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Effect of taurine on toxicity of vitamin A in rats

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Abstract

A study was undertaken to investigate the effect of taurine on the toxicity of vitamin A in male wistar rats. The rats were divided into six groups and fed different diets with or without supplements of 5% taurine and 25,000–50,000 (IU) vitamin A for 2 months. It was found that the body weight of rats, the ratios of liver and kidney weight to body weight, and the level of glutathione in the liver were decreased with increasing the dose of vitamin A. The levels of vitamin A in the liver and kidney, the levels of thiobarbituric acid-reactive substances (TBARS) in the plasma and liver, the activities of aspartate transaminase (AST) and alanine transaminase (ALT) in the plasma, and the levels of blood urea nitrogen (BUN) and creatinine in the plasma of rats were increased with the increasing dose of vitamin A. Hence, symptoms of vitamin A toxicity in rats included loss of body weight, hepatotoxicity and nephrotoxicity. However, these toxic effects of vitamin A were significantly reduced when the rats were fed the diet with the supplement of taurine. Furthermore, the level of vitamin A in the serum of rats treated with taurine and vitamin A was higher than that of rats treated with vitamin A alone. This indicated that taurine might play a role in reducing the toxic effect of vitamin A in rats.

Keywords: Vitamin A; Taurine; Toxicity; Hepatotoxicity; Nephrotoxicity

1. Introduction

Vitamin A is an essential nutrient for humans because it cannot be synthesized de novo within the body. The term vitamin A used generically for all β-ionone derivates (other than carotenoids) that have the biological activity of all-trans retinol. Forms of vitamin A include retinol, retinal (also called retinaldehyde), and various retinyl esters (Sauberlich et al., 1974). Retinoic acid can perform some but not all of the biological functions of vitamin A. Vitamin A toxicity is a well-described medical condition with a multitude of potential presenting symptoms and signs. In the past, most cases of systemic and hepatic toxicity due to vitamin A resulted from excessive ingestion of animal liver with its enormous quantities of vitamin A. This has been recognized for more than 50 years (Rodahl & Moore, 1943). The main clinical features of vitamin A poisoning are fever, anorexia, nausea, vomiting, headache, drowsiness, skin changes, papilledema, skeletal pain, hair loss, pseudotumor cerebri, liver disease, and psychiatric complaints (Shekelle, Lepper, & Liu, 1981). To date, many cases of hepatic injury associated with the clinical use of vitamin A have been reported in the United States and Western Europe (Elias & Williams, 1981; Josephs, 1944; Stimson, 1961), but cases resulting from excessive intake of yellow–green vegetables such as carrots and pumpkin are rare (A de Francisco, Zaman, Chowdhury, Chakraborty, & Yunus, 1995; Hathcock et al., 1990; Herbert, 1982; Kransinki et al., 1989; Leo & Lieber, 1988). Most cases of vitamin A poisoning are a result of excessive vitamin A supplementation or accidental ingestion of vitamin A. Vitamin A poisoning cases are rarely seen today in Taiwan where the inhabitants often eat marine foods. It is well known that marine foods, especially mollusks, contain high

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amounts of taurine (Konosu & Yamaguchi, 1982; Sakaguchi & Muratz, 1989). Taurine is a sulphur containing amino acid that conjugates with bile acids in the liver (Jacobsen & Smith, 1968), and is an agent for treating the fat soluble vitamins intoxification. It has been reported that taurine might possess a protective action against drug-induced injuries (Hamaguchi et al., 1988; Tokunaga, Yoneda, & Kuriyama, 1979). Taurine may play an important

Table 1
Composition of the experimental diet in each group for test vitamin A and taurine

Ingredient (%)	Diets[a] control	Taurine	Vitamin A 25,000	Tau + Vit A 25,000	Vitamin A 50,000	Tau + Vit A 50,000
Sucrose	20	20	20	20	20	20
Casein	35	35	35	35	35	35
Corn starch	30	25	30	25	30	25
Cellulose	5	5	5	5	5	5
Corn oil	5	5	5	5	5	5
Methionine	0.3	0.3	0.3	0.3	0.3	0.3
Choline	0.2	0.2	0.2	0.2	0.2	0.2
AIN mineral mix	3.5	3.5	3.5	3.5	3.5	3.5
AIN vitamin mix	1	1	1	1	1	1
Taurine	0	5	0	5	0	5
Vitamin A	0	0	25,000	25,000	50,000	50,000

[a] Taurine: 5% taurine in diet; vitamin A 25,000: 25,000 (IU) vitamin A in diet; Tau + vitamin A 25,000: 5% taurine and 25,000 (IU) vitamin A in diet; vitamin A 50,000: 50,000 (IU) vitamin A in diet; Tau + vitamin A 50,000: 5% taurine and 50,000 (IU) vitamin A in diet.

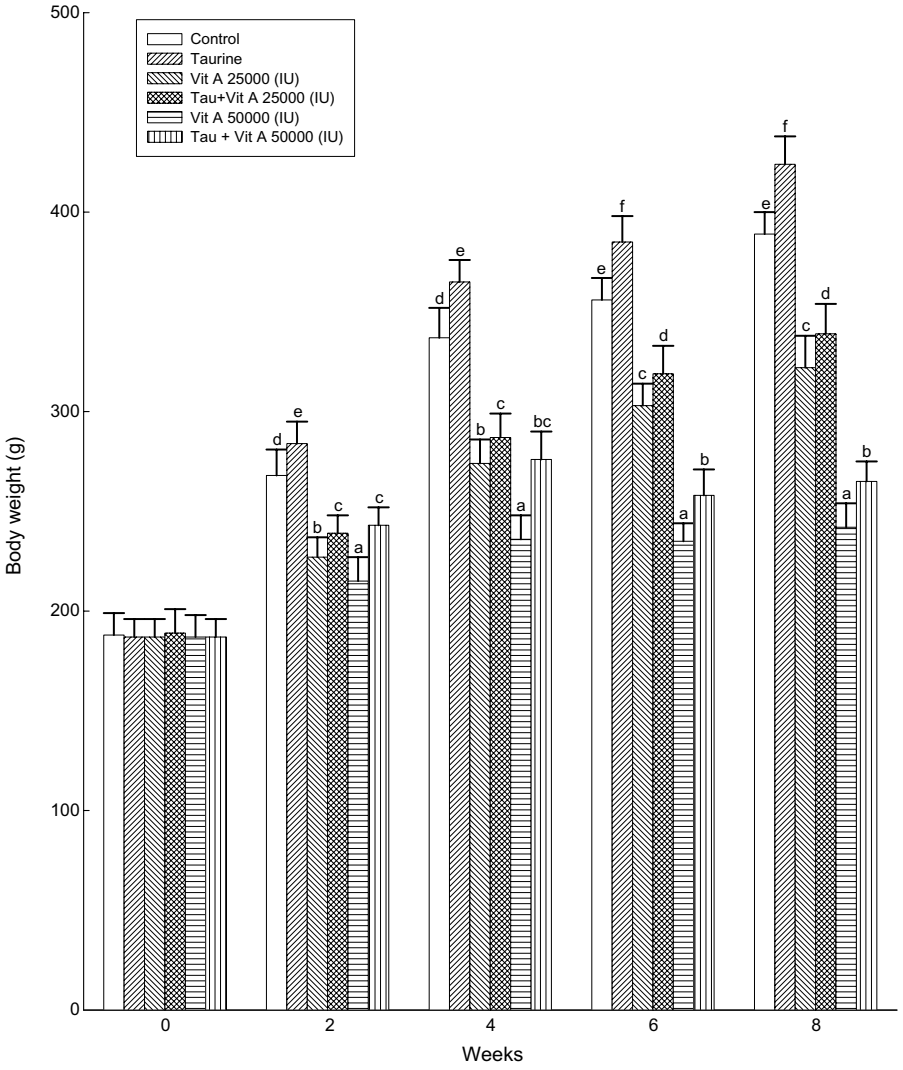

Fig. 1. Effect of vitamin A and taurine on the body weight of rats.

role in reducing the toxic effect of copper, cadmium, lead, and oxidized fish oil in rats (Hwang, Hour, & Cheng, 2000; Hwang & Wang, 2001; Hwang, Wang, & Cheng, 1998; Wang, Hwang, Jeng, & Cheng, 1997). Here we investigated the effect of taurine on the toxicity of vitamin A.

2. Materials and methods

2.1. Animals

Male weanling wistar rats were purchased from the National Taiwan University Hospital. They were kept in an air-conditioned room (23 ± 1 °C, 50–60% humidity) lit for 12 h per day (07:00–19:00 h). After acclimatising for 2 weeks with a commercial non-purified diet (Rodent Laboratory Chow 5001, Pruida Co., USA), 36 rats were divided into six groups. Six rats in each group were assigned to receive an 8-week course of one of six formulated diets (Table 1). The diets were formulated as described previously by the American Institute of Nutrition (1977) (AIN), because this formula is still commonly used in spite of new one recommended by AIN in 1993. The vitamin A used was from Sigma (St. Louis, MO, USA). Water and food were always available. After feeding, all rats were weighed. The blood of the rats was taken at a 2 weeks interval from the tail vein. Then, the plasma samples were collected by centrifugation (2000*g*, 15 min) from blood and examined for the level of thiobarbituric acid-reactive substances (TBARS), and the activities of aspartate transaminase (AST) and alanine transaminase (ALT) in the plasma were also assayed by a Vitalab Selectra (E. Merck, Germany) with an enzymatic kit. During the last 2 days of the 8-week course of diets, the serum of rats were collected and assayed for vitamin A level, and then the rats were weighed and anesthetized with diethyl ether. The liver and kidney of rats were quickly excised without perfusion and weighed. Both ratios of liver and kidney weight to body weight were obtained. Then, the liver and kidney samples were stored at −40 °C for vitamin A, glutathione (GSH) and TBARS determinations. The plasma was analyzed for TBARS, AST, ALT, blood urea nitrogen (BUN) and creatinine. The levels of BUN and creatinine in the plasma were also assayed by a Vitalab Selectra with an enzymatic kit.

2.2. TBARS production

Lipid peroxidation activities in blood and liver were assayed by measurements of malondialdehyde (MDA), an end-product of peroxidized fatty acids, and thiobarbituric

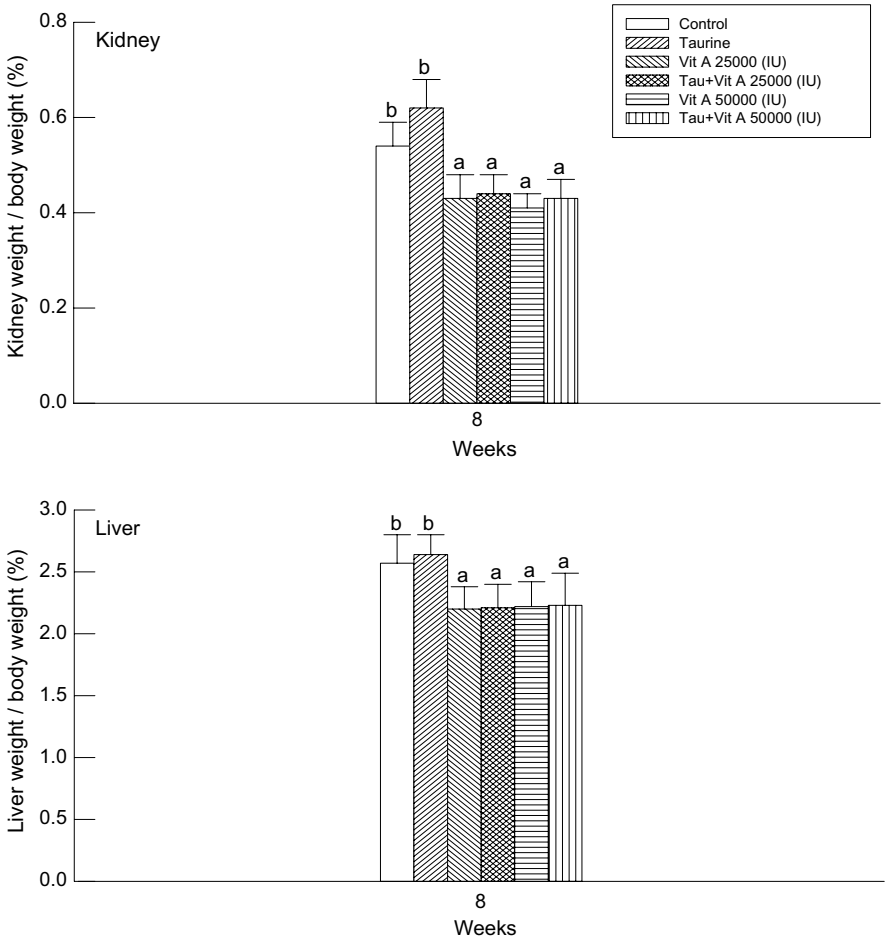

Fig. 2. Effect of vitamin A and taurine on the ratios of liver and kidney weight to body weight in rats after 8-week feeding.

acid (TBA) reaction product. Twenty microliters of plasma and 20% liver homogenate were separately mixed with 1.0 ml of 0.4% TBA in 0.2% HCl and 0.15 ml of 0.2% dibutylated toluene (BHT) in 95% ethanol. The samples were then incubated and analyzed with a fluorescence detector (Tatum, Changchit, & Chow, 1990).

2.3. Levels of GSH measurement

GSH of glutathione 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 DNTB, NADPH and GR are chosen such that the rate of the overall reaction is linearly proportional to the concentration of total glutathione. The rate of formation of TNB is followed spectrophotometrically, and the assay is calibrated using standards. If the sample is reacted with 2-vinylpyridine, GSH is derivatized, and only GSSG is detected during subsequent assay (Griffith, 1980).

2.4. Vitamin A analyses in liver, kidney, and serum

Vitamin A in liver and kidney homogenates (20% w/v in water) were extracted using diisopropyl ether, essentially according to Nilsson, Hanberg, Trossvik, and Håkansson (1996), and separated on a Nucleosil C-18 5 μm high performance liquid chromatography (HPLC) column using an ethanol:water gradient elution. Retinol, retinyl acetate, and retinyl palmitate were detected with a fluorescence detector with an excitation wavelength of 325 nm and emission wavelength of 475 nm (Model 821-FP, Jasco). Internal (retinyl acetate) and external (retinol and retinyl palmitate) standards were used for quantification. Serum analyses of retinoic acid and retinyl esters were done by AS Vitas (Oslo, Norway) on material shielded from light. Briefly, 200 μl of serum or standard solutions was mixed with 600 μl of 2-propanol and centrifuged at 4000*g*. The supernatant was analyzed by liquid chromatography on an HP-1100 HPLC system furnished with a Supersphere 100 RP-18 column (Agilent Technologies, Palo Alto, CA) and detected at 325 nm with an ultraviolet detector. The mobile phase consisted of methanoldichloromethane and the injection volume was 100 μl. A threepoint calibration curve, constructed with albumin solutions enriched with different concentrations of retinyl palmitate, was used to quantify all retinyl esters. The intra-assay variation was 5.1%.

2.5. Statistical analysis

Statistical analysis for differences among rats in the experimental groups was performed by the two-way analysis of variance procedure and Duncan's new multiple range tests (Puri & Mullen, 1980). A P value <0.05 was considered statistically significant.

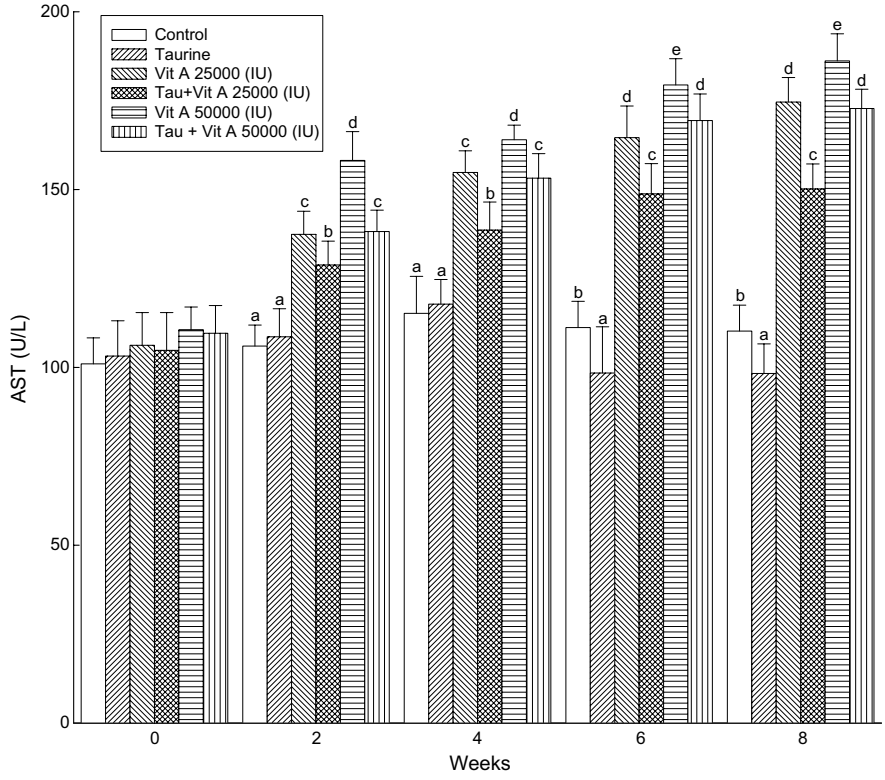

Fig. 3. Effect of vitamin A and taurine on the activity of aspartate transaminase (AST) in the plasma of rats.

3. Results

The effects of taurine and vitamin A on the growth of rats are shown in Fig. 1. After 2-week feeding, the weight of the rat was significantly decreased ($P < 0.05$) when the concentration of vitamin A in the diet was more than 25,000 (IU), but significantly increased when the diet was supplemented with taurine ($P < 0.05$). This indicated that taurine could improve the growth of rats when fed diets supplemented with 25,000–50,000 (IU) vitamin A. The effects of taurine and vitamin A on the ratios of liver and kidney weight to body weight in rats are shown in Fig. 2. After 8-week feeding, the ratios of liver and kidney weight to body weight of rats fed with vitamin A diet [either 25,000–50,000 (IU)] were more significantly decreased compared to those of rats fed with the control diet and taurine diet. However, the ratios of liver and kidney weight to body weight in rats fed diet supplemented with taurine and vitamin A were not significantly different from those of rats fed diet supplemented with vitamin A. This means that taurine might not significantly reduce the toxicity of vitamin A in the rats based on the ratios of liver and kidney weight to body weight. The effects of taurine and vitamin A on the activities of AST and ALT in the plasma are shown in Figs. 3 and 4. It was found that the activities of AST and ALT in the plasma of rats fed with the supplement of vitamin A were gradually increased with the feeding time course. The activities of AST and ALT in the plasma of rats are increased with the increasing level of vitamin A. The activities of AST and ALT in those rats fed the diet with the supplement of taurine were found significantly to reduce the toxicity of vitamin A ($P > 0.05$), indicating taurine might play a protective effect on vitamin A toxicity in rats. The effects of taurine and vitamin A on the TBARS production in the plasma in rats are shown in Fig. 5. After 6-week feeding, the level of TBARS in the plasma of rats fed with supplement of vitamin A was higher than that of control group ($P < 0.05$). After 8-week feeding, the level of TBARS in the liver of rats fed with the supplement of vitamin A was also higher than that of the control group

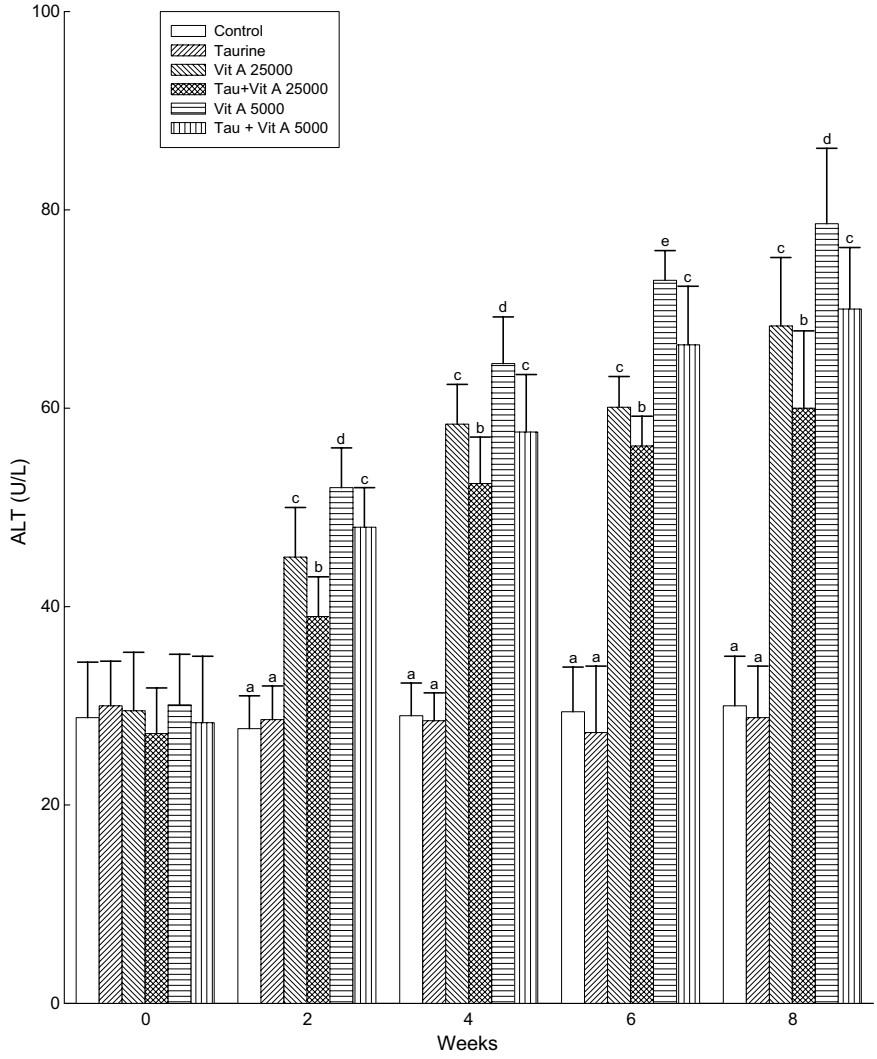

Fig. 4. Effect of vitamin A and taurine on the activity of alanine transaminase (ALT) in the plasma of rats.

(Fig. 6) ($P < 0.05$). The level of TBARS in the plasma and liver of rats was somewhat increased with the increasing of the concentration of vitamin A in the diet. The level of TBARS in the liver of rats fed a diet with the supplement of taurine and vitamin A was less than that of rats fed a diet only with supplement of copper ($P < 0.05$), but the effect on plasma of rats was not significant ($P > 0.05$). The level of GSH in the liver of rats was decreased with the increasing of the concentration of vitamin A in the diet. The level of GSH in the liver of rats fed the diet with the supplement of taurine and vitamin A was higher than that of rats fed a diet only with supplement of vitamin A ($P < 0.05$) (Fig. 6). The effects of taurine and vitamin A on the level of BUN and creatinine in the plasma of rats are also shown in Fig. 6. After 8-week feeding, the level of BUN and creatinine in the plasma was higher in the groups fed the diet with the supplement of vitamin A than in the control group. The level of BUN and creatinine in the plasma of rats was increased with the increasing dose of vitamin A in the diet. When the diet was supplemented with taurine, the level of BUN and creatinine was significantly reduced ($P < 0.05$). The effects of taurine and vitamin A on the level of vitamin A in the liver, kidney and serum of rats are shown in Fig. 7. After 8-week feeding, the level of vitamin A in the liver, kidney and serum was obviously higher in the groups fed the diet with supplementation of vitamin A than in the control group. The level of vitamin A in the liver, kidney and serum was increased with the increasing dose of vitamin A in the diet. When the diet was supplemented with taurine, the level of vitamin A in the liver and kidney was significantly reduced, and the level of vitamin A in the serum was slightly increased ($P < 0.05$).

4. Discussion

In this study, the toxic effect of vitamin A in rats was very similar to that of copper, cadmium and lead (Hwang et al., 1998; Wang et al., 1997). The symptoms of vitamin

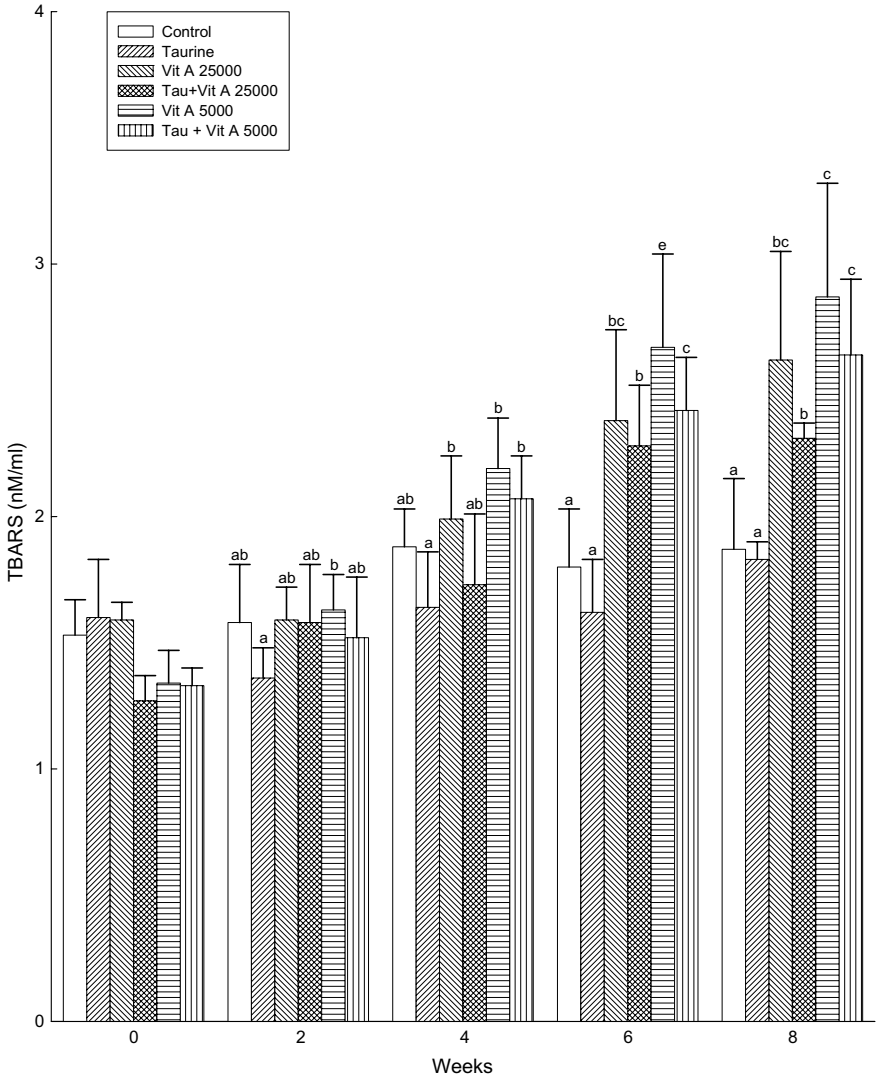

Fig. 5. Effect of vitamin A and taurine on the level of thiobarturic acid-reactive substances (TBARS) in the plasma of rats.

A toxicity in rats included reduced body weight, ratios of liver and kidney weight to body weight, and level of GSH in the liver, and increasing activities of AST and ALT in the plasma, levels of TBARS, BUN and creatinine in the plasma and/or liver, and concentrations of vitamin A in the liver and kidney of rats. In the clinical plasma examination, the activities of AST and ALT in plasma represent biomarkers for liver functions (Guyton, 1991; Ronald & Koretz, 1992). The activities of AST and ALT in the plasma of rats were significantly elevated by vitamin A, indicating vitamin A-related injury to the liver. This result is also reported in other papers (Leo et al., 1989; Leo & Lieber, 1988). Since taurine significantly reduced the AST and ALT activities in the plasma of rats, the hepatic injury by vitamin A could be ameliorated by taurine. This result was similar to that of body weight in rats. However, the levels of TBARS and GSH in the liver are additional indicators of liver injury. TBARS is an end-product of lipid peroxidation. The level of TBARS of the plasma and liver was increased with the increasing dose of vitamin A and the level of TBARS of the plasma was also increased with exposure time. The data does not prove that the mechanism of vitamin A injury is by lipid peroxidation but it is strongly suggestive that it plays an important role. Other papers also indicated that vitamin A might increase the level of TBARS in the tissues of experimental animals (Minuk, Kelly, & Hwang, 1988). The level of TBARS in the plasma and liver of rats was significantly reduced when the rats were fed the diet with the supplement of taurine. The level of GSH in the liver of rats was reduced by contaminated vitamin A, which was similar to that of other reports (Geoffrey, 1994). However, it was raised significantly when the rats were fed a diet with the supplement of taurine. This means that taurine may play an important role in the metabolism of GSH and in preventing lipid peroxidation, but these related mechanism should be studied further. On the other hand, the levels of BUN and creatinine in the plasma of rats are tested as indicators for kidney

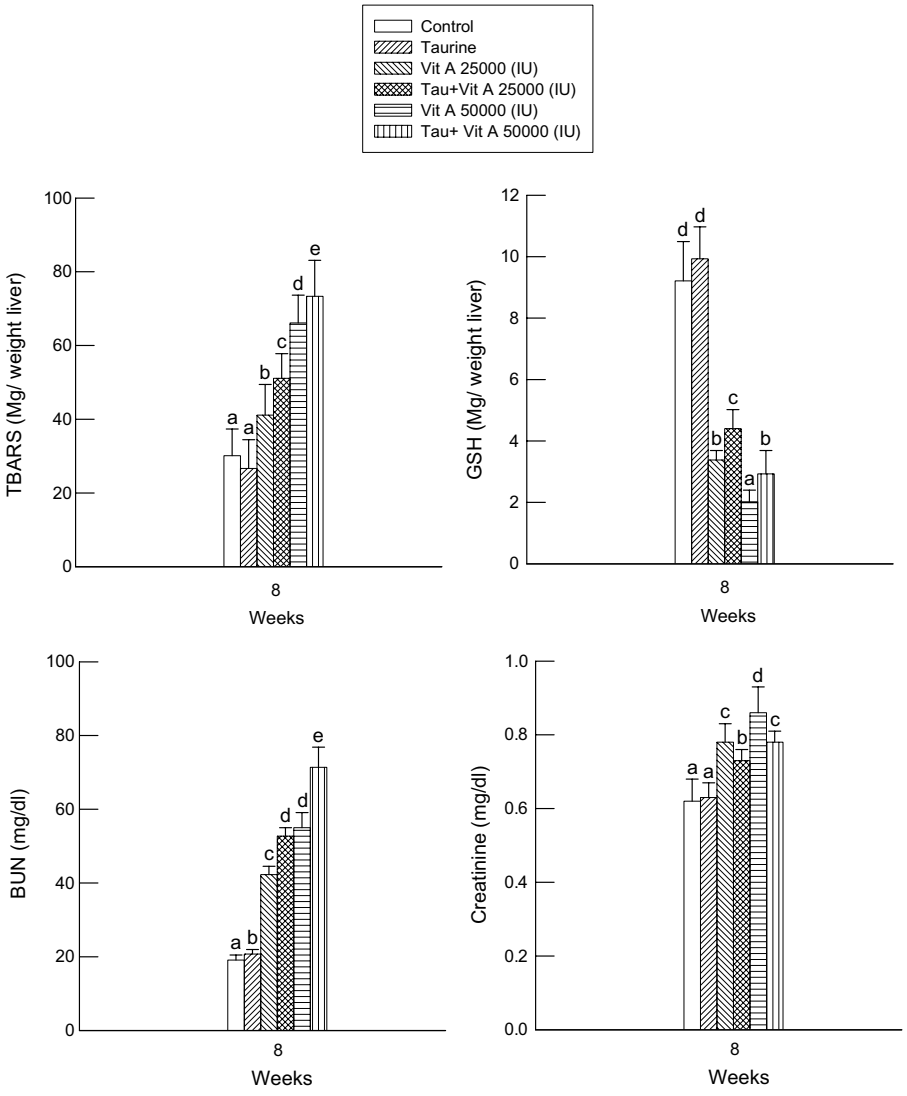

Fig. 6. Effect of vitamin A and taurine on the levels of TBARS and GSH in the liver and BUN and creatinine in the plasma of rats after 8-week feeding.

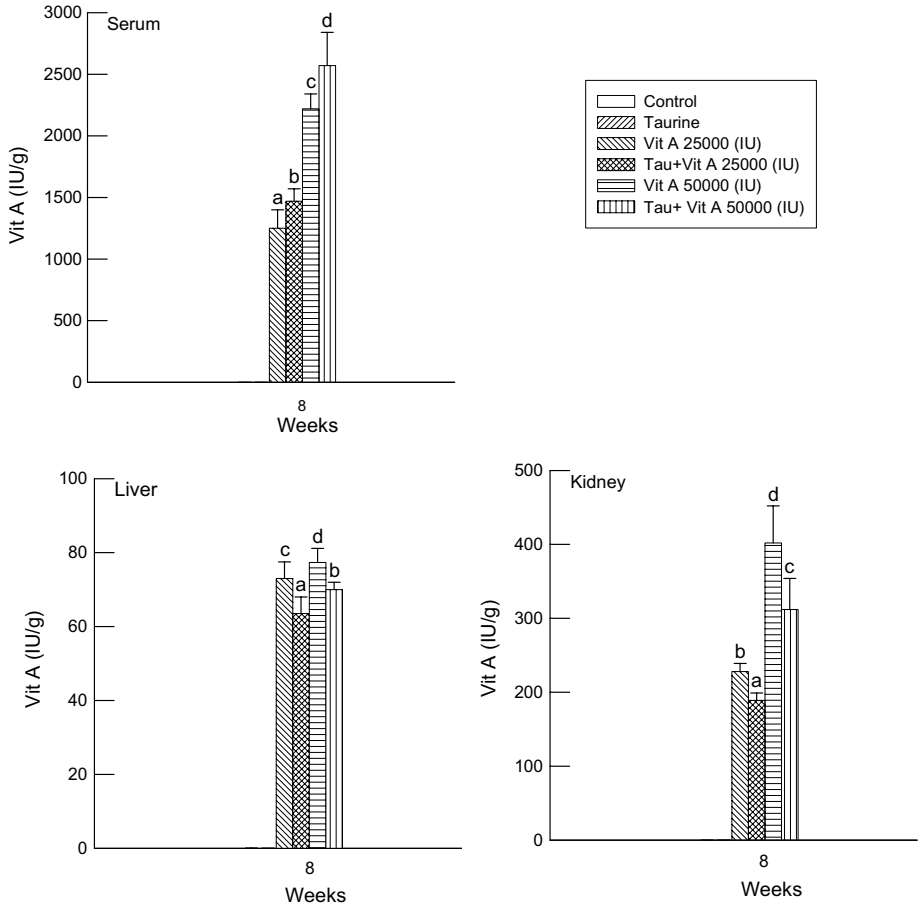

Fig. 7. Effect of vitamin A and taurine on the level of vitamin A in the liver, kidney and serum of rats after 8-week feeding.

functions (Hendriks, Bosma, & Brouwer, 1993; Thunberg, Ahlborg, & Johansson, 1979). Judging from both indicators and the ratio of kidney weight to body weight, vitamin A significantly induced the dysfunction of kidney. Although supplementing with taurine in the diet did not ameliorate the ratio of kidney weight to body weight, the levels of BUN and creatinine in the plasma of rats were significantly reduced. Furthermore, the level of vitamin A in the liver and kidney was significantly increased with increasing exposure to vitamin A in the diet. The accumulated amount of vitamin A was higher in the kidney than in the liver, which was the same as previous report (Vecchini et al., 1994). Accumulation of vitamin A is the net consequence of uptake, biotransformation and elimination processes within an individual. Once vitamin A is absorbed, taurine exerts synergistic actions in scavenging it to form vitamin-thionein. Although the half-life of vitamin-thionein in the liver and kidney is not known exactly, it is many years (Sakamoto et al., 2001) and with continued retention, there is progressive accumulation in these tissues. The accumulated amount of vitamin A in the tissue was effectively reduced by taurine. Taurine is a special amino acid, which possesses an amino group and a sulfonate group. These functional groups might bind with vitamin A, and then stimulate the excretion of such compounds. In this study, it was also found that the amount of vitamin A in the serum of rats fed with the supplement of taurine was slightly increased. There is no evidence that taurine directly reduces the production of free radicals but it may well operate by binding vitamin A which is then not absorbed or is more rapidly excreted. In other words it may act by reducing the overall bioavailability of vitamin A or the intracellular availability of absorbed vitamin A. Hence, dietary taurine may play a role to reduce the toxic effect of vitamin A in the liver and kidney of rats.

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