OGNJANOVIĆ[1], NATAŠA Z. ĐORĐEVIĆ[1], SNEŽANA D. MARKOVIĆ[1], A. Š. ŠTAJN[1], JELENA P. GAVRIĆ[2], and ZORICA S. SAIČIĆ[2*]

[1]*Institute of Biology and Ecology, Faculty of Science, University of Kragujevac,* 34000 Kragujevac, Serbia

[2]*Department of Physiology, Siniša Stanković Institute for Biological Research, University of Belgrade,* 11060 Belgrade, Serbia

Abstract –The role of oxidative stress in cisplatin (CP) toxicity and its prevention by pretreatment with selenium (Se) was investigated. Male Wistar albino rats were injected with a single dose of cisplatin (7.5 mg CP/kg b.m., i.p.) and selenium (6 mg Se/kg b.m, as Na_2SeO_3, i.p.) alone or in combination. The results suggest that CP intoxication induces oxidative stress and alters the glutathione redox status: reduced glutathione (GSH), oxidized glutathione (GSSG) and the GSH/GSSG ratio (GSH RI), resulting in increased lipid peroxidation (LPO) in rat liver. The pretreatment with selenium prior to CP treatment showed a protective effect against the toxic influence of CP on peroxidation of the membrane lipids and an altering of the glutathione redox status in the liver of rats. From our results we conclude that selenium functions as a potent antioxidant and suggest that it can control CP-induced hepatotoxicity in rats.

Keywords: Cisplatin, selenium, lipid peroxidation, glutathione redox status, liver, rat.

UDC 612:615.277:59

INTRODUCTION

Oxidative stress is caused by an imbalance between the production of reactive oxygen species (ROS) and a biological system's ability to readily detoxify the reactive intermediates or easily repair the resulting damage. Disturbances in this normal redox state can cause toxic effects through the production of peroxides and free radicals that damage all components of the cell, including proteins, lipids and DNA (Halliwell and Gutteridge, 2007). Oxidative stress (a deleterious imbalance between the production and removal of reactive oxygen/nitrogen species) plays a key role in the pathogenesis of many diseases, including cancer, inflammation, kwashiorkor (predominantly a protein deficiency), seizure, Alzheimer's disease, Parkinson's disease, sickle-cell anemia, liver disease, cystic fibrosis, HIV, AIDS, infection, heart attack, stroke, and diabetes (Matés, 2000).

Cisplatin (cis-diamminedichloroplatinum II, CP) is one of the most effective chemotherapeutic agents and plays a major role in the treatment of a variety of human solid tumors including those of the head, neck, testis, ovary, and breast. However, high-doses administered to patients produce nephrotoxic side effects and the dose of CP must often be limited (Jordan and Carmo-Fonseca, 2000; Yoshida et al., 2000). Hepatotoxicity is not considered as a dose limiting toxicity for CP, but liver toxicity can occur when the aneoplastic drug is administrated at high doses (Zicca et al., 2004; Pratibha et al., 2006). The treatment of tumor cells with CP provokes several responses including membrane peroxidation, dysfunction of mitochondria, inhibition of protein synthesis and DNA damage (Cohen and Lippard, 2001; Sadowitz et al., 2002). Formation of free radicals, leading to oxidative stress, has been shown to be one of the pathogenic mechanisms of these side effects (Jordan and Carmo-Fonseca, 2000).

Recent studies have focused on the role of antoxidants in CP toxicity. Administration of antioxidants such as NAC and GSH (Rybak et al., 1999), vitamin C (Antunes et al., 2000), vitamin E and selenium (Caffrey and Frenkel, 2000; Antunes et al., 2001; Naziroğlu et al., 2004) before treatment with CP has been used to protect against toxicity in human and experimental animals.

Among antioxidant micronutrients, selenium (Se) is an essential dietary trace element which plays an important role in a number of biological processes in humans and many other forms of life. Deficiency of this element induces some pathological conditions such as cancer, coronary heart disease, and liver necrosis (Saito et al., 2003; Agay et al., 2005). Se is an essential component of several enzymes such as glutathione peroxidase (GSH-Px), thioredoxin reductase (TR) and selenoprotein P (SeP), which contains Se as a selenocysteine. It is also well known that Se is essential for cell culture when a serum-free medium is used (Kim and Combs, 1993; Saito et al., 2003). Many experimental studies in animals have demonstrated the ability of Se to prevent carcinogenesis. A recent widely publicized chemo-prevention study has shown that selenium supplements can decrease the incidence of certain types of cancer (Spallhoz, 1994; Conklin, 2000).

The aim of the present study was to investigate a protective effect of Se pretreatment on LPO concentration and the glutathione redox status (GSH, GSSG and GSH RI) in the liver of rats acutely treated with CP.

MATERIAL AND METHODS

Male *Wistar* albino rats (about 3 months old, weighing 250 ± 20 g) were used. The animals were kept at 21±2°C, fed with pellet rat diet and exposed to a 12 h light/12 h dark cycle. The animals were randomly divided into four groups. The first group was used as a control (C). The rats of the experimental groups (2) were injected i.p. with a single dose of 7.5 mg CP/kg body mass in 0.1 ml saline, (3) i.p. with a single dose of 6 mg Se/kg body mass as Na_2SeO_3 in 0.1 ml saline and (4) Se + CP (in the above-mentioned amounts). The animals were treated with Se 1 h prior to treatment with CP. Each group consisted of 6 animals. All chemicals were from Sigma (St. Louis, Mo. U.S.A.).

After the treatment (48 h after injection), all animals were killed by decapitation. Before extraction of the liver, perfusion through the portal vein with ice-cold saline was done in order to remove the remaining blood. Tissues were stored at -80 °C until further analysis.

The tissues were dissected, thoroughly washed with ice-cold saline, weighed, minced and homogenized with a Thomas Sci Co. glass-type homogenizer (Teflon pestle) at 4°C (10% w/v) using 1.15% KCl for lipid peroxide (LPO) determination. The concentration of LPO measured as thio-barbituric acid reactive substances (TBARS) in the tissues of liver was assayed by the method of Ohkawa et al. (1979) using thiobarbituric acid (TBA. In this reaction, a colored complex was formed and absorbance was determined spectro-photometrically (UV/VIS Spectrophotometer, Jan-way, GBR) at 530 nm. The results were expressed in nmol MDA/g tissue using a molar extinction coefficient for MDA of $1.56 \times 10^5\ M^{-1}\ cm^{-1}$.

Tissue samples for glutathione (reduced glutathione-GSH and oxidized glutathione-GSSG) assays were homogenized on ice with 20 volumes of precipitating solution (1.5 mL 100 mmol/L Na-phosphate/5 mmol/L EDTA buffer, pH 8.0 and 0.4 mL 25% metaphosphoric acid). The total homogenate was centrifuged at 4°C at 10,000 *g* for 30 minutes to obtain clear supernatants for the GSH and GSSG assay.

The concentrations of GSH were determined based on GSH oxidation with DTNB (5, 5′-dithio-bis-2-nitrobenzoic acid), (Beutler, 1975) and the concentration of GSSG was determined enzy-matically by glutathione reductase after the inhibition of GSH oxidation by NEM (N-ethylmaleimide) (Beutler, 1975). The optical density

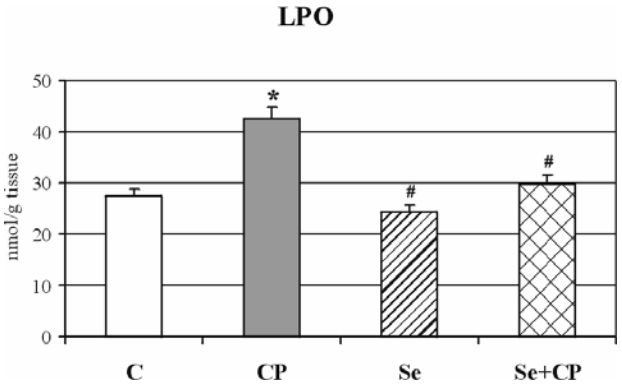

Figure 1. Concentration of lipid peroxides (LPO) in the rat livers of control and experimental groups. Results are expressed as means ± S.E.M. $n = 6$ for each treatment group. *Statistically different from the control group, $p < 0.05$ and #statistically different from the CP - treated group, $p < 0.05$.

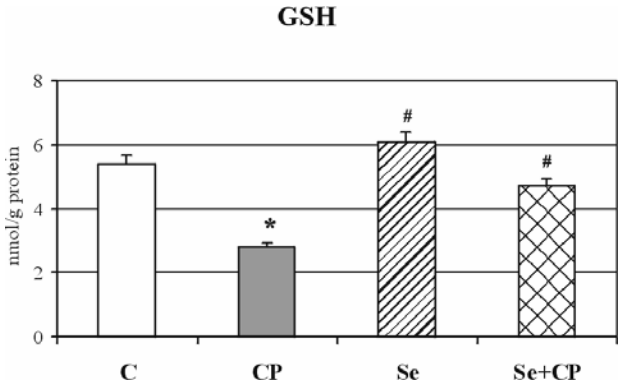

Figure 2. Concentration of reduced glutathione (GSH) in the rat livers of control and experimental groups. Results are expressed as means ± S.E.M. $n = 6$ for each treatment group. *Statistically different from the control group, $p < 0.05$ and #statistically different from the CP - treated group, $p < 0.05$.

of the reaction product was read immediately at 412 nm on a spectrophotometer (UV/VIS Spectrophotometer, Janway, GBR). The concentrations of GSH and GSSG were expressed as nmol/g protein.

Since it is a usable marker of the reciprocal relationship between GSH and GSSG, the glutathione redox index (GSH RI) was also estimated. GSH RI was calculated and expressed in arbitrary units.

Protein contents in various samples were determined by the method of Lowry et al. (1951) using Folin's reagent and bovine serum albumin (BSA) as standard.

The data were expressed as the mean ± S.E.M. and were analyzed by means of one-way analysis of variance (ANOVA). Statistical evaluation of the data was done following Student's t-test. A difference was considered significant at $p < 0.05$.

RESULTS

The concentration of LPO in the liver of rat is shown in Fig. 1. The LPO concentration significantly increased in the liver of rats after acute administration of CP ($p < 0.05$), while Se pretreatment reversed this change to control values.

The data presented in Figures 2-4 show significant changes in the glutathione redox status (GSH, GSSG and GSH RI) during the treatment of rats with CP and Se. The results of the experiments show that the concentrations GSH in the liver significantly decreased ($p < 0.05$) in the CP-treated rats with respect to the control animals (Fig. 2). Pretreatment with Se reversed the concentrations of GSH to the control levels.

In the animals exposed to CP, the concentration of GSSG (Fig. 3), as well as GSH RI (Fig. 4) significantly increased in respect to the controls ($p < 0.05$). The pretreatment with Se prior to CP intoxication reversed these changes. The concentration of GSSG and GSH RI significantly decreased in comparison to the animals given CP alone ($p < 0.05$).

DISCUSSION

Cisplatin is a potent antitumor drug. It is a widely used chemotherapeutic agent against various types of malignant tumors (Jordan and Carmo-Fonseca, 2000; Mansour et al., 2006). High doses of CP have also been known to produce hepatotoxicity and

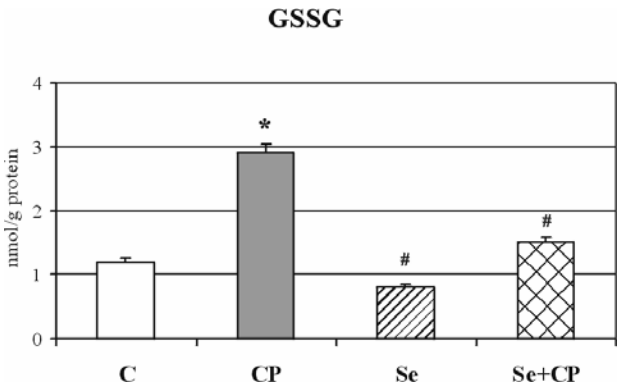

Figure 3. Concentration of oxidized glutathione (GSSG) in the rat livers of control and experimental groups. Results are expressed as means ± S.E.M. $n = 6$ for each treatment group. *Statistically different from the control group, $p < 0.05$ and #statistically different from the CP - treated group, $p < 0.05$.

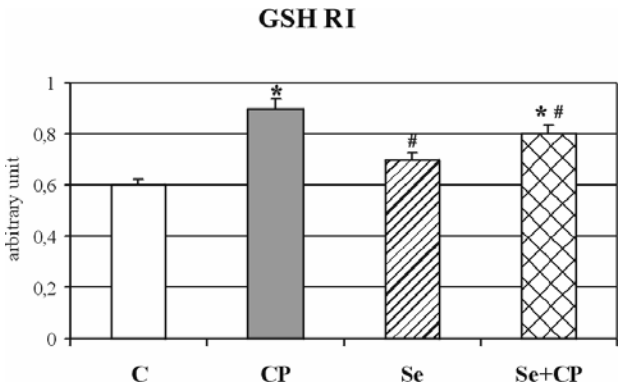

Fig. 4. Glutathione redox index (GSH RI) in the rat livers of control and experimental groups. Results are expressed as means ± S.E.M. $n = 6$ for each treatment group. *Statistically different from the control group, $p < 0.05$ and #statistically different from the CP - treated group, $p < 0.05$.

several studies suggest that supplemental antioxidants can reduce cisplatin-induced hepatotoxicity (Zicca et al., 2004; Koc et al., 2005; Mansour et al., 2006; Pratibha et al., 2006).

There are many studies which have demonstrated the involvement of oxidative stress, lipid peroxidation and mitochondria dysfunction in CP-induced liver and kidney toxicity (Antunes et al., 2000; Jordan and Carmo-Fonseca, 2000; Mansour et al., 2006; Atasayar et al., 2009). A mechanism by which CP exerts its cytotoxicity is through the generation of ROS (Antunes et al., 2001; Atasayar et al., 2009). The administration of CP causes an increase in lipid peroxide levels and a decrease in the activity of antioxidant defense enzymes, as well as in the concentrations of non-enzymatic components of AOS that prevent, or protect against, lipid peroxidation in the tissues (Naziroğlu et al., 2004). It is accepted that both correlate to oxidative stress and cause an imbalance between the generation of oxygen derived radicals and the organism's antioxidant potential (Halliwell and Gutteridge, 2007).

Lipid peroxidation is one of the main manifestations of oxidative damage and has been found to play an important role in the toxicity of many xenobiotics (Matés, 2000). Several patho physiological mechanisms have been proposed to explain the increased LPO and decreased antioxidant levels in the CP toxicity. Moreover, it has been shown that various antioxidants and antioxidant defense systems protect cells from the CP induced toxicity.

The prevention of lipid peroxidation is essential for all aerobic organisms; therefore the organism is well equipped with antioxidants that directly or indirectly protect cells against the adverse effects of xenobiotics, carcinogens and toxic radicals (Halliwell and Gutteridge, 2007). The role of antioxidants in reversing this oxidative stress has been of long-standing interest to basic scientists and clinicians (Matés, 2000).

The data obtained in our study (Fig. 1) confirm that acute intoxication with CP causes a significant increase of LPO concentration in the liver of rats. Pretreatment with Se was very effective in the prevention of the oxidative damage induced by CP, which resulted in a significantly lower LPO concentration in liver. These results can be explained by the important role of Se in preventing lipid peroxidation and in protecting the integrity and functioning of tissues and cells.

Many experimental studies in animals have demonstrated the ability of Se to prevent carcinogenesis, and epidemiological studies have suggested

that a decreased Se status in humans is associated with an increased risk of cancer (Agay et al., 2005). Supplementation of the antioxidant vitamin E and Se has been reported to inhibit lipid peroxide in various conditions such as CP-induced nephrotoxicity and hepatotoxicity (Naziroğlu et al., 2004).

Recent studies have focused on the role of antioxidants in CP toxicity. Administration of antioxidants such as vitamin E and vitamin C, curcumin or Se before and during treatment with CP has been used to protect against toxicity in humans and experimental animals (Spallhoz, 1994; Rybak et al., 1999; Antunes et al., 2000 and 2001; Caffrey and Frenkel, 2000; Naziroğlu et al., 2004; Atasayar et al., 2009).

The reduction-oxidation (redox) state of a cell is largely determined by the balance between generated ROS and endogenous expression of thiol buffers such as glutathione (Shelly, 2009). GSH is a ubiquitous intracellular peptide with diverse functions that include detoxification, antioxidant defense, maintenance of thiol status, and modulation of cell proliferation. GSH is synthesized in the cytosol of all mammalian cells in a tightly regulated manner (Sies, 1999; Shelly, 2009). The measurement of GSH and GSSG in biological samples is essential for the evaluation of the redox and detoxification status of cells and tissues in relation to the protective role of GSH against oxidative and free-radical-mediated cell injury (Richie et al., 1996). In healthy cells and tissue, more than 90% of the total GSH pool is in the reduced form (GSH) and less than 10% exists in the disulfide form (GSSG). An increased GSSG-to-GSH ratio is considered indicative of oxidative stress (Griffith, 1999; Shelly, 2009).

The results suggest that CP intoxication induces oxidative stress and alters the glutathione redox status (GSH, GSSG and GSH RI), (Figs. 2 - 4) in the rat liver. The CP-induced oxidative damage has been demonstrated by the increased lipid peroxidation and inhibition of enzymes required to prevent such oxidative damage (Antunes et al., 2000; Naziroğlu et al., 2004). In addition, GSH, the most abundant intracellular thiol and a critical cellular antioxidant, executes the intracellular inactivation of CP and detoxification of ROS as a mechanism for CP resistance (Atasayar et al., 2009). Accordingly, the depletion of GSH, an increase in GSSG and the lowering of GSH RI in the blood, liver and kidney were consistent with the accumulation of CP in these tissues. These changes seem to be due to the generation of ROS (Atasayar et al., 2009). GSH is known to protect the cellular system against the toxic effects of lipid peroxidation (Griffith, 1999). GSH functions as a direct free radical scavenger, a co-substrate for GSH-Px activity and a co-factor for many enzymes and forms conjugated in endogenous and xenobiotic reactions (Griffith, 1999; Sies, 1999; Shelly, 2009).

GSH is necessary for resistance to oxidative stress through detoxification of ROS. It can also detoxify many endogenous toxins, including CP, through the formation of GSH adducts (Hrubisko et al., 1993; Chen et al., 1995). Also, the GSH redox cycle, which includes GSH, GSH-Px and GR, plays an important role in the detoxification of ROS that are generated by CP, so as to protect cells from potential toxicity and carcinogenesis (Hrubisko et al., 1993; Griffith, 1999; Atasayar et al., 2009). GSTs are a family of enzymes that catalyze the conjugation of GSH to a variety of substrates. Several isoforms of GST have been shown to bind CP *in vivo* (Hrubisko et al., 1993; Sadzuka et al., 1994). Of the studies in which increased resistance to CP was observed, none determined whether the inactivation of CP was due to GST binding to the CP or catalyzing its conjugation to GSH.

Increased intracellular GSH concentrations correlate with decreased platinum-DNA binding in freshly isolated peripheral blood mononuclear cells (Sadowitz et al., 2002). Studies of tumor cell lines have shown a correlation between increased levels of intracellular GSH and resistance to CP (Hrubisko et al., 1993; Chen et al., 1995).

In the present study, Se also reduced the cellular toxicity caused by CP, induced ROS and protected the liver antioxidant system. The treatment with Se

reversed the CP induced alterations in liver GSH, GSSG or GSH RI (Figs. 2 - 4). Se can reduce the nephrotoxicity and hepatotoxicity of CP without reducing the antitumor activity of the drug. The protection correlates with higher levels of Se in the kidney and with higher levels of GSH in the kidney, both compared to tumors. Selenite is metabolized into selenols, specifically into methylselenol and glutathionylselenol. This bioactivation of selenite into selenols is a GSH-dependent process. HPLC with on-line radioactivity detection of ^{195m}Pt showed that methylselenol was capable of forming a complex with CP *in vitro*. ^{1}H-NMR gave evidence that the complex contained one or more Pt—Se—CH_3 bond. Attempts to obtain further structural information by Desorption Chemical Ionization and Fast Atom Bombardment mass-spectrometry failed. It is proposed that the formation of a CP-selenol complex also takes place *in vivo*, especially in the kidney, thereby preventing CP to exert its nephrotoxic activity (Caffrey and Frenkel, 2000; Antunes et al., 2001; Naziroğlu et al., 2004; Agay et al., 2005).

In conclusion, the obtained data in our study suggest that CP intoxication induces oxidative stress and alters the glutathione redox status (GSH, GSSG and GSH RI), resulting in increased lipid peroxidation in the rat liver. Se inhibits LPO, thus preventing free-radical mediated oxidant injuries. Treatment with Se significantly prevents CP-induced liver damage. Our results show that Se may ameliorate CP-induced oxidative stress by decreasing LPO and altering the glutathione redox status in the liver of rats, thus demonstrating protection from CP-induced oxidative damage.

Acknowledgements – This study was supported by the Ministry of Science and Technological Development, Republic of Serbia, Grant No. 143035B. The authors are thankful to Radmila Paunović Štajn, MSc, for proofreading the manuscript.

REFERENCES

Agay, D., Sandre, C., Ducros, V., Faure, H., Cruz, C., Alonso, A., Roussel, A. M., and *Y. Chancerelle* (2005). Optimization of selenium status by a single intraperitoneal injection of Se in Se-deficient rat: possible application to burned patient treatment. *Free Radic. Biol. Med.* **39,** 762-768.

Antunes, L. M. G., Darin, J. D. C., and *M. L. P. Bianchi* (2000). Protective effects of vitamin C against cisplatin-induced nephrotoxicity and lipid peroxidation in adult rats: a dose-dependant study. *Pharmacol. Res.* **41,** 405-411.

Antunes, L. M. G., Darin, J. D. C., and *M. L. P. Bianchi* (2001). Effects of the antioxidants curcumin or selenium on cisplatin-induced nephrotoxicity and lipid peroxidation in rats. *Pharmacol. Res.* **43,** 145-150.

Atasayar, S., Gürer-Orhan, H., Orhan, H., Gürel, B., Girgin, G., and *H. Özgüneş* (2009). Preventive effect of aminoguanidine compared to vitamin E and C on cisplatin-induced nephrotoxicity in rats. Exp. Toxicol. Pathol. 61, 23-32.

Beutler, E. (1975). Reduced glutathione (GSH). In: *Red cell metabolism, a manual of biochemical methods,* (Ed. E. Beutler), 112-114. Grune and Straton, New York.

Beutler, E. (1975). Oxidized glutathione (GSSG). In: *Red cell metabolism, a manual of biochemical methods,* (Eds. E. Beutler), 115-117. Grune and Straton, New York.

Caffrey, P. B., and *G. D. Frenkel* (2000). Selenium compounds prevent the induction of drug resistance by cisplatin in human ovarian tumor xenografts in vivo. *Cancer Chemother. Pharmacol.* **46,** 74-78.

Chen, G., Hutter, K. J., and *W. J. Zeller* (1995). Positive correlation between cellular glutathione and acquired cisplatin resistance in human ovarian cancer cells. *Cell Biol. Toxicol.* **11,** 273–281.

Cohen, S. M., and *S. J. Lippard* (2001). Cisplatin: from DNA damage to cancer chemotherapy. *Prog. Nucleic Acis. Res. Mol. Biol.* **67,** 93-130.

Conklin, K. A. (2000). Dietary antioxidants during cancer chemotherapy: impact on chemotherapeutic effectiveness and development of side effects. *Nutr. Cancer* **37,** 1-18.

Griffith, O. W. (1999). Biologic and pharmacologic regulation of mammalian glutathione synthesis. *Free Radic. Biol. Med.* **27,** 922–935.

Halliwell, B., and *J. M. C. Gutteridge* (2007). Free Radicals in Biology and Medicine, 4rd Ed. Oxford University Press, New York.

Hrubisko, M., Mc Gown, A. T., and *B. W. Fox* (1993). The role of metallothionein, glutathione, glutathione S-transferases and DNA repair in resistance to platinum drugs in a series of L1210 cell lines made resistant to anticancer platinum agents. *Biochem. Pharmacol.* **45,** 253–256.

Jordan, P., and *M. Carmo-Fonseca* (2000). Molecular mechanisms involved in cisplatin cytotoxicity. *Cell Mol. Life Sci.* **57,** 1229–1235.

Kim, Y. S., and *J. G. F. Combs* (1993). Effects of dietary selenium and vitamin E on glutathione concentrations and glutathione S-transferase activities in chick liver and plasma. *Nutr. Res.* **13,** 455-463.

Koc, A., Duru, M., Ciralik, H., Akcan, R., and *S. Sogut* (2005). Protective agent, erdosteine, against cisplatin-induced hepatic oxidant injury in rats. *Mol. Cell Biochem.* **278,** 79-84.

Lowry, O. H., Rosebrough, N. J., Farr, A. L., and *R. J. Randall* (1951). Protein measurement with the Folin phenol reagent. *J. Biol. Chem.* **193,** 265-267.

Mansour, H. H., Hafez, F. H., and *N. M. Fahmy* (2006). Silymarin modulates cisplatin-induced oxidative stress and hepatotoxicity in rats. *J. Biochem. Mol. Biol.* **39,** 656-661.

Matés, M. (2000). Effects of antioxidant enzymes in the molecular control of reactive oxygen species toxicology. *Toxicology* **153**, 83-104.

Naziroğlu, M., Karaoglu, A., and *A. O. Askoy* (2004). Selenium and high dose vitamin E administration protects cisplatin-induced oxidative damage to renal, liver and lens tissues in rats. *Toxicology* **195,** 221-230.

Ohkawa, H., Okishi, N., and *K. Yagi* (1979). Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. *Anal. Biochem.* **95**, 351-358.

Pratibha, R., Sameer, R., Rataboli, P. V., Bhiwgade, D. A., and *C. Y. Dhume* (2006). Enzymatic studies of cisplatin-induced oxidative stress in hepatic tissue of rats. *Eur. J. Pharmacol.* **532,** 290-293.

Richie, J. P., Jr, Skowronski, L., Abraham, P., and *Y. Leutzinger* (1996). Blood glutathione concentrations in a large-scale human study. *Clin. Chem.* **42,** 64-70.

Rybak, L. P., Whitworth, C., and *S. Somani* (1999). Application of antioxidants and other agents to prevent cisplatin ototoxicity. *Laryngoscope* **109,** 1740–1744.

Sadowitz, P. D., Hubbard, B. A., Dabrowiak, J. C., Goodisman, J., Tacka, K. A., Aktas, M. K., Cunningham, M. J., Dubowy, R. L, and *A. K. Souid* (2002). Kinetics of cisplatin binding to cellular DNA and modulations by thiol-blocking agents and thiol drugs. *Drug Metab. Dispos.* **30,** 183–190.

Sadzuka, Y., Shimizu, Y., and *Y. Takino* (1994). Role of glutathione S-transferase isoenzymes in cisplatin-induced nephrotoxicity in the rat. *Toxicol Lett.* **70,** 211–222.

Saito, Y., Yoshida Y., Akazawa, T., Takahashi, K., and *E. Niki* (2003). Cell death caused by selenium deficiency and protective effect of antioxidants. *J. Biol. Chem.* **278,** 39428-39434.

Shelly, C. Lu. (2009). Regulation of glutathione synthesis. *Mol. Aspec. Med.* **30,** 42-59.

Sies, H. (1999). Glutathione and its cellular functions. *Free Radic. Biol. Med.* **27,** 916-921.

Spallhoz, J. E. (1994). On the nature of selenium toxicity and carcinostatic activity. *Free Radic. Biol. Med.* **17,** 45-64.

Yoshida, M., Itzuka, K., Hara, M., Nishijima, H., Shimada, A., Nakada, K., Satoh, Y., Akama, Y., and *A. Terada* (2000). Prevention of nephrotoxicity of cisplatin by repeated oral administration of ebselen in rats. *Tohoku J. Exp. Med.* **191,** 209-220.

Zicca, A., Cafaggi, S., Mariggio, M. A., Vannozzi, M. O., Ottone, M., Bocchini, V., Caviglioli, G., and *M. Viale* (2004). Reduction of cisplatin hepatotoxicity by procainamide hydrochloride in rats. *Eur. J. Pharmacol.* **442,** 265-272.

ЕФЕКТИ ЦИСПЛАТИНА НА ЛИПИДНУ ПЕРОКСИДАЦИЈУ И ГЛУТАТИОН РЕДОКС СТАТУС У ЈЕТРИ ПАЦОВА: ЗАШТИТНА УЛОГА СЕЛЕНА

ИВАНА С. ТРБОЈЕВИЋ[1], БРАНКА И. ОГЊАНОВИЋ[1], НАТАША З. ЂОРЂЕВИЋ[1], СНЕЖАНА Д. МАРКОВИЋ[1], А. Ш. ШТАЈН[1], ЈЕЛЕНА П. ГАВРИЋ[2] и ЗОРИЦА С. САИЧИЋ[2*]

[1]*Институт за биологију и екологију, Природно-математички факултет, Универзитет у Крагујевцу,* 34000 Крагујевац, Србија
[2]*Одељење за физиологију, Институт за биолошка истраживања "Синиша Станковић", Универзитет у Београду,* 11060 Београд, Србија

У нашој студији испитивана је улога оксидационог стреса у токсичности цисплатина (CP) и његова превенција претретманом селеном (Se). Мужјаци *Wistar* albino пацова су иницирани једном дозом цисплатина (7.5 mg CP/kg т.м., и.п.) и селена (6 mg Se/kg т.м, као Na_2SeO_3, и.п.) појединачно или у комбинацији. Резултати показују да интоксикација CP узрокује оксидациони стрес и промену глутатион редокс статуса: редукованог (GSH), оксидованог (GSSG) и GSH/GSSG индекса (GSH RI), као и повећање липидне пероксидације (LPO) у јетри пацова. Третман Se који је претходио третману CP показао је заштитне ефекте против токсичног деловања CP на пероксидацију липида мемебране и промену глутатион редокс статуса у јетри пацова. На основу наших резултата закључујемо да Se, делује као снажан антиоксиданс и да може имати улогу у контроли CP индуковане хепатотоксичности код пацова.