Amino Acids (2004) 27: 91–96
DOI 10.1007/s00726-004-0066-8

Amino Acids
Printed in Austria

Taurine restores ethanol-induced depletion of antioxidants and attenuates oxidative stress in rat tissues

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Received August 28, 2003
Accepted December 15, 2003
Published online April 26, 2004;

Summary. Ethanol by its property of generating free radicals during the course of its metabolism causes damage to cell structure and function. The study investigates the protective effects of the antioxidant aminoacid taurine on ethanol-induced lipid peroxidation and antioxidant status. Male Wistar rats of body weight 170–190 g were divided into 4 groups and maintained for 28 days as follows: a control group and taurine-supplemented control group, taurine supplemented and unsupplemented ethanol-fed group. Ethanol was administered to rats at a dosage of 3 g/kg body weight twice daily and taurine was provided in the diet (10 g/kg diet). Lipid peroxidation products and antioxidant potential were quantitated in plasma and in following tissues liver, brain, kidney and heart.

Increased levels of thiobarbituric acid substances (TBARS) and lipid hydroperoxides (LHP) in plasma and tissues, decreased activities of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) were observed in hemolysate and tissues of ethanol-fed rats. The contents of reduced glutathione (GSH), α-tocopherol and ascorbic acid in plasma and tissues were significantly reduced in these animals as compared to control animals. Simultaneous administration of taurine along with ethanol attenuated the lipid peroxidation process and restored the levels of enzymatic and non-enzymatic antioxidants. We propose that taurine may have a bioprotective effect on ethanol-induced oxidative stress.

Keywords: Ethanol – Taurine – Lipid peroxidation – Antioxidants – Tissues – Oxidative stress

Introduction

Ethanol is the most frequently abused drug and is a preferred fuel once consumed. Ethanol ingestion produces a wide variety of pathological disturbances affecting a number of organs. Being a small molecule and soluble in both water and lipids, ethanol permeates all tissues of the body and affects most vital functions of virtually all organs including liver, kidney, brain, heart and pancreas (Lieber, 1995).

The toxic effects of ethanol are attributed to increased generation of free radicals and the development of a state of oxidative stress. Increased oxidative stress occurs directly due to ethanol and its oxidation products. Ethanol is reported to be converted to ethyl and 1-hydroxyethyl radicals (Reinke et al., 1997). Furthermore, acetaldehyde, the product of ethanol oxidation, reacts with hepatic glutathione, a major cytosolic antioxidant in liver and causes depletion (Lieber, 2000). Previous studies from our laboratory have shown that administration of cysteine (a constituent of GSH) to alcohol fed rats can reduce oxidative stress and cell injury by preventing lipid peroxidation and normalization of antioxidant status (Anuradha and Vijayalakshmi, 1995).

Taurine (2-amino ethane sulfonic acid) is a sulphur containing amino acid present in many tissues of man and animals. Conjugation with bile acids, neurotransmitter and reaction with certain xenobiotics are its firmly established functions. Taurine has protective properties also when administered therapeutically. For example, supplementation studies have documented antihypertensive (Dawson et al., 2000), antidiabetic (Trachtman et al., 1995), antioxidative (Green et al., 1991) and hepatoprotective (Dogru-Abbasoglu, 2001) properties of taurine. Recently it was reported that the inhibitory amino acid taurine may constitute an important neuroprotective mechanism during excitotoxicity and could be effective in alcohol-withdrawal symptomology (Bleich and Degner, 2000).

In view of the above, a study was undertaken to determine the role of taurine in ethanol-fed rats. We now report the effects of taurine on lipid peroxidation process, enzymatic and non-enzymatic antioxidants in plasma, hemolysate and tissues of ethanol-treated rats. The data obtained are compared with those of untreated ethanol-fed rats.

Materials and methods

Animals

Adult male albino rats of Wistar strain, bodyweight 170–190 g were purchased from the Central Animal House, Rajah Muthiah Medical College and were fed on pellet diet [Kamadhenu Agencies, Bangalore, India] and water *ad libitum*. The animals were housed in polypropylene cages under controlled conditions of 12 h light/12 h dark cycle, 50% humidity and at 30°C. All procedures for experimentation were cleared by the Institutional Animal Ethics Committee, Rajah Muthiah Medical College, Annamalai Nagar.

Experimental design

The animals were divided into four groups of six each and were maintained as follows:

Group I Received glucose from a 40% glucose stock solution every day, which was isocaloric to ethanol.
Group II Received ethanol at a dosage of 3 g/kg bodyweight from 30% stock solution twice daily.
Group III Received ethanol and fed with taurine supplemented diet.
Group IV Received glucose from a 40% glucose stock solution every day, which was isocaloric to ethanol and fed with taurine supplemented diet.

Ethanol and glucose were administered by oral gavage. Taurine was added to the powdered diet at a level of 10 g/kg diet. Groups I and II rats were fed with commercial rat chow and water *ad libitum*, while groups III and IV rats were fed with taurine supplemented diet *ad libitum*. Treatments were carried out for 28 days.

At the end of experimental period the rats were sacrificed by decapitation after an overnight fast. Blood was collected in heparinised tubes and plasma was separated. The erythrocytes were washed thrice with physiological saline and hemolysate was prepared (Dodge et al., 1963). The animals were dissected and tissues (liver, brain, kidney and heart) were removed and cleared off blood and immediately transferred to ice-cold containers containing 0.89% sodium chloride and homogenized in 0.1 M Tris-HCl buffer, pH 7.4.

Biochemical analysis

The content of thiobarbituric acid reactive species (TBARS) was measured by the method of Niehaus and Samuelson (1972) and hydroperoxides (LHP) by that of Jiang et al. (1990). Superoxide dismutase (SOD) was determined by the method of Kakkar et al. (1984), catalase (CAT) by the method of Sinha (1972) and glutathione peroxidase (GPx) by the method of Rotruck et al. (1973). Reduced glutathione by the method of Ellman (1959) and ascorbic acid by that of Omaye et al. (1971) in plasma and tissues were determined. α-Tocopherol was estimated in plasma and lipid extracts of tissues following the method of Baker et al. (1968). Protein content of tissues by Lowry et al. (1951) and hemoglobin content of hemolysate by Drabkin et al. (1932) were determined.

Statistical analysis

Values are given as mean ± SD. The differences between groups were analysed using ANOVA followed by Duncan's Multiple Range Test (DMRT). The level of statistical significant was set at $p < 0.05$.

Results

Table 1 shows the body and organ weight changes of animals. The initial bodyweight of each group was between 170–190 g. The control and taurine treated animals (Groups I, III and IV) registered a significant weight gain while animals fed ethanol alone (Group II) showed a progressive reduction in bodyweight during the experimental period.

Table 2 gives the levels of lipid peroxidation products in plasma and tissues of experimental animals. The contents of TBARS and LHP were significantly increased in both plasma and tissues of untreated ethanol fed rats as compared to control rats. Group III rats treated with ethanol and taurine showed near-normal levels of TBARS and LHP. Group IV rats fed only with taurine showed no significant alterations in TBARS and LHP as compared to Group I.

Table 3 gives the activities of enzymatic antioxidants SOD, CAT and GPx in plasma and tissues of experimental animals. The activities of these antioxidants were significantly lower in Group II rats fed ethanol as compared with Group I control rats. Group III rats fed with ethanol and

Table 1. Body and organ weights of control and experimental animals

	Group I	Group II	Group III	Group IV
Body weight (g)				
Initial	180 ± 6.35	180 ± 10.36	180 ± 9.36	180 ± 10.36
Final	245.50 ± 15.36	222.31 ± 16.36[a]	241.66 ± 12.36[b]	244.16 ± 15.36
Weight gain	65.50 ± 4.03	42.31 ± 2.47[a]	61.66 ± 2.25[b]	64.16 ± 3.71
Organ weight (g)				
Liver	8.90 ± 0.31	6.98 ± 0.45[a]	8.36 ± 0.61[b]	8.92 ± 0.48
Brain	1.81 ± 0.16	1.34 ± 0.11[a]	1.78 ± 0.10[b]	1.80 ± 0.11
Kidney	1.86 ± 0.11	1.40 ± 0.11[a]	1.79 ± 0.10[b]	1.82 ± 0.08
Heart	0.95 ± 0.05	0.68 ± 0.52[a]	0.90 ± 0.04[b]	0.94 ± 0.03

Group I – control; Group II – ethanol treated; Group III – ethanol and taurine treated and Group IV – control treated with taurine
Values are mean ± SD; n = 6
[a] significant as compared to control (DMRT $p < 0.05$); [b] significant as compared to alcohol (DMRT $p < 0.05$)

Table 2. Levels of thiobarbituric acid reactive substances and lipid hydroperoxides in circulation (μmol/L) and tissues (nmol/mg protein) of control and experimental animals

Parameters	Group I	Group II	Group III	Group IV
TBARS				
Plasma	1.27 ± 0.06	3.32 ± 0.21^{a}	1.32 ± 0.10^{b}	1.21 ± 0.21
Liver	0.85 ± 0.07	2.54 ± 0.14^{a}	0.88 ± 0.14^{b}	0.76 ± 0.05
Brain	1.26 ± 0.12	2.50 ± 0.13^{a}	1.26 ± 0.12^{b}	1.19 ± 0.05
Kidney	1.27 ± 0.08	2.62 ± 0.09^{a}	1.42 ± 0.10^{b}	1.22 ± 0.06
Heart	0.62 ± 0.04	1.56 ± 0.10^{a}	0.63 ± 0.03^{b}	0.59 ± 0.007
LHP				
Plasma	8.89 ± 0.38	13.79 ± 0.20^{a}	8.99 ± 0.22^{b}	8.94 ± 0.05
Liver	87.96 ± 2.37	149.29 ± 2.09^{a}	87.92 ± 1.53^{b}	86.49 ± 1.37
Brain	118.40 ± 4.59	171.54 ± 1.54^{a}	120.36 ± 6.16^{b}	116.06 ± 1.33
Kidney	68.41 ± 0.72	175.34 ± 0.93^{a}	68.80 ± 1.89^{b}	67.43 ± 1.71
Heart	82.25 ± 0.81	114.28 ± 1.15^{a}	82.81 ± 1.36^{b}	81.96 ± 1.02

Group I – control; Group II – ethanol treated; Group III – ethanol and taurine treated and Group IV – control treated with taurine

Values are mean $\pm$ SD; $n = 6$

[a] significant as compared to control (DMRT $p < 0.05$); [b] significant as compared to ethanol (DMRT $p < 0.05$)

Table 3. Activities of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) in hemolysate and tissues of control and experimental animals

Parameters	Group I	Group II	Group III	Group IV
SOD (Units)*				
Hemolysate	2.64 ± 0.17	1.46 ± 0.03^{a}	2.56 ± 0.19^{b}	2.73 ± 0.09
Liver	7.64 ± 0.27	3.85 ± 0.03^{a}	7.44 ± 0.10^{b}	7.49 ± 0.14
Brain	9.33 ± 0.26	4.79 ± 0.04^{a}	9.05 ± 0.86^{b}	9.16 ± 0.12
Kidney	6.11 ± 0.17	2.87 ± 0.09^{a}	5.83 ± 0.43^{b}	5.84 ± 0.17
Heart	6.26 ± 0.07	3.89 ± 0.06^{a}	5.93 ± 0.75^{b}	6.31 ± 0.03
CAT (Units)#				
Hemolysate	47.71 ± 1.32	26.49 ± 1.89^{a}	47.58 ± 3.83^{b}	47.54 ± 1.71
Liver	73.77 ± 1.61	38.10 ± 2.09^{a}	72.57 ± 6.13^{b}	72.71 ± 2.34
Brain	2.80 ± 0.10	1.57 ± 0.04^{a}	2.70 ± 0.24^{b}	2.82 ± 0.21
Kidney	40.88 ± 2.20	26.27 ± 2.13^{a}	40.11 ± 1.20^{b}	42.32 ± 1.57
Heart	46.66 ± 1.57	36.27 ± 1.88^{a}	45.07 ± 0.68^{b}	46.32 ± 1.15
GPx (Units)¶				
Hemolysate	12.92 ± 0.21	8.57 ± 0.18^{a}	12.94 ± 0.72^{b}	12.94 ± 0.17
Liver	10.08 ± 0.13	5.16 ± 0.13^{a}	10.09 ± 0.27^{b}	10.23 ± 0.26
Brain	5.22 ± 0.10	2.52 ± 0.13^{a}	4.96 ± 0.40^{b}	5.16 ± 0.11
Kidney	7.27 ± 0.16	4.46 ± 0.13^{a}	7.12 ± 0.18^{b}	7.21 ± 0.17
Heart	5.60 ± 0.14	4.16 ± 0.13^{a}	5.39 ± 0.35^{b}	5.57 ± 0.13

Group I – control; Group II – ethanol treated; Group III – ethanol and taurine treated and Group IV – control treated with taurine. Values are mean $\pm$ SD; $n = 6$

[a] significant as compared to control (DMRT $p < 0.05$); [b] significant as compared to alcohol (DMRT $p < 0.05$). * 1 unit corresponds to the amount of enzyme which gave 50% inhibition of chromogen formation/mg hemoglobin for hemolysate and that/mg protein for tissues. # Units – μmol/min/mg hemoglobin for hemolysate and μmol/min/mg protein for tissues. ¶ Units – μg GSH utilised/min/mg hemoglobin for hemolysate and μg GSH utilised/min/mg protein for tissues

taurine showed marked increases in the activities of these enzymatic antioxidants as compared with Group II rats fed with ethanol alone.

Table 4 shows the levels of non-enzymatic antioxidants namely GSH, α-tocopherol and ascorbic acid in plasma and tissues of control and experimental animals. Group II

Table 4. Levels of non-enzymatic antioxidants GSH, vitamin E and vitamin C in plasma and tissues of control and experimental animals

Parameters	Group I	Group II	Group III	Group IV
GSH*				
Plasma	31.59 ± 0.48	19.49 ± 0.97^{a}	31.39 ± 0.31^{b}	31.91 ± 0.58
Liver	6.35 ± 0.32	5.06 ± 0.41^{a}	6.34 ± 0.08^{b}	6.53 ± 0.09
Brain	4.59 ± 0.04	3.19 ± 0.02^{a}	4.57 ± 0.03^{b}	4.61 ± 0.03
Kidney	5.39 ± 0.31	3.94 ± 0.32^{a}	5.36 ± 0.21^{b}	5.66 ± 0.03
Heart	6.19 ± 0.03	4.47 ± 0.03^{a}	6.11 ± 0.14^{b}	6.26 ± 0.10
Vitamin E*				
Plasma	2.29 ± 0.13	0.79 ± 0.04^{a}	2.16 ± 0.22^{b}	2.16 ± 0.05
Liver	5.08 ± 0.41	3.50 ± 0.27^{a}	5.00 ± 0.41^{b}	5.17 ± 0.34
Brain	3.23 ± 0.35	1.30 ± 0.11^{a}	3.22 ± 0.21^{b}	3.36 ± 0.27
Kidney	3.62 ± 0.06	1.71 ± 0.15^{a}	3.60 ± 0.16^{b}	3.65 ± 0.11
Heart	3.09 ± 0.30	1.49 ± 0.15^{a}	2.88 ± 0.21^{b}	3.08 ± 0.13
Vitamin C*				
Plasma	2.35 ± 0.19	1.06 ± 0.07^{a}	2.30 ± 0.21^{b}	2.48 ± 0.25
Liver	0.75 ± 0.10	0.52 ± 0.02^{a}	0.73 ± 0.04^{b}	0.73 ± 0.06
Brain	0.50 ± 0.02	0.37 ± 0.03^{a}	0.50 ± 0.03^{b}	0.52 ± 0.01
Kidney	0.60 ± 0.01	0.42 ± 0.06^{a}	0.55 ± 0.08^{b}	0.61 ± 0.01
Heart	0.47 ± 0.01	0.32 ± 0.02^{a}	0.46 ± 0.03^{b}	0.48 ± 0.01

Group I – control; Group II – ethanol treated; Group III – ethanol and taurine treated and Group IV – control treated with taurine

Values are mean $\pm$ SD; $n = 6$

[a] significant as compared to control (DMRT $p < 0.05$); [b] significant as compared to alcohol (DMRT $p < 0.05$); * plasma – μmol/L; tissues – μmol/mg tissue

rats fed with ethanol showed significant reductions in the non-enzymatic antioxidants as compared with Group I rats. Group III rats fed with ethanol and taurine showed significant elevations in GSH, α-tocopherol and ascorbic acid as compared to Group II rats fed with ethanol only. Group IV rats fed only with taurine showed no significant alterations in their antioxidant status when compared with that of Group I control rats.

Discussion

Increased levels of lipid peroxidation products (TBARS and LHP) in plasma, liver, kidney, brain and heart were observed in rats fed with ethanol. The increased peroxidation results from the increased oxidative stress in hepatic and extrahepatic tissues induced by ethanol and its oxidation. Oxidation of ethanol by alcohol dehydrogenase (ADH) generates NADH and increased production of reactive oxygen species by NADH-oxidases in various organelles after chronic ethanol treatment (Kukielka et al., 1996). Induction of the microsomal ethanol oxidising system (MEOS) and NADPH oxidase reaction can also facilitate free radical production (Rashba-Step et al., 1993). Increased peroxidation has been reported in other tissues such as heart (Remla et al., 1991), kidney (Seef et al., 1986) and brain (Sohda et al., 1993) besides liver during ethanol intoxication.

Taurine supplementation reduced lipid peroxidation in plasma and tissues of ethanol treated rats as evidenced by reduction in TBARS and LHP. Free radical induced damage to membranes is associated with increased permeability to ions and water. Ethanol has been shown to reduce ionic transfer through alterations in the monovalent cation pump and the antiport system (Guiet-Bara et al., 1995). Taurine administration may contribute to protect cell structures by avoiding ion overloading and the subsequent water accumulation (Pasantes-Morales and Cruz, 1985). It is also evidenced that taurine exerts a restorative effect on hepatic lipids and attenuates oxidative stress (Balkan et al., 2002), reverses fatty liver and hepatic lipid peroxidation (Kerai et al., 1999) and completely inactivates the alcohol metabolizing cytochrome P450 2E1 in liver in ethanol fed rats (Kerai et al., 1998).

SOD scavenges the superoxide ions produced as cellular byproducts during ethanol metabolism. CAT reduces hydrogen peroxide produced by dismutation reaction and prevents generation of hydroxy radicals thereby protecting the cellular constituents from oxidative damage in peroxisomes. The reduced activities of SOD, CAT and GPx in ethanol treated rats result in the accumulation of

superoxide radical and H_2O_2 respectively, which produce deleterious effects. Increased lipid peroxidation and decreased antioxidant enzyme activities in tissues of ethanol treated animals has been reported (D'Almedia, 1994; Jaya and Menon, 1993; Lieber, 2000).

GSH, α-tocopherol and ascorbic acid are major endogenous antioxidants which counterbalance free radical mediated damage. It is well known that GSH is involved in the protection of normal cell structure and function by maintaining the redox homeostasis, quenching of free radicals and by participating in detoxification reactions. Insufficiency in non-enzymatic antioxidant status in tissues in ethanol-intoxicated rats could be the consequence of increased utilization for trapping free radicals. Acetaldehyde promotes peroxidation reaction by binding to cysteine and/or glutathione, which causes depletion of GSH (Lieber et al., 1990). Significant decreases in the levels of GSH, α-tocopherol and ascorbic acid have been reported in alcohol-administered rats (Anuradha and Vijayalakshmi, 1995; Balkan, 2002).

Taurine supplementation showed normalization of the activities of SOD, CAT and GPx. It also restored GSH, α-tocopherol and ascorbic acid that could be attributed to antioxidant property of taurine. The normalization of antioxidants is implicated in the reduced levels of lipid peroxidation. The antioxidant action of taurine has been demonstrated in a variety of *in vitro* (Devamanoharan et al., 1998) and *in vivo* systems (Michalk et al., 1997; Anitha Nandhini et al., 2002).

All four groups were treated isocalorically with either glucose or ethanol and had free access to food and water. However the body weight changes show that rats given ethanol alone gained consistently less weight than the control group. This may be related to the toxicity of ethanol. Alcohol also impairs the activation and utilization of nutrients and secondary malnutrition may result from either maldigestion or malabsorption caused by gastrointestinal complications associated with alcoholism (Lieber, 2000). Treatment with taurine restored body weight gain and organ weight. It is possible that group II rats were receiving less nutrients from the *ad libitum* diet and that the taurine effect was related to increasing appetite and better utilization of nutrients in the diet, leading to increases in body weight and organ weight.

Administration of vitamin E (Porta, 1997) or sulphur-containing amino acids like methionine (Lieber et al., 1990) and cysteine (Anuradha and Vijayalakshmi, 1995) to ethanol fed rats repletes the levels of antioxidants and minimizes oxidative stress. However taurine has advantages over these substances. Cysteine is reported to be relatively toxic and has poor bioavailability. Extremely large amounts of cysteine can be toxic to nerve cells in rats (Olney and Ho, 1970) and may not be effective in preventing oxidative damage (Kleinveld et al., 1992). Furthermore the adverse effect of vitamin E by conversion to a prooxidant molecule at high dietary concentration have been reported (Bowry et al., 1992). Taurine has no adverse effects and is considered to be safe even at very high dietary intake (Trachtman et al., 1995).

Taurine protects against a plethora of oxidative stress conditions induced by ammonia (Saransaari and Oja, 1997), acetaminophen (Waters et al., 2001) and gentamicin (Erdem et al., 2000). Therefore it is possible that taurine may modify factors underlying susceptibility to toxic chemicals. Histological studies and investigations on the influence of ethanol and taurine on specific macromolecular targets of oxidant stress such as nuclear and mitochondrial DNA are needed.

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