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Protective effects of taurine on glutathione and glutathione-dependent enzymes in ethanol-fed rats

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Ethanol, by its property of generating free radicals during the course of its metabolism, alters redox homeostasis and causes damage to cell structure and function. This study investigated the effect of taurine on ethanol-induced experimental toxicity in rats. Ethanol was administered chronically to rats for 28 days. This resulted in significant increases in the activities of transaminases, alkaline phosphatase (ALP), γ-glutamyl transpeptidase (GGT) and bilirubin in plasma. The activities of glutathione peroxidase (GPx), glutathione-S-transferase (GST) and the contents of glutathione (GSH) and thiols in plasma and tissues were significantly reduced as compared to control animals. Simultaneous administration of taurine along with ethanol prevented the leakage of enzymes into circulation and restored glutathione and tissue thiols. The activities of antioxidant enzymes were normalized. We propose that taurine may have a bioprotective effect on ethanol-induced toxicity.

1. Introduction

Ethanol, one of the most abused drugs, is a preferred fuel once consumed. Although moderate alcohol consumption has been reported to be beneficial in reducing cardiovascular risk, chronic alcohol abuse and heavy drinking produces hematological, biochemical and metabolic alterations. Chronic alcoholism is associated with numerous degenerative and inflammatory disorders in many organs, including the liver, brain, kidney, heart, skeletal muscle and pancreas (Brooks 1997). The toxic effects are shown to be directly due to ethanol and its oxidation products. Among the various mechanisms of ethanol toxicity, the depletion of the antioxidant tripeptide glutathione (GSH) in liver and in circulation is important owing to the wide range of functions of GSH. Previous studies from our laboratory have shown that administration of cysteine (a constituent of GSH) to alcohol fed rats can replete GSH and minimize alcohol-induced oxidative stress (Anuradha and Vijayalakshmi 1995). Furthermore, supplementation of the sulphur-containing amino acid methionine, has been reported to attenuate alcohol toxicity (Lieber et al. 1990).

Taurine (2-amino ethane sulfonic acid) is a sulphur-containing amino acid present in many tissues of man and animals (Huxtable 1992). Conjugation with bile acids, neurotransmission and reaction with certain xenobiotics (Emudianughe et al. 1983; Skare et al. 1982) are firmly established as its functions. Taurine also has protective properties as an exogenous compound when administered therapeutically. For example supplementation studies have documented antihypertensive (Dawson et al. 2000), antiatherogeneic (Murakami et al. 1996), antidiabetic (Trachtman et al. 1995) and antioxidative (Green et al. 1995) and hepatoprotective (Dogru-Abbasoglu et al. 2001) properties of taurine. It has recently been reported that the inhibitory amino acid taurine may constitute an important neuroprotective mechanism during excitotoxicity and could be effective in alcohol-withdrawl 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 thiol status in plasma and tissues, on the activities of glutathione peroxidase (GPx) and glutathione-S-transferase (GST), two GSH-utilising enzymes, and on markers of hepatocellular damage in ethanol-treated rats. The data are compared with untreated ethanol-fed rats to assess the efficiency of taurine.

2. Investigations and results

2.1. Effect of taurine on body and organ weight changes

Table 1 shows the body and organ weight changes of the animals. The initial bodyweight of each group was between 170 and 190 g. The control and taurine treated animals (Groups 1, 2 and 4) registered a significant weight gain while untreated ethanol-fed animals (Group 2) showed a progressive reduction in bodyweight during the experimental period.

2.2. Effect of taurine on plasma enzymes and bilirubin

The changes in the activities of enzyme markers and in bilirubin content in plasma of control and experimental animals are presented in Table 2. Plasma aspartate transaminase (AST) and alanine transaminase (ALT) were significantly increased in alcohol-treated animals (Group 2)

Table 1: Body and organ weight of control and experimental animals

Body weight (g)	Group 1	Group 2	Group 3	Group 4
Initial	180 ± 6.35	180 ± 10.36[a]	180 ± 9.36[b]	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

Values are given as mean ± SD from six rats in each group
Group 1 – control; Group 2 – ethanol; Group 3 – ethanol + taurine and Group 4 – control + taurine
a – significant as compared to control (DMRT $p < 0.05$)
b – significant as compared to alcohol (DMRT $p < 0.05$)

as compared to controls (Group 1). No significant differences in enzyme activities were observed between animals Groups 1, 3, and 4). Plasma alkaline phosphatase (ALP), a marker of bile duct damage, was significantly raised by alcohol treatment (Group 2) as compared to other groups (Group 1, 3 and 4). Plasma γ-glutamyl transpeptidase (GGT) activity, a marker of alcohol abuse, was raised significantly only in alcohol treated animals (Group 2). No significant differences in GGT activity were observed between Groups 1, 3 and 4. Conjugated and unconjugated bilirubin levels were raised in ethanol-treated animals (Group 2) as compared to Groups 1, 3 and 4.

2.3. Effect of taurine on GSH and thiols

The content of GSH in plasma and tissues and content of total and protein thiols in tissues are presented in Table 3. Group 2 animals fed with ethanol showed significant reductions in GSH and thiol content as compared to control animals (Group 1). Group 3 animals fed with ethanol and taurine showed significant elevation in GSH and thiol content as compared to Group 2. Group 4 animals fed with taurine showed no alteration in the thiol status in plasma and tissues as compared to that of Group 1 animals.

2.4. Effect of taurine on enzymatic antioxidants

The activities of glutathione-dependent enzymes GPx, GST in tissues and hemolysate were significantly lower in ethanol treated animals (Group 2) as compared to Group 1 animals (Table 4). Group 3 animals treated with ethanol and taurine showed marked increase in the activities of these enzymes as compared to Group 2 animals fed with ethanol only.

3. Discussion

Increases in the activities of transaminases, ALP and GGT in ethanol fed rats indicate damage to tissues and leakage of enzymes into plasma. Increase in bilirubin levels reflects hepatic and bile duct injury. Changes in serum bilirubin levels are reported to be proportional to the extent of liver and bile duct damage (Mitra et al. 2000).

It is well know that GSH is involved in the protection of normal cell structure and function by maintaining redox homeostasis, quenching free radicals and participating in detoxification reactions. Reduction in GSH may be attributed to the increased utilization of GSH to trap free radicals and to maintain the redox balance. Continued oxidation of ethanol generates more reducing equivalents in the form of NADH causing an imbalance in the redox system (Lieber and DeCarli, 1991). The reduction in GSH may also be attributed to the inhibition of GSH synthesis and slow regeneration from its oxidized form after acute ethanol administration. Increased oxidized glutathione in bile occurs after long-term alcohol consumption (Vendemiale et al. 1984). Further, acetaldehyde formed from ethanol by alcohol dehydrogenase reaction can bind to GSH thus causing depletion of GSH. A significant decrease in the level of GSH has been reported in the plasma of rats administered alcohol (Ketterer 1986).

GPx and GST have protective effects against potentially damaging oxidants (D' Almedia et al. 1994). GPx and GST utilize GSH as one of their substrates. GPx acts on peroxides while GST plays an important role in detoxification of xenobiotics (Kaplowitz 1980). GST provides protection by facilitating the conjugation between GSH and reactive metabolites of ethanol oxidation. Previous studies have shown that the activity of GPx was decreased significantly in ethanol fed rats (Genc et al. 1998). The decreased activities of these enzymes may be due to the interaction of the

Table 2: Enzyme markers and bilirubin in plasma of control and experimental animals

Parameters	Group 1	Group 2	Group 3	Group 4
AST (IU/L)	34.14 ± 1.3	52.63 ± 1.43[a]	35.65 ± 2.91[b]	36.51 ± 1.98
ALT (IU/L)	34.88 ± 2.48	52.71 ± 4.47[a]	36.24 ± 1.62[b]	34.99 ± 1.82
ALP (IU/L)	72.88 ± 4.21	96.40 ± 4.55[a]	73.58 ± 1.53[b]	74.01 ± 1.60
GGT (IU/L)	0.61 ± 0.007	2.54 ± 0.06[a]	0.65 ± 0.03[b]	0.63 ± 0.03
Bilirubin (mg/dL)				
Unconjugated	0.99 ± 0.18	2.55 ± 0.27[a]	1.13 ± 0.07[b]	1.02 ± 0.12
Conjugated	0.38 ± 0.08	0.91 ± 0.077[a]	0.43 ± 0.07[b]	0.40 ± 0.05

Values are given as mean ± SD from six rats in each group
Group 1 – control; Group 2 – ethanol; Group 3 – ethanol + taurine and Group 4 – control + taurine
a – significant as compared to control (DMRT $p < 0.05$)
b – significant as compared to alcohol (DMRT $p < 0.05$)

Table 3: Levels of GSH in plasma and tissues and total (TSH) and protein-bound thiols (PBSH) in tissues of control and experimental animals

Parameters	Group 1	Group 2	Group 3	Group 4
GSH (units A)				
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
TSH (μmol/mg tissue)				
Liver	15.99 ± 0.65	10.30 ± 0.72[a]	15.83 ± 0.82[b]	16.60 ± 0.46
Brain	9.72 ± 0.59	6.50 ± 0.90[a]	9.33 ± 0.73[b]	10.04 ± 0.17
Kidney	13.77 ± 0.72	10.95 ± 0.61[a]	13.74 ± 0.77[b]	13.97 ± 0.15
Heart	13.87 ± 0.54	9.7 ± 0.50[a]	13.76 ± 0.47[b]	13.88 ± 0.47
PBSH (μmol/mg tissue)				
Liver	9.64 ± 0.61	5.24 ± 0.24[a]	9.49 ± 0.83[b]	10.05 ± 0.49
Brain	5.18 ± 0.11	3.31 ± 0.36[a]	5.09 ± 0.10[b]	5.426 ± 0.16
Kidney	8.38 ± 0.18	7.01 ± 0.36[a]	8.29 ± 0.35[b]	8.30 ± 0.1
Heart	7.68 ± 0.50	5.22 ± 0.49[a]	7.58 ± 0.29[b]	7.62 ± 0.45

Values are given as mean ± SD from six rats in each group
Group 1 – control; Group 2 – ethanol; Group 3 – ethanol + taurine and Group 4 – control + taurine
a – significant as compared to control (DMRT $p < 0.05$)
b – significant as compared to alcohol (DMRT $p < 0.05$)
A – plasma – μmol/l; tissue – μmol/mg tissue

accumulated free radicals and amino acids at the active site of these enzymes.

Ethanol-treated animals co-administered with taurine showed near normal activities of plasma enzymes, thiol status and GSH dependent enzymes indicating restoration of cell and organ function. Taurine, being an antioxidant, has a scavenging action against free radicals. Thus the observed benefits of taurine may be related to a decrease in free radical production and attenuation of oxidative stress.

The favourable effects of taurine in ethanol toxicity have been shown by other investigators. Co-administration of taurine with alcohol results in almost complete inactivation of cytochrome P450 2E1 in the liver (Kerai et al. 1998). Taurine exerts a restorative effect on hepatic lipids and oxidative stress in ethanol treated rats (Balkan et al. 2002). It has also been shown that hepatic steatosis and lipid peroxidation caused by chronic alcohol consumption in rats can be reversed by taurine (Kerai et al. 1999). Taurine protects against a plethora of oxidative stress conditions induced by ammonia (Saransaari 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.

All four groups were treated isocalorically with either glucose or ethanol and had free access to food and water. However rats given ethanol alone consistently gained less weight than the control group. This may be related to the toxicity of ethanol. Alcohol 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 2 rats were receiving less nutrients from the *ad libitum* diet

Table 4: Activities of glutathione peroxidase (GPx) and glutathione-S-transferase (GST) in hemolysate and tissue of control and experimental animals

Parameters	Group 1	Group 2	Group 3	Group 4
GPx (Units A)				
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
GST (Units B)				
Hemolysate	6.00 ± 0.02	4.81 ± 0.02[a]	5.97 ± 0.15[b]	6.02 ± 0.10
Liver	5.52 ± 0.18	4.59 ± 0.03[a]	5.50 ± 0.19[b]	5.50 ± 0.03
Brain	5.31 ± 0.03	4.27 ± 0.03[a]	5.35 ± 0.09[b]	5.40 ± 0.14
Kidney	5.51 ± 0.29	3.94 ± 0.03[a]	5.43 ± 0.27[b]	5.57 ± 0.17
Heart	4.67 ± 0.22	3.87 ± 0.05[a]	4.70 ± 0.03[b]	4.73 ± 0.29

Values are given as mean ± SD from six rats in each group
Group 1 – control; Group 2 – ethanol; Group 3 – ethanol + taurine and Group 4 – control + taurine
a – significant as compared to control (DMRT $p < 0.05$)
b – significant as compared to alcohol (DMRT $p < 0.05$)
A – μg GSH utilised/min/mg protein
B – μmol CDNB-GSH conjugate formed/min/mg protein

and that the taurine effect could be related to increasing appetite and better utilization of nutrients in the diet, leading to increases in body weight and organ weight.
The findings suggest that alterations in thiol status and GSH-dependent enzymes occur during ethanol oxidation and that taurine treatment minimizes the associated pathology. The need for intensive molecular and biochemical studies on the important role that taurine may play in modulating the effects of ethanol is indicated.

4. Experimental

4.1. Animals

Adult male albino Wistar strain rats of bodyweight 170–190 g were purchased from the Central Animal House, Rajah Muthiah Medical College and were fed on a 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 approved by the Institutional Animal Ethics Committee, Rajah Muthiah Medical College, Annamalai Nagar.

4.2. Drugs and chemicals

Taurine was purchased from Sisco Research Laboratories, Mumbai, India. Absolute ethanol (analytical grade) was obtained from Hayman Limited, England. All other chemicals and solvents used were of analytical grade were obtained from S.D Fine Chemicals limited, Mumbai.

4.3. Experimental design

The animals were divided into four groups of six each and were maintained as follows: Group 1 received glucose from a 40% stock glucose solution every day, which was isocaloric to ethanol. Group 2 received ethanol 3 g/kg body weight from 30% stock solution twice daily. Group 3 received 30% ethanol and 2% taurine in drinking water. Group 4 received taurine along with isocaloric amount of glucose. Treatments were carried out for 28 days and rats were fed with commercial rat chow and water *ad libitum*.
At the end of the experiment period the rats were sacrificed after an overnight fast by decapitation, blood was collected in heparinised tubes and plasma was separated. The animals were dissected and tissues (liver, brain, kidney and heart) were removed and cleared of blood and immediately transferred to ice-cold containers containing 0.89% sodium chloride and homogenized in 0.1 M Tris-HCI buffer, pH 7.4.

4.4. Analytical methods

Plasma ALT (E.C. 2.6.1.2) and AST (E.C. 2.6.1.1) were assayed by the method of Rietman and Frankel (1957) and ALP (E.C. 3.1.3.1) by the method of King and Armstrong (1934). GGT (E.C. 2.3.2.2) activity was assayed by the fixed time method of Rosalki and Rau (1972). Conjugated and unconjugated bilirubin was measured by the method of Malloy and Evelyn (1937) and glutathione by the method of Ellman (1959) in plasma. The tissue homogenates were assayed for total, nonprotein and protein thiols by the method of Sedlack and Lindsay (1968). The activity of GPx (E.C. 1.15.1.9) was assayed in hemolysate and tissue homogenates by the method of Rotruck et al. (1973) GST (E.C. 2.5.1.14) in tissue homogenates was assayed by the method of Habig and Jacoby (1974).

4.5. Statistical analysis

Statistical evaluation of data was performed by Duncan's Multiple Range Test to make comparison between groups (Duncan 1957). The level of significance was set at $p < 0.05$.

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