Journal of Animal and Veterinary Advances 9 (1): 37-43, 2010
ISSN: 1680-5593
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Taurine Prevents Nonylphenol-Induced Oxidative Stress in Rats

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Abstract: The present study was designed to determine the possible protective effects of taurine against oxidative damage induced by nonylphenol in rats. The rats were divided into 5 groups each containing 8 Wistar-albino male rats rats: Control group (C) by standart rat feed, Taurine group (T) by standart rat feed + 3% taurine (v w^{-1}) in drinking water, Nonlyphenol group (NF) by standart rat feed + 50 μg kg^{-1} diet Nonlyphenol, Nonlyphenol + Taurine group (NFT) by standart rat feed + 50 μg kg^{-1} diet Nonlyphenol + 3% taurine (v w^{-1}) in drinking water and Alchol group (A) by standart rat feed + 50 μL kg^{-1} diet alchol were fed *ad-libitum* for 30 days during the study. Malondialdehyde (MDA), reduced Glutathione (GSH) levels, superoxide dismutase activity and Nitric Oxide (NOx) were determined in blood. MDA levels in blood of the rats significantly increased in NF and A group compared to control, T and NFT groups ($p<0.05$). On the other hand, the blood GSH concentrations significantly decreased in NF group compared to control and other groups ($p<0.001$). The SOD activities in blood significantly decreased in NF and A groups compared to control, T and NFT groups ($p<0.01$). The plasma NOx levels in NF group significantly decreased compared to control and other groups ($p<0.01$). Consequently, taurine could be used as a potential antioxidant aganist nonylphenol toxication with its antioxidant properties.

Key words: Nonylphenol, oxidative stress, taurine, toxication, free radicals, antioxidants

INTRODUCTION

Nonylphenol (NP), an environmental contaminant, is the final degradation product of Alkylphenol Polyethoxylates (APE), which are widely used in the preparation of lubricating oil additives, resins, plasticizers, surface-active agents, detergents, paints, cosmetics and other formulated products. It is also found in polyvinyl chloride, which is used in the food processing and packaging industry and contaminates the water flowing through polyvinyl chloride pipes (Junk *et al*., 1974). The annual worldwide production of APEs, mainly nonylphenol ethoxylate, amounts to about 300,000 tons (Naylor *et al*., 1992). NP and APE are released into the environment mainly via industrial and municipal wastewaters and can be found in contaminated rivers at concentrations up to 200 μg L^{-1} (Severin, 2000; Bennie, 1999). Nonylphenol is classified by the U.S. Environmental Protection Agency as an inert of toxicological concern that must be identified on pesticide labels (Brigs and Council, 1992). Nonylphenol is probably diverse routes of human exposure; not only via contaminated foods and drinking water, but also via dermal absorption or inhalation (Clark *et al*., 1992; Ahel *et al*., 1993). NP has weak estrogenic activity. It has been demonstrated that NP could interfere with reproduction in fish, reptiles and mammals and induce the cell death in gonads and changes to other reproductive parameters (Gong and Han, 2006).

Normal cellular function depends on a balance between reactive oxygen species produced and antioxidant defense mechanisms available to the cell. Reactive Oxygen Species (ROS) arise as by-products of normal cellular metabolism or may be the consequence of exposure to certain chemicals (Kerr *et al*., 1996; Moslen, 1994; Krieger and Caruso, 2001). Reactive species derived from chemicals, oxygen, or nitrogen have been implicated as putative noxious intermediates responsible for cellular damage. Because electrophilic metabolites or radicals and excited species can readily interact with essential biomolecules, covalent binding to cellular components or their oxidative modification can occur, leading to structural and functional alterations (Fernandez *et al*., 2003; Comporti, 1989; Kappus, 1987). However, owing to ROS overproduction or inadequate antioxidant defense, this equilibrium is hampered favouring the ROS upsurge that

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culminates in oxidative stress. The ROS readily attack and induce oxidative damage to various biomolecules including proteins, lipids, lipoproteins and DNA (Fidan and Dundar, 2008).

During the last decade, numerous *in vitro* and *in vivo* studies have suggested that antioxidants numerous potentially beneficial medicinal properties. Taurine is a ubiquitous sulphur-containing amino acidhich is normally present in most mammalian tissues has been proposed to be an antioxidant (Eppler and Dawson, 2001). It plays various important physiological functions including osmoregulation, bile acid conjugation, pharmacological actions, pathological states and prevention of oxidant induced injury in many tissues (Lallemand and De Witte, 2004). The useful effects of taurine as an antioxidant in biological systems have been attributed to its capability to stabilize biomembranes, to scavenge reactive oxygen species and to decrease the peroxidation of unsaturated membrane lipids (Banks *et al*., 1992; Kilic and Yildirim, 2008).

The aim of the present study is to evaluate the protective effects of suplementation of taurine on the oxidative stress status of blood of nonylphenol-induced rats by biochemical analysis and to elucidate the mechanism involved in this effect.

MATERIALS AND METHODS

Chemicals: The chemicals used in the study were purchased from Sigma-Aldrich (Sigma-Aldrich Chemical Co. St. Louis, MO, USA).

Animals and experimental design: Male Wistar-albino rats, weighing about 175 and 250 g and aged between 3 and 4 months were used in the study. They were housed under standard conditions of temperature (23±2°C), humidity and dark-light ycle (lights on from 6:00 am to 6:00 pm). The animals were maintained on standard rat feed supplied by Bil-Yem Ltd. (Turkey). Tap water was available ad libitum. All the animals were carefully monitored and maintained in accordance with the ethical recommendation of the University of Afyonkarahisar Kocatepe Animal Ethics Committee. The rats were randomly divided into five experimental groups: Control (c) (n = 8); experimental group I (Taurine (T)) (n = 8), group III (Nonylphenol (NP)) (n = 8), group IV (Nonylphenol + Taurine (NP + T)) (n = 8) and group V (alchol (A)) (n = 8). Control group (C) by standart rat feed, Taurine group (T) by standart rat feed + 3% taurine (v w^{-1}) in drinking water, Nonlyphenol group (NF) by standart rat feed + 50 μg kg^{-1} diet Nonlyphenol, Nonlyphenol + Taurine group (NFT) by standart rat feed + 50 μg kg^{-1} diet Nonlyphenol + 3% taurine (v w^{-1}) in drinking water and Alchol group (A) by standart rat feed + 50 μL kg^{-1} diet alchol were fed *ad-libitum* for 30 days during the study.

At the end of the experimental period, the rats were anaesthetized and killed by cervical dislocation. Blood samples were taken into heparinized tubes in the fasting state in all subjects from heart, to measure Malondialdehyde (MDA) Superoxide Dismutase activity (SOD), Nitric Oxide (NOx) and reduced Glutathione (GSH).

Lipid peroxidation was determined by measuring the MDA concentration. The Blood MDA levels, an index of lipid peroxidation, were measured by the double heating method of Draper and Hadley (1990). SOD activity was measured by using the method described by Marklund (1990). Nitric oxide decomposes rapidly in aerated solutions to form stable Nitrite/Nitrate products (NOx). Plasma nitrite/nitrate concentration was measured by a modified method of Griess assay, described by Miranda *et al*. (2001). The blood GSH concentration was measured using the method described by Beutler *et al*. (1963).

Statistical analysis: All data were presented as mean±SE for parametric variables. Parametric variables were compared using one-way analysis of variance with post-hoc analysis using the Duncan test. Data were analyzed using the SPSS® for Windows computing program (version 10.0) and $p<0.001$, $p<0.01$ and $p<0.05$ were considered statistically significant (Sokal and Rohlf, 1969).

RESULTS AND DISCUSSION

The results of blood MDA, GSH, SOD and NOx levels in controls and other experimental groups were summarised in Table 1.

As shown in Table 1, MDA levels in blood of the rats significantly increased in NF and A group compared to control, T and NFT groups ($p<0.05$). On the other hand, the blood GSH concentrations significantly decreased in NF group compared to control and other groups ($p<0.001$). The SOD activities in blood significantly decreased in NF and A groups compared to control, T and NFT groups ($p<0.01$). The plasma NOx levels in NF group significantly decreased compared to control and other groups ($p<0.01$).

The interest in ROS in biology and medicine has been increased because of their strong relationship with phenomena such as aging and disease processes (Cao *et al*., 1995). A wide variety of ROS are produced in the course of the normal metabolism in biological systems and they have several important physiological functions, but their accumulation beyond the needs of the cell can potentially damage macro molecules (Schulz *et al*., 2000).

Table 1: Levels of biochemical parameters in control and experimental groups of rats

Parameters	Control $\bar{X}$ ±SE	T group $\bar{X}$ ±SE	NF group $\bar{X}$ ±SE	NFT group $\bar{X}$ ±SE	A group $\bar{X}$ ±SE
MDA (nmol mL^{-1})	$13.75\pm0.27^{***b}$	$14.23\pm0.25^{***ab}$	$14.84\pm0.29^{***a}$	$14.39\pm0.21^{***ab}$	$14.98\pm0.25^{***a}$
GSH (mg L^{-1})	$41.34\pm3.22^{*ab}$	$46.75\pm2.50^{*a}$	$30.27\pm1.30^{*c}$	$36.64\pm1.42^{*bc}$	$35.03\pm1.40^{*bc}$
SOD (U mL^{-1} blood)	$130.69\pm6.48^{**a}$	$135.51\pm7.98^{**a}$	$110.22\pm2.5^{**b}$	$125.88\pm3.03^{**a}$	$104.20\pm3.99^{**b}$
NOx (μmol L^{-1})	$31.48\pm2.24^{**bc}$	$35.83\pm2.80^{**ab}$	$26.69\pm1.99^{**c}$	$40.33\pm3.02^{**a}$	$35.73\pm2.29^{**ab}$

Values are shown as mean±SE. Values with different letters show statistically significant differences (*: $p<0.001$, **: $p<0.01$, ***: $p<0.05$)

However, excessive generation of free radicals can occur due to endogenous biological or exogenous environmental factors, such as exposure to radiation, pollution or chemical substances (Misra and Fridovich, 1972). A cell defends itself against ROS by elaborating systems of biological defence including antioxidant compounds (glutathione, arginine, citrulline, taurine, creatine, selenium, zinc, vitamin E, vitamin C, vitamin A) and antioxidant enzymes (superoxide dismutase, catalase, glutathione reductase and glutathione peroxidases). In spite of numerous biological defense systems, increased free radical generation has the potential to result in oxidative stress. Oxidative stress may result from an imbalance between ROS and antioxidants levels (Lightboy *et al*., 2001). It is well known that, when the organism cannot balance free radical generation with the defense systems, a cellular injury and tissue damage might occur. The main damage induced by ROS results in alterations of cellular macromolecules (membrane lipids, proteins and DNA) and changes in intracellular calcium and intracellular pH, or cell death (Dorval *et al*., 2003; Fidan and Dundar, 2008).

The impact made by free radicals on lipids is named as Lipid Peroxidation (LP). LP is a complicated radical chain reaction leading to the formation of various products including lipid hydroperoxides, conjugated dienes and malondialdehyde. Detection of lipid hydroperoxides and conjugated dienes and Thiobarbituric Acid-reactive Substances (TBARS) such as MDA, are often applied to the study of lipid peroxidation reactions (Diplock, 1994). Since, membrane phospholipids are major targets of oxidative damage, lipid peroxidation is often the first parameter analyzed for proving the involvement of free radical damage. Thus, the presence of MDA is considered as an indicator of free-radical damage through membrane lipid peroxidation (Katz *et al*., 1996).

The antioxidant defense system includes small molecular antioxidants, antioxidant enzymes and metal chelating agents. The efforts of the endogenous antioxidant enzymes to remove the continuously generated free radicals initially increase due to an induction but later enzyme depletion results, resulting in oxidative cell damage (Vidyasagar *et al*., 2004). Enzymatic scavengers like SOD, CAT, Glutathione Peroxidase (GPx), glutathione reductase (GR) etc. protect the system from deleterious effects of reactive oxygen species and Superoxide Dismutase (SOD) is an antioxidant enzyme of great importance for the regulation of free radical-mediated processes in biological systems. On the other hand, reduced GSH and its metabolizing enzymes provide the major defense against ROS-induced cellular damage (Celik and Suzek, 2008). GSH serves as a reductant in oxidation reactions resulting in the formation of GSSG. GSH can protect cells against the damage of ROS and free radicals that arise during conditions of oxidative stress (Loch-Caruso *et al*., 2005). Thereby decreased GSH levels may reflect depletion of the antioxidant reserve. As a consequence of GSH deficiency, a number of related functions may be impaired such as a decrease in reducing capacity, protein biosynthesis, immune function, accumulations of lipid peroxidation products and detoxification capacity (Sen, 2000; Hayes and McLellan, 1999).

Alkylphenol ethoxylates have been widely used as plastic additives and components of surfactants, paints, herbicides and insecticides (Messina and Dawson, 2000). Approximately, 80% of these chemicals are reported to be Nonylphenol Ethoxylate (NPE) (Naylor, 1996). Nonylphenol is classified by the US Environmental Protection Agency as an inert of toxicological concern that must be identified on pesticide labels (Brigs and Council, 1992). Most research to date on NP has focused on the growth of reproductive organs in animals (Laws *et al*., 2000; Lee and Lee, 1996). The multigeneration studies in rats showed that NP affected not only reproductive organs but also nonreproductive organs such as kidney and liver (Chapin *et al*., 1999; Nagao *et al*., 2001). The mechanism of action of nonylphenol on the production of ROS remains unclear. Various environmental contaminants can induce oxidative stress by generating Reactive Oxygen Species (ROS) such as hydrogen peroxide (H_2O_2) and superoxide anion (O_2-) (Chitra *et al*., 2003; Wang *et al*., 2003). NP has been shown to produce oxidative stress, enhancing ROS generation in human blood neutrophils (Okai *et al*., 2004). Furthermore, NP administration increased ROS level and lipid peroxidation and depressed the activity of antioxidant enzymes such as superoxide dismutase and glutathione reductase in rat testis (Chitra and Mather, 2004). Recently, treatment of rats with NP was found to induce hydroxyl radical formation in the brain (Obata and Kubota, 2000). Gong and Han (2006) reported that 10-40 μM NP for 24 h caused intracellular accumulation of reactive oxygen species, in testicular sertoli cells. Nonylphenol has been shown to affect the

activity of cytochrome P450 in rats (Lee *et al*., 1996). Cytochrome P450 has been shown to provoke Reactive Oxygen Species (ROS) (Griveau *et al*., 1995). Nonylphenol has been shown to inhibit the activities of Cytochrome P450-1A (CYP1A) in rat hepatic microsomal fractions (Lee *et al*., 1996). The present study shows that, MDA levels increased significantly in the blood after nonylphenol exposure, in agreement with the previous studies. In addition, the results showed that lipid peroxidation appeared to increase in all the experiment groups in proportion to the controls. As reported by other researchers, LP is one of the main manifestations of oxidative damage in cells. LP produces a progressive loss of cell membrane integity, imparement in membrane transport function and disruption of cellular ion homeostasis (Bano and Bhatt, 2007). The results in the present study also showed that, SOD activity and GSH concentrations significantly decreased in rat blood by nonylphenol intoxication, paralel to the previous studies in rat. In this context, it is possible that the observed insufficiency in antioxidant power could be due to direct modification of the antioxidant defenses by nonylphenol.

Nitric oxide, a magic free radical gas molecule, has been shown to be involved in numerous physiological and pathophysiological processes. Nitric oxide is a endothelium-derivated relaxing factor as a signaling molecule in the normal physiology of mammalian (Boeckxstaens *et al*., 1991). The role of NO seems to be controversial, because it has been shown that tissue dysfunction or injury could occur after inhibition of NO. However, high production of NO has been suggested as a cause of tissue injury (Bohloli *et al*., 2007). Stimulation of tissue production of 'NO is also associated with adverse events such as hypotension, inhibition of intermediary metabolism and the production of the potent oxidant peroxynitrite ($ONOO^-$) following radical-radical reaction with superoxide (Rubbo *et al*., 1994). The bioavailability of NO is reduced due to the increased level of superoxide radical, which transforms NO to peroxynitrite Zourek *et al*. (2008). In the present study, nonylphenol-treated rats showed a significant decrease in the level of NOx concentrations.

Taurine, 2-amino ethanesulfonic acid, is a amino acid, which is normally present in most mammalian tissues has been proposed to be an antioxidant Eppler and Dawson (2001). It is a potent antioxidant and prevents tissue injury mainly through antioxidation. It is also involved in cell volume homeostasis, protein stabilization and stress responses. It can prevent DNA damage at concentrations normally found in cells (Messina and Dawson, 2000). The useful effects of taurine as an antioxidant in biological systems have been attributed to its capability to stabilize biomembranes, to scavenge reactive oxygen species and to decrease the peroxidation of unsaturated membrane lipids (Banks *et al*., 1992). Taurine could protect tissues against GSH pool depletion by preventing the decreases in glutathione reductase activities Rikans and Hornbrook (1997). Taurine is a well known substance that has antioxidant properties in peroxidatively damaged tissues. Decreased malondialdehyde level, which is an indicator of lipid peroxidation, increases in taurine deficiency (Cakatay *et al*., 2003). In an earlier study, the rat liver MDA level was significantly reduced by age after 7 days treatment with 200 mg/kg/day taurine (Yildirim *et al*., 2007).

The present study reports that the administration of Nonylphenol cause on oxidative stress in blood in rats. The marker of lipid peroxidation MDA levels in blood, significantly increased in NF group, in agreement with the previous studies. However, the results in the present study also showed that, SOD activity and GSH concentrations significantly decreased in blood, by Nonylphenol intoxication, parallel to the previous studies. The results in the present study also showed that, plasma NOx concentrations was decreased in NF group. In this context, it is possible that the observed insufficiency in antioxidant activity could be due to direct modification of the antioxidant defenses by Nonylphenol. On the other hand, in this study NFT group was fed by Taurine. Taurine supplementation has affected the MDA concentration in blood of the rats during Nonylphenol toxication. The results in the present study also showed that the SOD activity and GSH concentrations, significantly increased in NFT group blood by adding 3% taurine in dirinking water. These results suggested that Taurine supplementation exhibited direct antioxidant properties by reducing basal MDA formation and protective antioxidant effect. Furthermore, this protective effect could be oving to its capability to stabilize biomembranes, to scavenge reactive oxygen species and to decrease the peroxidation of unsaturated membrane lipids (Banks *et al*., 1992). Taurine may also inhibit the lipid peroxidation by inducing GPx and SOD. Taurine could protect tissues against GSH pool depletion by preventing the decreases in of glutathione reductase activity (Rikans and Hornbrook, 1997). In the present study, it was also determined that the blood SOD activity was significantly increased in the NFT group compared to the NF group. Redmond *et al*. (1996) reported that taurine attenuates hepatocyte apoptosis and necrosis through inhibition of both NO and reactive oxygen intermediate. While, taurine acts directly as an antioxidant, its effects on NO may occur at the messenger RNA level. In the present study contrary to the this report, taurine supplementation increased plasma NOx concantration in NFT and T groups. Whereas plasma NOx levels decreased

in NF group in contrast to the other experimental groups. Depending on the acquired results, new studies should be carried out to understand this mechanism in details.

CONCLUSION

The study shows that, nonylphenol induced oxidative stress in rat blood by decreasing the activities of antioxidant enzymes and generation of free radicals in rats. Although, taurine treatment decreases the oxidative stress in nonylphenol-induced oxidative damage by maintaining the GSH recycling activity, increasing the SOD activity and free radical scavenging potential. Moreover, the results demonstrate that in animals exposed to Nonylphenol, taurine could provide great advantages against to side effects of nonlyphenol toxication. On the other hand, it was believed further studies should be carried out to determine the relationship between taurine, NO and nonlyphenol toxication. Consequently, taurine could be used as a potential antioxidant aganist nonylphenol toxication with its antioxidant properties.

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