Journal of Food and Drug Analysis, Vol. 16, No. 3, 2008, Pages 74-82 藥物食品分析 第十六卷 第三期

Effect of Taurine on Toxicity of Oxidized Cholesterol in Rats

YEN-HUNG YEH[1]*, MING-HSIUNG CHEN[2], YA-TING LEE[3], HUNG-SHENG HSIEH[4] AND DENG-FWU HWANG[2]

[1.] *Department of Nutrition and Health Science, Toko University, Chia-Yi, Taiwan, R.O.C.*
[2.] *Department of Food Science, National Taiwan Ocean University, Keelung, Taiwan, R.O.C.*
[3.] *Department of Beauty Science, Chienkuo Technology University, Changhua, Taiwan, R.O.C.*
[4.] *Department of Health and Nutrition Biotechnology, Asia University, Taichung, Taiwan, R.O.C.*

(Received: August 1, 2007; Accepted: November 7, 2007)

ABSTRACT

This research was aimed to study the effect of dietary taurine on the toxicity of oxidized cholesterol in male Wistar rats. The rats were divided into eight groups and fed different diets with or without supplement of 5% taurine and 3% oxidized cholesterol for 8 weeks. To evaluate effects of taurine at the same time, before diets and after diets in the food, after feeding diet with 3% oxidized cholesterol and 5% taurine at the same time, taurine could improve the decrease of body weight and the glutathione (GSH) level in the liver, and the increase of relative ratio of liver or kidney weight to body weight and thiobarbituric acid-reactive substances (TBARS) level in the liver of rats caused by oxidized cholesterol ($P < 0.05$). It also could inhibit the activities of aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP) in the plasma of rats caused by oxidized cholesterol ($P < 0.05$). It was also found that taurine possessed a good recovering effect and a short-term preventing effect the toxicity of oxidized cholesterol in rats. Judging from these data, on taurine may play an important role in diminishing the toxic effect of oxidized cholesterol in rats.

Key words: taurine, oxidized cholesterol, toxic effect, rats, liver function

INTRODUCTION

Cholesterol is found in foods of animal sources, for example, egg yolks, meat and cheese. Pure cholesterol is essential for cell survival, whereas even small amounts of oxidized cholesterol produce significant toxicity. Cholesterol is readily oxidized in common foods through exposure to oxygen and high temperature, ultraviolet irradiation and reaction with free radicals during processing or storage. Oxidized cholesterol exhibits deleterious biological activities including cytotoxicity, mutagenicity, carcinogenicity, atherogenicity, inhibition of sterol biosynthesis and modulation of immune function in many *in vitro* studies[1-4]. Research provides evidence that some cholesterol oxides are toxic and may facilitate the development of coronary artery disease and certain cancers.[1, 5-10]. Thus, dietary oxidized cholesterol seems to be a biologically deleterious agent on lipid metabolism; however, the regulation against oxidized cholesterol-induced untoward actions has not been explored until now.

Taurine (2-amino ethanesulfonic acid) is the major free intracellular amino acid present in many tissues and has various biological and physiological functions, including cell membrane stabilization[11], antioxidation[12], detoxification[13], osmoregulation[14], neuromodulation[15], and brain and retinal development[16]. Also, taurine plays an important role in lipid metabolism to produce the bile acid conjugates in the liver; that is, taurine increases the utilization of bile acid which is the degrading metabolite of cholesterol and participates in fat absorption[17]. A number of studies concerning the hypocholesterolemic action of taurine have been conducted using cholesterol-loading animals. Previous studies demonstrated that taurine had a cholesterol lowering effect in rats and mice, but not in rabbits[18-20]. In this study, the model was used for an evaluation of oxidized cholesterol on dietary protection of taurine at the same time, before diets and after diets in the rats was studied.

* Author for correspondence. Tel.: +886-5-3622-889;
Fax: +886-5-3622-899;
E-mail address: yhyeh@mail.toko.edu.tw (Y. H. Yeh).

MATERIALS AND METHODS

I. *Reagents*

Taurine was purchased from Dokui Chemical Company (Taiwan), purify of 99.5% to add of 5% in the feed. The corn oil was supplied from President Co. (Taiwan).

Journal of Food and Drug Analysis, Vol. 16, No. 3, 2008

II. *Preparation of Oxidized Cholesterol*

Cholesterol (99.9% purity, Wako Chemical, Osaka, Japan) was heated at 150°C for 12 h to produce oxidized cholesterol[21], a peroxide value (POV) of approximately 50.2 meq/kg oil, a content of the thiobarbituric acid reactive substances (TBARS) of 1.58 mg/kg oil and a content of the acid value (AV) 1.74 mg/g oil. The value of POV, AV and TBA in the oil was determined by AOAC method[22].

III. *Animals*

Male weanling Wistar rats were purchased from the National Laboratory Animal Center. They were kept in an air-conditioned room (23 ± 1°C, 50-60% humidity) lit for 12 hr/day (7 AM to 7 PM). Experimental protocol was approved by the Institutional Animal Care and Use Committee of Toko University. After acclimatizing for 2 wk with a commercial non-purified diet (rodent Laboratory Chow 5001, Purina Co., USA), 48 rats were divided into eight groups. Six rats in each group were assigned to receive an 8-wk period of one or two of four formulated diets (Table 1). The diets were synthesized as described previously by the American Institute of Nutrition[23] and included: basal diet (received the control diet), taurine diet (5% taurine in diet), oxidized cholesterol diet (3% oxidized cholesterol), and oxidized cholesterol+taurine diet (3% oxidized cholesterol+5% taurine). The concentration of taurine in fish read 5%[24], so 5% taurine was added in the experimental diets. The diet regimen used in each group was as follows. The oxidized cholesterol on dietary protection of taurine at the same time, before diets and after diets in the rats was studied. Dietary of taurine at the same time Group A: rats were fed with basal diet for 2 months. Group B: rats were fed with taurine diet for 2 months. Group C: rats were fed with oxidized cholesterol diet for 2 months. Group D: rats were fed with taurine+oxidized cholesterol diet for 2 months. Taurine after diets Group E: rats were fed with oxidized cholesterol diet for 1 month and then with taurine diet for 1 month. Taurine before diets Group F: rats were fed with oxidized cholesterol diet for 1 month and then with basal diet for 1 month. Group G: rats were fed with taurine diet for 1 month and then with oxidized cholesterol diet for 1 month. Group H: rats were fed with basal diet for 1 month and then with oxidized cholesterol diet for 1 month (Table 2). During the experimental period, water and food were always available. After feeding, all rats were weighed. Blood samples taken from the tail veins of the rats at 0, 2, 4, 6 and 8 weeks intervals were analyzed. The plasma of blood samples were collected by centrifugation (2000 g for 15 min) from blood and examined for aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP) activites. On the 8 th week, livers and kidneys of the rats were quickly excised and weighed. Both relative ratios of liver or kidney weight to body weight were obtained. The liver was stored at -40°C for glutathione (GSH) and TBARS determinations.

Table 1. Composition of the experimental diets for animal diet of taurine and oxidized cholesterol

Ingredient	Diets			
	Basel diet (%)	Taurine diet (%)	Oxidized cholesterol diet (%)	Tau+oxidized cholesterol diet (%)
Casein	20	20	20	20
Methionine	0.3	0.3	0.3	0.3
Cellulose	5	5	5	5
Corn oil	2	2	2	2
Cholesterol	3	3	0	0
Oxidized cholesterol	0	0	3	3
Choline	0.2	0.2	0.2	0.2
Mineral mix[a]	3.5	3.5	3.5	3.5
Vitamin mix[b]	1	1	1	1
Taurine	0	5	0	5
Corn starch	65	60	65	60

(a) Minerals per 100 g diet: NaCl 7.4 g, $K_2C_6H_5O_7$ H_2O 22g, K_2SO_4 5.2 g, $CaHPO_4$ 50 g, MgO 2.4 g, $FeC_6H_5O_7$ $5H_2O$ 0.6 g, $MnCO_3$ 0.35 g, $CuCO_3$ 30 mg, $CrK(SO_4)_2$ $12H_2O$ 55mg, $CoCl_2$ $6H_2O$ 10 mg, KI 1 mg, $ZnCO_3$ 160 mg.

(b) Vitamin per 100 g diet: thiamine 100 mg, riboflavin 150 mg, pyridoxine HCl 100mg, nicotinamide 1000 mg, D-panthenate 500 mg, folic acid 50 mg, vitamine B_{12} 0.1 mg, vitamin A 2.5×10^5 IU, vitamin E 100 mg, calciferol 2×10^4 IU, vitamin C 3.7×10^3 mg.

Table 2. The experimental diets in each group for 2 months

Months	Group							
	A	B	C	D	E	F	G	H
1	basal diet	taurine diet	oxidized cholesterol diet	taurine+oxidized cholesterol diet	oxidized cholesterol diet	oxidized cholesterol diet	taurine diet	basal diet
2	basal diet	taurine diet	oxidized cholesterol diet	taurine+oxidized cholesterol diet	taurine diet	basal diet	oxidized cholesterol diet	oxidized cholesterol diet

IV. *Assays of Enzymatic Activities*

The plasma was determined for AST, ALT and ALP activities by using enzymatic kit with Selectra Analyser (Merck Co. Ltd, Germany).

V. *Thiobarbituric Acid-Reactive Substances (TBARS) Production*

Lipid peroxidation activities in the liver were assayed by measurement of malondialdehyde (MDA), an end-product of peroxidized fatty acids, and thiobarbituric acid (TBA) reaction product. The sample of 20% liver homogenate was mixed with 1.0 mL 0.4% TBA in 0.2 N HCl and 0.15 mL 0.2% BHT in 95% ethanol. The samples were incubated in a 90°C water-bath for 45 min. After incubation, the TBAMDA adduct was extracted with isobutanol. The isobutanol extract was mixed with methanol (2:1) prior to injection into the system of high performance liquid chromatography (HPLC) on a Hitachi liquid chromatograph of Model L-6200 pump (Tokyo, Japan). The supernatant was examined by HPLC monitored by excitation at 515 nm and an emission at 550 nm on a Hitachi fluorescence detector of Model L-4000 (Tokyo, Japan)[25].

VI. *Levels of Glutathione (GSH) Measurement*

GSH reacts non-enzymatically with 5, 5'-dithiobis (2-nitrobenzoic acid) (DTNB) to yield glutathione disulfide (GSSG) and 2-nitro-5-thiobenzoic acid (TNB). GSSG is then reduced enzymatically by NADPH and glutathione reductase (GR) to regenerate GSH. Concentrations of DTNB, NADPH and GR were chosen such that the rate of the overall reaction is linearly proportional to the concentration of total GSH. The rate of formation of TNB was followed spectrophotometrically, and the assay was calibrated using standards. If the sample was reacted with 2-vinylpyridine, GSH is derivatized, and only GSSG can be detected during subsequent assay[26].

VII. *Statistical Analysis*

Statistical analysis for differences among rats in the experimental groups was performed by the 2-way analysis of variance procedure and Duncan's new multiple range tests[27]. A P value < 0.05 was considered statistically significant.

RESULTS

The effects of taurine and oxidized cholesterol on the growth of rats are shown in Figure 1. After 8 wk of feeding, the weight of rats fed without oxidized cholesterol diet (group A and group B) was significantly gained among all tested groups ($P < 0.05$). This indicated that oxidized cholesterol retarded the growth of rats. The weight of rats fed with oxidized cholesterol diet for 2 months (group C), was less than that of rats fed with taurine+oxidized cholesterol diet for 2 months (group

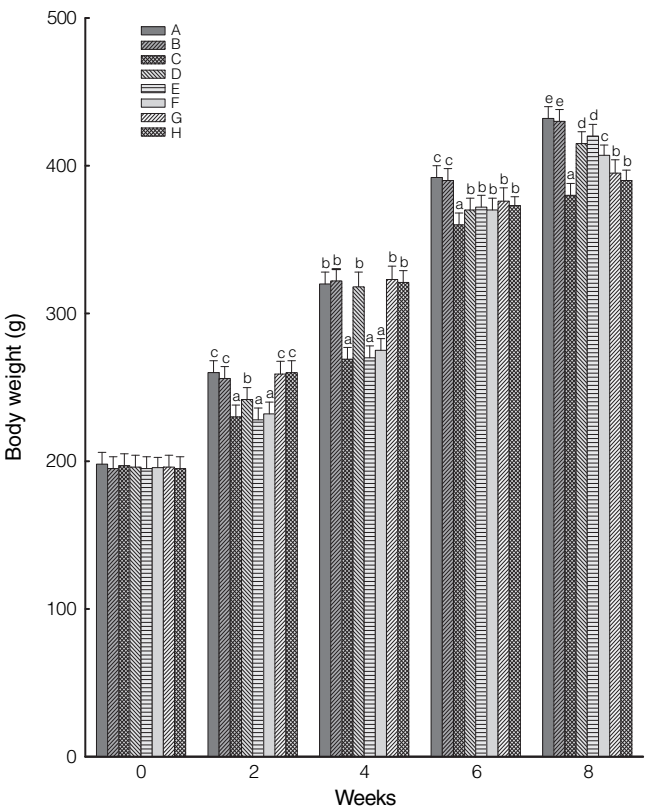

Figure 1. Effect of oxidized cholesterol and taurine on the growth of rats. a-e: values in the same week with different superscript are significantly different ($P < 0.05$).

Journal of Food and Drug Analysis, Vol. 16, No. 3, 2008

D) ($P < 0.05$). This meant that taurine reduced the toxicity of oxidized cholesterol on the weight of rats. Rats fed with oxidized cholesterol diet for 1 month and then with taurine diet for 1 month (group E), were heavier than rats fed with oxidized cholesterol diet for 1 month and then with basal diet for 1 month (group F). This showed that taurine exhibited a recovering effect on the toxicity of oxidized cholesterol. However, the weight of rats fed with taurine diet for 1 month and then with oxidized cholesterol diet for 1 month (group G) was not significantly different from that of rats fed with basal diet for 1 month and then with basal diet for 1 month (group H) ($P < 0.05$), meaning that taurine had no preventing effect from the toxicity of oxidized cholesterol on the weight of rats. The effects of taurine and oxidized cholesterol on the relative ratios of liver and kidney weight to body weight in rats are shown in Figure 2. After 8 wk of feeding, the ratios of liver and kidney weight to body weight of rats fed with oxidized cholesterol diet for 2 months (group C) were more significantly increased than those of rats fed with control diet (group A), taurine diet (group B) and taurine+oxidized cholesterol diet (group E) ($P < 0.05$). On the other hand, the ratio of liver or kidney weight to body weight in rats fed with taurine+oxidized cholesterol diet (group E) was not significantly different from those of rats, fed with control diet (group A) and taurine diet (group B) ($P < 0.05$). This meant that taurine might reduce the toxicity of oxidized cholesterol in the rats based on the relative ratio of liver or kidney to body weight of rats. The ratios of liver or kidney weight to body weight in rats fed oxidized cholesterol diet for 1 month and then with taurine diet for 1 month (group E) was significantly less than those of rats fed with oxidized cholesterol diet for 1 month and then with basal diet for 1 month (group F) ($P < 0.05$), indicating that taurine exhibited a recovering effect on the toxicity of oxidized cholesterol. Meanwhile, the ratios of liver or kidney weight to body weight in rats fed with taurine diet for 1 month and then with oxidized cholesterol diet for 1 month (group G) was not significantly different from those of rats fed with basal diet for 1 month and then with basal diet for 1 month (group H) ($P < 0.05$). This meant that taurine had no preventing effect from the toxicity of oxidized cholesterol based on the ratio of liver or kidney weight to body weight in rats. The effects of oxidized cholesterol and taurine on the activities of AST, ALT and ALP in the plasma were, respectively, shown in Figures 3-5.

It was found that the activities of ALT and ALP in the plasma of rats fed oxidized cholesterol diet for 2

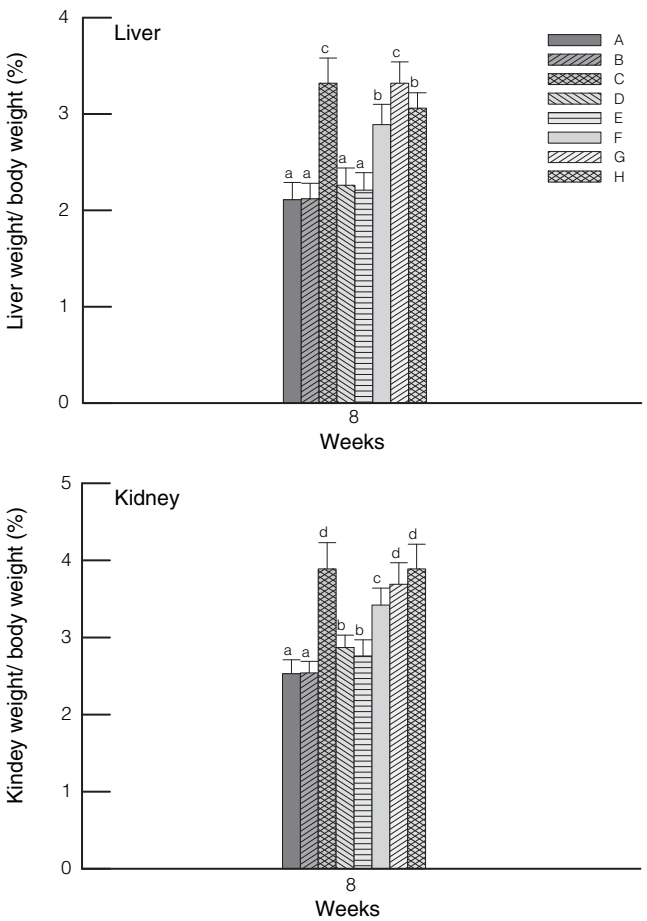

Figure 2. Effect of oxidized cholesterol and taurine on the ratios of liver and kidney weight to body weight in rats. a-d: values in the same week with different superscript are significantly different ($P < 0.05$).

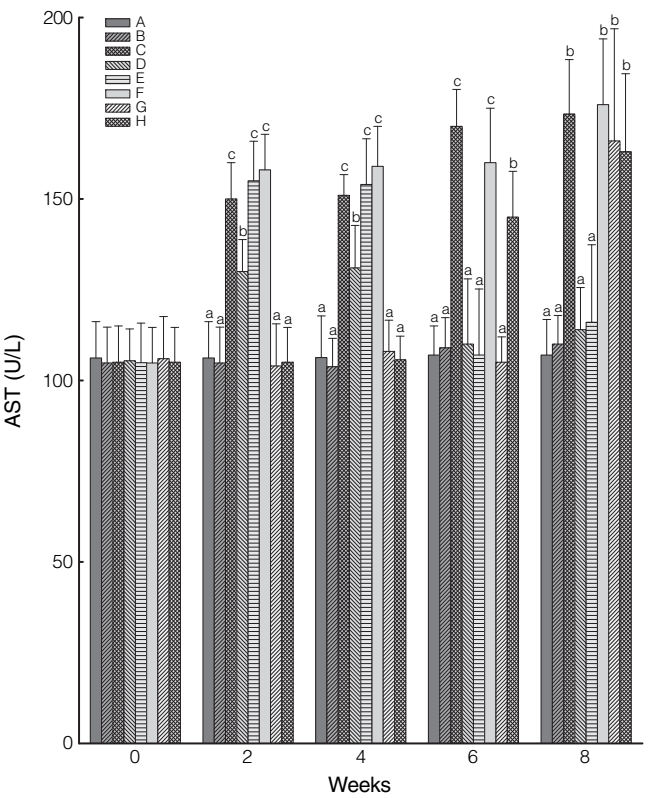

Figure 3. Effect of oxidized cholesterol and taurine on the activity of aspartate transamine (AST) in the plasma of rats. a-c: values in the same week with different superscript are significantly different ($P < 0.05$).

months (group C) were the most significantly elevated among all tested groups (Figure 4 and Figure 5) ($P < 0.05$). The activities of AST, ALT and ALP in those rats fed taurine+oxidized cholesterol diet for 2 months (group D) were significantly less than those of rats fed with oxidized cholesterol diet for 2 months (group C) ($P < 0.05$), which indicated that taurine showed a reducing effect on the toxicity of oxidized cholesterol based on the activities of AST, ALT and ALP in the plasma of rats. The activities of AST, ALT and ALP in the plasma of rats fed oxidized cholesterol diet for 1 month and then with taurine diet for 1 month (group E) were significantly less than those of rats, fed with oxidized cholesterol diet for 1 month and then with basal diet for 1 month (group F) ($P < 0.05$). This indicated that taurine exerted a recovering effect on the toxicity of oxidized cholesterol. Furthermore, the activities of ALT, AST and ALP in the plasma of rats fed the taurine diet for 1 month and then with oxidized cholesterol diet for 2 wk (group G) were significantly less than those of rats fed with basal diet for 1 month and then with oxidized cholesterol diet for 2 wk (group H) ($P < 0.05$). However, ALT and ALP activities in the plasma of rats fed taurine diet for 1 month and then with oxidized cholesterol diet for 1 month (group G) were also less than those of rats fed the taurine diet for 1 month and then with oxidized cholesterol diet for 1 month (group H) ($P < 0.05$), indicating that taurine exhibited a short-term preventing effect from the toxicity of oxidized cholesterol on the activities of AST, ALT and ALP in the plasma of rats. The effects of taurine and oxidized cholesterol based on the concentrations of TBARS and GSH in the liver of rats are shown in Figure 6. After 8 wk of feeding, the level of TBARS in the liver of rats, fed with oxidized cholesterol diet for 2 months (group C) and fed with oxidized cholesterol diet for 1 month and then with basal diet for 1 month (group H) was higher than that of other groups ($P < 0.05$). This indicated that taurine revealed a reducing effect on the toxicity of oxidized cholesterol based on the concentration of TBARS. The level of TBARS in the liver of rats fed the oxidized cholesterol diet for 1 month and then the taurine diet for 1 month (group E) was less than that of rats fed with oxidized cholesterol diet for 1 month and then with basal diet for 1 month (group F), indicating that taurine exerted a recovering effect on the toxicity of oxidized cholesterol. No difference was found between levels of TBARS in the liver of rats in group G (fed with taurine diet for 1 month and then with oxidized cholesterol diet for 1 month) and group H (fed with basal diet for 1 month and then oxidized cholesterol for 1 month) ($P < 0.05$), showing that taurine did not have a preventing effect from the toxicity of oxidized cholesterol based

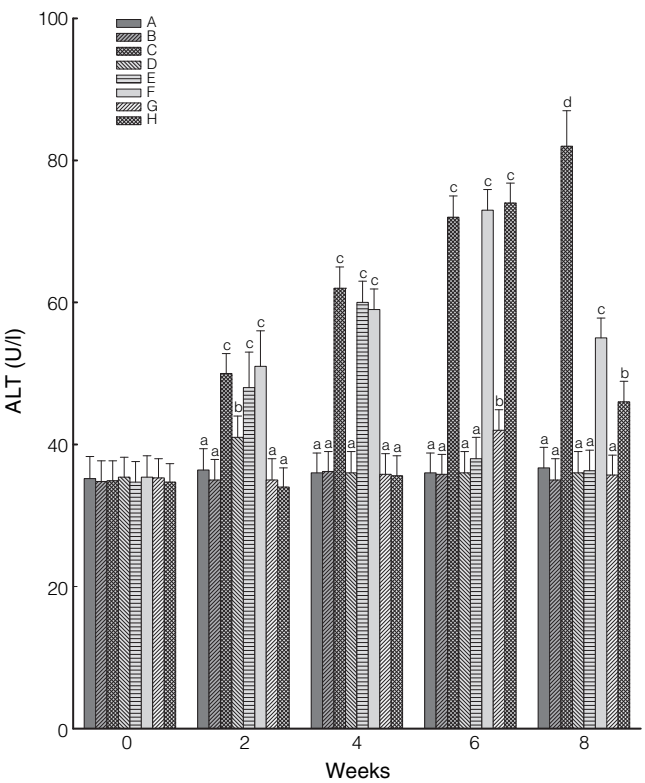

Figure 4. Effect of oxidized cholesterol and taurine on the activity of alanine transamine (ALT) in the plasma of rats. a-d: values in the same week with different superscript are significantly different ($P < 0.05$).

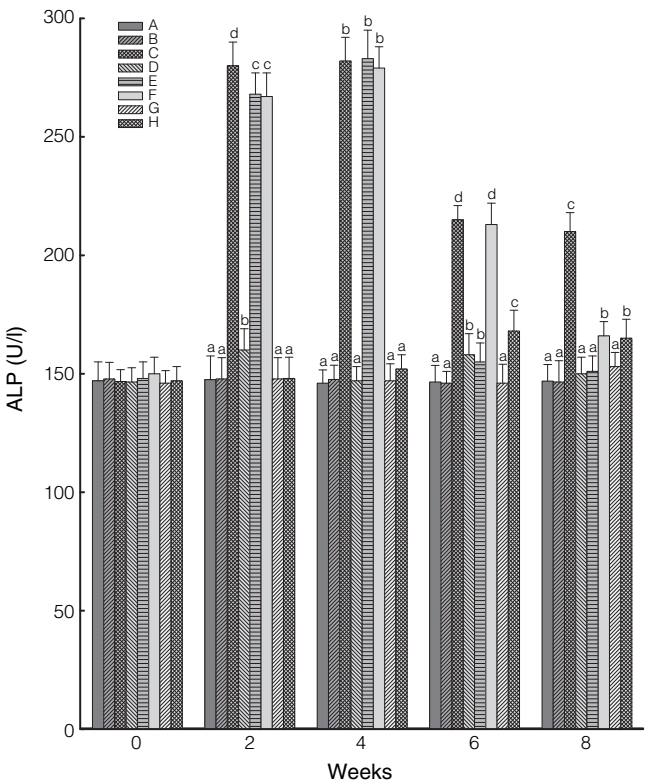

Figure 5. Effect of oxidized cholesterol and taurine on the activity of alkaline phosphatase (ALP) in the plasma of rats. a-d: values in the same week with different superscript are significantly different ($P < 0.05$).

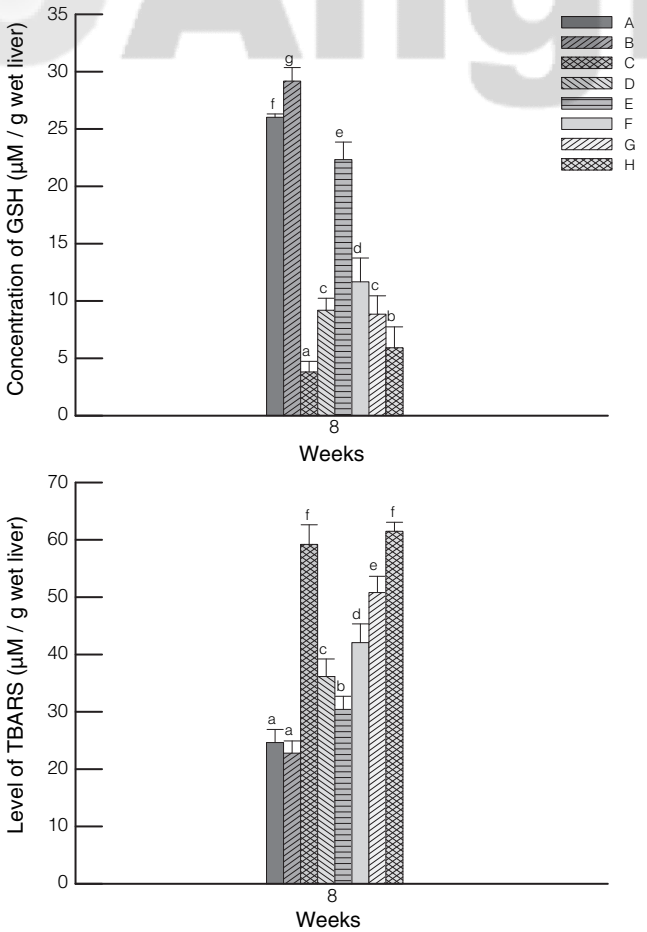

Figure 6. Effect of oxidized cholesterol and taurine on the concentration of glutathione (GSH) and level of thiobarbituric acid reactive substances (TBARS) in the liver of rats. a-g: values in the same week with different superscript are significantly different ($P < 0.05$).

on the TBARS level. The concentration of GSH in the liver of rats fed with taurine diet for 2 months (group B) was the highest among all tested groups (Figure 6), meaning that taurine played a role in increasing the GSH level of liver in rats. The concentration of GSH in the liver of rats fed the oxidized cholesterol diet for 1 month and then basal diet for 1 month (group E) was less than that of rats fed the oxidized cholesterol diet for 1 month and then the taurine diet for 1 month (group F) ($P < 0.05$) indicated that taurine exhibited a recovering effect on the toxicity of oxidized cholesterol. The concentration of GSH in the liver of rats fed taurine diet for 1 month and then oxidized cholesterol diet for 1 month (group G) was higher than that of rats fed with basal diet for 1 month and then the oxidized cholesterol diet for 1 month (group H) ($P < 0.05$), showing that taurine revealed a preventing effect from the toxicity of oxidized cholesterol. But this functional effect was low because the level of GSH in the liver of rats was increased slightly. Judging from the above data, taurine might play an important role in reducing the toxic effect of oxidized cholesterol in rats. Taurine could increase the body weight of rats and GSH level of liver in rats, and decrease the enlargement of liver and kidney, the enzymatic activities of AST, ALT and ALP in the plasma, and TBARS level in the liver of rats. Taurine showed a good function in reducing toxicity of oxidized cholesterol in rats when the rats fed diet with the supplement of oxidized cholesterol and taurine at the same time, or fed diet with the supplement of oxidized cholesterol and then taurine. Taurine also showed a short-term preventing effect in reducing the toxicity of oxidized cholesterol.

DISCUSSION

In this study, the activities of AST, ALT and ALP in the plasma of rats were shown to be significantly affected by oxidized cholesterol. In the clinical plasma examination, AST, ALT and ALP activities in plasma serve as biomarkers for liver functions[28], The activities of AST for 8 wk were most significantly elevated meaning that oxidized cholesterol might injure liver function. Taurine significantly reduced the enzymatic activities of AST, ALT and ALP in the plasma of rats, indicating that the liver injury by oxidized cholesterol could be ameliorated by taurine. Wright *et al.*[29] pointed out that the function of taurine for preserving liver cells was presented by the high content of taurine in cell membrane. In the experimental period, the food consumption of rats was found to significantly decrease in those groups of rats fed with oxidized cholesterol diet. However, it is accompanied by adverse side effects such as nephrotoxicity and hepatotoxicity[3]. The palatability of the diet might also be affected. Therefore, the oxidized cholesterol diet may induce liver injury and reduce diet palatability in rats. TBARS is an end-product of lipid peroxidation. The level of TBARS in the liver was increased when the rats were fed oxidized cholesterol. This means that the liver injury caused by feeding with oxidized cholesterol was due to the induction of the lipid peroxidation of liver cells. The level of TBARS in the liver of rats was significantly reduced when the rats were fed with the supplement of taurine. This result is the same as that reported previously[30-34]. Therefore, it is reasonable to assume that taurine may act as a good scavenger in reducing the production of lipid peroxidation induced by drugs[30], heavy metal[31], vitamin A [32] and oxidized cholesterol. Meanwhile, the function of GSH to protect biological organisms from xenobiotic injuries is well known[25, 35-37].

Lipid peroxidation is a chemical mechanism capable of disrupting the structure and function of the biological membranes that occurs as a result of free radical attacking on lipids. When reactive oxygen species (ROS) begin to accumulate, hepatic cells exhibit a defensive mechanism by various antioxidant enzymes. The main detoxifying systems for peroxides are catalase and GSH[38]. Catalase

is an antioxidant enzyme, which destroys H_2O_2 that can form a highly reactive hydroxyl radical in presence of iron as a catalyst[39]. By participating in the glutathione redox cycle, GSH together with GSH-Px convert H_2O_2 and lipid peroxides to non-toxic products. Reduced activity of one or more antioxidant systems due to the direct toxic effect of oxidized cholesterol leads to increased lipid peroxidation, oxidative stress, and hepatotoxicity. In the current study, oxidized cholesterol depleted GSH reservoir and reduced catalase and GSH-Px activities. These results are in harmony with other investigations[40]. For example, oxidized cholesterol induced hepatotoxicity was exacerbated by GSH depletion. In the current study, the depletion of GSH reservoir can account for the inhibition of GSH-Px activity. In addition, high levels of peroxides may explain catalase activity inhibition[41].

Taurine supplementation in our study significantly mitigated oxidized cholesterol induced oxidative stress and hepatotoxicity. This was clearly manifested by the improvement in all the biochemical variables determining oxidized cholesterol hepatotoxicity (Figures. 3-6). In addition, taurine inhibited lipid peroxidation, diminished the decrease in catalase and GSH-Px activities, and abrogated GSH depletion induced by oxidized cholesterol.

Consistent with our finding, taurine has been demonstrated to protect against hepatotoxicity induced by several free radicals generating insults including lipopolysaccharide[42], acetaminophen[43], thioacetamide[44], and ischemia/reperfusion[45]. Moreover, the antioxidant effect of taurine was shown in other organs including the lung[46], kidney[47] and heart[48]. In addition, other antioxidants have been shown to reduce oxidized cholesterol induced hepatotoxicity.

Taurine has been demonstrated to function as a direct antioxidant that scavenges or quenches oxygen free radicals, thus inhibiting lipid peroxidation, and as an indirect antioxidant that prevents the increase in membrane permeability resulting from oxidant injury in many tissues including liver[45]. Taurine might stimulate s-nitrosylation of GSH producing s-nitrosoglutathione, which is approximately 100 times more potent than the classical GSH. In addition, *s*-nitrosylation of cysteine residues by nitrosoglutathione can inactivate caspase-3, thus preventing hepatic cell apoptosis[49]. Moreover, taurine might lessen oxidized cholesterol induced oxidative injury either by forming chloramines, known to be more stable and less reactive molecules, with hypochlorous (HOCl) and HOCl-metalloproteins, or by binding free metal ions such as Fe^{2+} to its sulfonic acid group[50,51].

As an indirect antioxidant, taurine has been proposed as a membrane stabilizer that can maintain membrane organization, prevent ion leakage and water influx, and subsequently, avoid cell swelling[45,48]. The stabilizing effect of taurine on cellular membrane has been suggested to be associated with the interaction between taurine and polyunsaturated fatty acids in the membrane, which results in increasing in the affinity of taurine for its carrier transport and the interaction between taurine and the sites related to anion transport and water influx. This property of taurine may also partly account for its protection against oxidized cholesterol induced hepatocyte necrosis.

On the other hand, taurine can also function as a regulator of intracellular calcium homeostasis[13] that can be disturbed due to oxidized cholesterol toxicity. Taurine has been shown to protect against endothelial cell death by modulating intracellular calcium fluxes[52]. Finally, taurine may ameliorate oxidized cholesterol induced hepatic injury by enhancing the activities of endogenous antioxidants. Support for this concept comes from our results, which show that taurine promoted a remarkable significant increase in hepatic GSH level and GSH-Px and catalase activities. This could be attributed to the role of taurine in maintaining a normal IGF-I level[53] and its antioxidant action against lipid peroxidation, thus conserving the internal antioxidants system. The stimulatory effect of taurine on endogenous antioxidants was reported by others[47,54]. Together, the results of the present study demonstrate that administration of taurine has a therapeutic role in preventing cyclosporine-induced hepatotoxicity, possibly through its unique cytoprotective properties such as antioxidant activity.

In conclusion, we suggest that: (a) the imbalance between production of oxygen free radicals and the endogenous antioxidant defense system, as a result of the effect of oxidized cholesterol, is the main mechanism responsible for peroxide accumulation and hepatotoxicity; and (b) taurine reduces the oxidative stress through the inhibition of lipid peroxidation (a widely known mechanism).

REFERENCES

1. Bösinger, S., Luf, W. and Brandl, E. 1993. Oxysteroles: their occurrence and biological effects. Int. Dairy J. 3: 1-33.
2. Finocchiaro, E. T. and Richardson, T. 1983. Sterol oxides in food stuffs: a review. J. Food Prot. 46: 917-925.
3. Paniangvait, P., King, A. J., Jone, A. D. and German, B. G. 1995. Cholesterol oxides in foods of foods of animal origin. J. Food Sci. 52: 57-62.
4. Peng, S. K. and Taylor, C. B. 1984. Cholesterol autoxidation, health and arteriosclerosis. World Rev. Nutr. Diet 34: 653-659.
5. Maercker, G. 1987. Cholesterol autoxidation-current status. J. Am. Oil Chem. Soc. 64: 388-392.
6. Chow, C. K. 1992. Biological effects of oxidized fatty acids. In fatty acids in foods and heir health implications. pp. 689-705. Marcel Dekker Inc, New York.
7. Morin, R. J. and Peng, S. K. 1991. Cholesterol oxides in plasma and tissues. In biological effects of cholesterol oxides. pp. 89-101. CRC Press, Ann Arbor.

8. Morin, R. J., Hu, B., Peng, S. K. and Sevanian, A. 1992. Cholesterol oxidation and cancer. In Biological Effects of Cholesterol Oxides. pp. 191-202. CRC Press, Ann Arbor.
9. Haumann, B. F. 1993. Health implications of lipid oxidation. Inform. 4: 800-810.
10. Kubow, S. 1993. Lipid oxidation products in food and atherogenesis. Nutr. Rev. 51: 33-40.
11. Pasantes-Morales H., Wright, C. E. and Gaull, G. E. 1985. Taurine protection of lymphoblastoid cells from iron-ascorbate-induced damage. Biochem. Pharmacol. 34: 2205-2207.
12. Nakamura, T., Ogasawara, M., Nemoto, M. and Yoshida, T. 1993. The protective effect of taurine on the biomembrane against damage produced by oxygen radicals. Biol. Pharm. Bull. 16: 970-972.
13. Huxtable, R. J. 1992. Physiological actions of taurine. Phys. Rev. 72: 101-163.
14. Thurston, J. H., Hauhart, R. E. and Dirgo, J. A. 1980. A role in osmotic regulation of mammalian brain and possible clinical significance. Life Sci. 26: 1561-1568.
15. Kuriyama, K. 1980. Taurine as a neuromodulator. Fed. Proc. 39: 2680-2684.
16. Sturman, J.A. 1986. Nutritional taurine and central nervous system development. Ann. N.Y. Acad. Sci. 477: 196-213.
17. Yamanaka, Y., Tsuji, K. and Ichikawa, T. 1986. Stimulation of chenodeoxycholic acid excretion in hypercholesterolemic mice by dietary taurine. J. Nutr. Sci. Vitaminol. 32: 287-296.
18. Gandhi, V. M., Cherian, K. M. and Mulky, M. J. 1992. Hypolipidemic action of taurine in rats. Indian J. Exp. Biol. 30: 413-417.
19. Mochizuki, H., Takido, J., Oda, H. and Yokogoshi, H. 1999. Improving effect of dietary taurine on marked hypercholesterolemia induced by a high-cholesterol diet in streptozotocin-induced diabetic rats. Biosci. Biotechnol. Biochem. 63: 1984-1987.
20. Yokogoshi, H., Mochizuki, H., Nanami, K., Hida, Y., Miyachi, F. and Oda, H. 1999. Dietary taurine enhances cholesterol degradation and reduces serum and liver cholesterol concentrations in rats fed a high-cholesterol diet. J. Nutr. 129: 1705-1712.
21. Osada, K., Kodama, T., Noda, S., Yamada, K. and Sugano, M. 1995. Oxidized cholesterol modulates age-related change in lipid metabolism in rats. Lipids 30: 405-413.
22. AOAC (Association of Official Analytical Chemists). 1990. Official Methods of Analysis. 15th ed. pp. 242-273. Helrich, K. ed. AOAC, Washington, D. C.
23. American Institute of Nutrition. 1977. Report of the American Institute ad hoc committee on standards for nutritional studies. J. Nutr. 107: 1340-1348.
24. Konosu, S. and Yamaguchiv, K. 1982. The flavor components in fish and shellfish. In Chemistry and Biochemistry of Marine Food Products. Martin, I. and Roy, E. ed. pp. 367-385. Avi, Westport.
25. Tatum, V. L., Changchit, C. and Chow, C. K. 1990. Measurement of malondialdehyde by high performance liquid chromatography with fluorescence detection. Lipids 25: 226-229.
26. Griffith, O. W. 1980. Determination of glutathione and glutathione disulfide using glutathione reductase and 2- vinylpyridine. Anal. Biochem. 106: 207-217.
27. Puri, S. C. and Mullen, K. 1980. Multiple comparisons. In Applied statistics for food and agricultural scientists. pp.146-162. Hall, G. K. ed. Medical Publishers, Boston.
28. Ronald, L. and Koretz, M. D. 1992. Chronic hepatitis: science and superstition. Current Hepatology. Gitnick, G. ed. Mosby-Year, Chicago.
29. Wright, C. E., Tallan, H. H. and Lin, Y. Y. 1986. Taurine: Biological update. Ann. Rev. Biochem. 55: 427-453.
30. Alvarez, J. G. and Storey, B. T. 1983. Taurine, hypotaurine, epinephrine and albumin inhibit lipid peroxidation in rabbit spermatozoa and protect against loss of motility. Biol. Rep. 29: 548-555.
31. Hwang, D. F., Wang, L. C. and Cheng, H. M. 1998. Effect of taurine on toxicity of copper in rats. Food Chem. Toxicol. 36: 239-244.
32. Yeh, Y. H., Lee, Y. T., Hsieh, H. S. and Hwang, D. F. 2008. Effect of taurine on toxicity of vitamin A in rats. Food Chem. 106: 260-268.
33. Tadolini, B., Gianfrance, P., Gavino, G. P., Federico, B. and Flavia, F. 1995. Effect of taurine and hypotaurine on lipid peroxidation. Biochem. Biophys. Res. Commun. 213: 820-826.
34. Wang, L. C., Hwang, D. F., Jeng, S. S. and Cheng, H. M. 1997. Effect of high dose of dietary taurine on toxicity of lead in rats. J. China. Agric. Chem. Soc. 35: 612-619.
35. Casini, A. F., Pompella, A. and Comporti, M. 1985. Liver glutathione depletion induced by bromobenzene, isodobenzene and diehylmaleate poisoning and its relation to lipid peroxidation and necrosis. Am. J. Pathol. 118: 225-237.
36. Maellaro, E., Casini, A. F., Bello, B. D. and Comporti, M. 1990. Lipid peroxidation and antioxidant systems in the liver injury produced by gluthathione depleting agents. Biochem. Pharmacol. 39: 1513-1521.
37. Meister, A. and Anderson, M. E. 1983. Glutathione. Ann. Rev. Biochem. 52: 711-760.
38. Meister, A. 1983. Selective modification of glutathione metabolism. Science 22: 472-478.
39. Gutteridg, J. M. C. 1995. Lipid peroxidation and antioxidant as biomarkers of tissue damage. Clin. Chem. 14: 1819-1828.
40. Al Khader, A., Al Sulaiman, M., Kishore, P. N., Morais, C. and Tariq, M. 1996. Quinacrine attenuates cyclosporine-induced nephrotoxicity in rats. Transplantation 62: 427-435.
41. Ghadermarzi, M. and Moosavi-Movahedi, A. A. 1996. Determination of the kinetic parameters for the "suicide substrate" inactivation of bovine liver catalase

by hydrogen peroxide. J. Enzyme Inhib. 10: 167-175.
42. Kim, S. K. and Kim, Y. C. 2002. Attenuation of bacterial lipopolysaccharide-induced hepatotoxicity by betaine or taurine in rats. Food Chem. Toxicol. 40: 545–549.
43. Waters, E., Wang, J. H., Redmond, H. P., Wu, Q. D., Kay, E. and Bouchier-Hayes, D. 2001. Role of taurine in preventing acetaminophen-induced hepatic injury in the rat. Am. J. Physiol. Gastrointest. Liver Physiol. 280: G1274-G1279.
44. Dogru-Abbasoglu, S., Kanbagli, O., Balkan, J., Cevikbas, U., Aykac-Toker, G. and Uysal, M. 2001. The protective effect of taurine against thioacetamide hepatotoxicity of rats. Hum. Exp. Toxicol. 20: 23-27.
45. Chen, Y. X. 1993. Protective action of taurine on ischemiareperfusion liver injury in rats and its mechanisms. Chin. Med. J. Engl. 73: 276-279.
46. Banks, M. A., Porter, W. D., Martin, W. G. and Castranova, V. 1992. Taurine protects against oxidant injury to rat alveolar pneumocytes. Adv. Exp. Med. Biol. 315: 341-354.
47. Saad, S. Y. and Al-Rikabi, A. C. 2002. Protection effects of taurine supplementation against cisplatin-induced nephrotoxicity in rats. Chemotherapy 48: 42-48.
48. Milei, J., Ferreira, R., Llesuy, S., Forcada, P., Covarrubias, J. and Boveris, A. 1992. Reduction of reperfusion injury with preoperative rapid intravenous infusion of taurine during myocardial revascularization. Am. Heart J. 123: 339-345.
49. Chiueh, C. C. and Rauhala, P. 1999. The redox pathway of snitrosoglutathione. Free Radic. Res. 31: 641-650.
50. Trachtman, H., Del Pizza, R. and Futterweit, S. 1992. Taurine attenuates renal disease in chronic aminonucleoside nephropathy. Am. J. Physiol. 262: F117-F123.
51. Schuller-Levis, G., Quinn, M. R., Wright, C. and Park, E. 1994. Taurine protects against oxidant-induced lung injury: possible mechanisms of action. Adv. Exp. Med. Biol. 359: 31-39.
52. Wang, J. H., Redmond, H. P., Watson, R. W. G., Condron, C. and Bouchier-Hayes, D. 1996. The beneficial effect of taurine on the prevention of human endothelial cell death. Shock 6: 331-338.
53. Dawson, Jr. R., Liu, S., Eppler, B. and Patterson, T. 1999. Effects of dietary taurine supplementation or deprivation in aged male Fischer 344 rats. Mech. Ageing Dev. 107: 73-91.
54. Erdem, A., Gundogan, N. U., Usubutun, A., Kiine, K., Erdem, R. S., Kara, A. and Bozkurt, A. 2000. The protective effect of taurine against gentamicin-induced acute tubular necrosis in rats. Nephrol. Dial. Transplant. 15: 1175-1182.