

Taurine Supplementation Reduces the Oxidative Stress Associated with Galactosamine-Induced Fulminant Hepatic Failure in Rats

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The hepatoprotective effect of taurine on galactosamine (GalN)-induced hepatitis, an experimental model for fulminant hepatic failure was studied in Wistar strain male rats. Among the four groups of rats taken for the study, group one served as the control, group two rats were administered with taurine, group three rats were injected intraperitoneally with GalN to induce hepatitis and group four rats were administered with taurine prior to induction of hepatitis. The parameters studied were (i) the concentration of hepatic reduced glutathione (GSH); (ii) levels of hepatic thiobarbituric acid reactive substances (TBARS); (iii) the levels of hepatic antiperoxidative enzymes; (iv) the concentration of liver specific enzymes in serum; and (v) substantiating the biochemical findings by histopathological evidence. Both taurine administered and control rats showed similar values for all the parameters studied, indicating that taurine does not have any undesirable effect. A significant ($p < 0.001$) increase in the levels of enzymes in serum, and levels of TBARS in liver and decrease in the concentration of GSH and antiperoxidative enzymes in liver were observed in GalN-intoxicated rats. Prior treatment with taurine had negated the adverse effects of GalN-induced hepatitis as evidenced by decline in enzyme levels in serum and hepatic TBARS and the restoration of levels of GSH and antiperoxidative enzymes in liver. Liver histopathology shows that prior treatment with taurine protects liver from extensive hepatocellular necrosis caused by GalN intoxication. The present study revealed that administration of taurine reduces oxidative stress in hepatitis-induced rats, attenuates hepatic lipid peroxidation and protects GSH levels.

Key words : Taurine, fulminant hepatic failure, galactosamine, antiperoxidative effect, oxidative stress

Fulminant hepatic failure has an acute and rapid onset (Silva *et al.*, 2005). It is one of the major causes of morbidity and mortality worldwide. Hepatitis is associated with increased free radical production and elevated oxidative stress in hepatocytes (Hagen *et al.*, 1994). D-galactosamine (GalN)-induced hepatitis is an experimental model of human fulminant hepatic failure (Keppler *et al.*, 1968; Makin *et al.*, 1997; El-Mofty *et al.*, 1975). GalN is known to produce various toxic effects in liver. Its adverse effect ultimately is associated with the depletion of uridine triphosphate nucleotides followed by the formation of uridine diphosphate hexosamines (Kmiec *et al.*, 2000) that inhibit transcription and consequently the

translation processes (Keppler *et al.*, 1974). Among other metabolic and morphological mechanisms, oxidative stress has been reported as one of the major causes by which GalN induces liver damage (Andreani *et al.*, 1982; Hu & Chen, 1992; Han *et al.*, 2006). Therapeutic strategies that attempt to minimize the oxidative damage may protect the liver from injury. The sulfur containing β -amino acid taurine (2-aminoethanesulfonic acid) is found in relatively high concentrations in liver, where it accounts for 25% of the free amino acid pool in humans and 50% in rodents (Oudit *et al.*, 2004). Taurine, a conditionally essential amino acid, possesses a number of cytoprotective properties through its actions as an antioxidant, osmoregulator,

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and intracellular calcium flux regulator. In mammals, taurine is neither metabolized nor incorporated into cellular proteins, suggesting an important requirement for free cytosolic taurine. Emerging evidence supports two major mechanisms for the actions of taurine. First, taurine affects simultaneously ion channels, transporters, and enzymes, leading to modulation of intracellular Ca^{2+} levels [Sole & Jeejeebhoy, 2000; Schaffer *et al.*, 2000; Huxtable & Sebring, 1986; Satoh, 1996; Holloway *et al.*, 1999]. Second, taurine's potent antioxidant property enables it to stabilize membranes under various pathophysiological conditions (Satoh, 2001). It is reasonable to hypothesize that taurine, by virtue of its effective antioxidative and membrane stabilizing properties can put in place an effective antioxidant system comprising of antioxidant enzymes and molecules that would protect from GalN-induced peroxidative liver damage. The aim of the study was to evaluate the potential of taurine in alleviating the peroxidative changes that accompany GalN-induced hepatic failure in male albino rats, with a view to draw reasonable conclusions for human beings.

Materials and Methods

GalN and taurine were obtained from M/s. Sigma Chemical Company, St. Louis, MO, USA. All chemicals used were of analytical grade. Twenty four male albino rats of Wistar strain weighing 100-120 g each were obtained from animal facility of the institute. The animals were housed in polypropylene cages maintained at controlled temperature ($22 \pm 2^\circ\text{C}$) and 12 hour day and 12 hour night cycle. Food and water were provided *ad libitum*. The animals were allowed to acclimatize with the laboratory conditions prior to the study by maintaining at the above mentioned conditions for a period of 21 days. Their body weights and feed intake per day were recorded. The study was implemented according to the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), New Delhi, India and

authorized by the Animal Ethics Committee of the Institute.

Four groups of six rats each were fed with commercial pellet diets: Group I rats that served as normal control were injected with physiological saline for 21 days and group II rats were intraperitoneally (i.p.) injected with taurine (100 mg kg^{-1} body wt day⁻¹, dissolved in saline) for 21 days. The dosage of taurine administered and the duration of the study were optimized after conducting preliminary studies with varying amounts of taurine for different time periods (Asha, 2010). Fulminant hepatic failure was induced in group III rats by injecting GalN (500 mg kg^{-1} body wt. day⁻¹), i.p. for 2 days (Hu & Chen, 1992) at the end of experimental period. Group IV was treated with taurine for 21 days prior to induction of GalN hepatitis. At the end of the experimental period, *viz.*, 24 h after the last injection of GalN, the experimental animals were euthanized by placing in chloroform saturated chamber, blood was collected and serum separated. Liver tissue was excised immediately and washed with chilled isotonic saline. Accurately weighed tissue was homogenized in icecold 0.1 M Tris-HCl buffer, having pH 7.2 and centrifuged. The serum and tissue homogenate were used for various biochemical analyses.

Antiperoxidative enzymes catalase (CAT) (Takahara *et al.*, 1960), superoxide dismutase (SOD) (Misra & Fridovich, 1972), glutathione peroxidase (GPX) (Pagila & Valentine, 1974) and glutathione S transferase (GST) (Habig *et al.*, 1974) were estimated in liver tissue homogenate. Thiobarbituric acid reactive substances (TBARS) (Ohkawa *et al.*, 1979), reduced glutathione (GSH) (Ellman, 1959) and protein (Lowry *et al.*, 1951) content of liver tissue were also determined. Serum was used for the assay of liver diagnostic marker enzymes such as alanine aminotransferase (ALT) [EC 2.6.1.2], aspartate aminotransferase (AST) [EC 2.6.1.1], (Mohur & Cook, 1954), acid phosphatase (ACP) [EC 3.1.3.2], alkaline

phosphatase (ALP) [EC 3.1.3.1] (King, 1965), lactate dehydrogenase (LDH) [EC 1.1.1.27] (King, 1965) and gamma glutamyl transferase (GGT) [EC 2.3.2.2] (Szasz, 1969). Histopathological studies of liver tissue were conducted as described by Chowdary *et al.* (1992). The liver tissue from rats was carefully isolated, trimmed of fat and fixed in 10% buffered formalin. The formalin fixed specimens were then dehydrated with ethanol and embedded in paraplast. Sections of 5 to 6 mm size were cut and stained with hematoxylin and eosin. Results are expressed as mean $\pm$ SD. One-way analysis of variance (ANOVA) was carried out, and the statistical comparisons among the groups were performed with Tukey's test using SPSS 10.0 for Windows. A p value of less than 0.05 was considered significant.

Results and Discussion

Levels of liver specific enzymes in serum are presented in Fig. 1 & 2. The levels of ALT, AST, LDH, ALP, ACP and GGT increased significantly ($p < 0.001$) in the

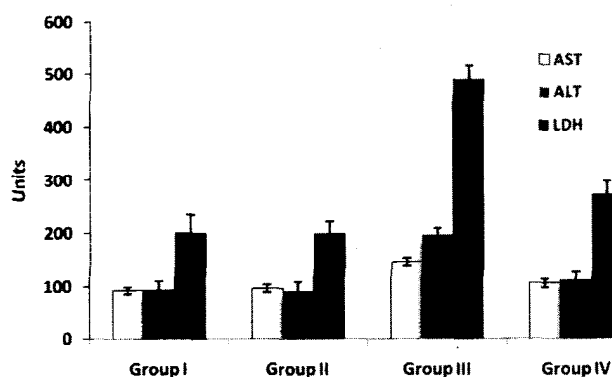


Fig. 1. Levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), in serum of normal and experimental groups of rats. Group I normal control; Group II, treated with taurine (i.p.) (100 mg kg⁻¹ body wt day⁻¹ for 21 days), Group III rats fed on commercial pellet diet and fulminant hepatic failure induced by injecting GalN [500 mg (dissolved in physiological saline) 100 mg kg⁻¹ body weight day⁻¹ for 2 days] and Group IV rats treated with taurine prior to fulminant failure induction. Results are mean $\pm$ SD for six animals. Values expressed: ALT, AST and LDH μ mol pyruvate liberated/h/l.

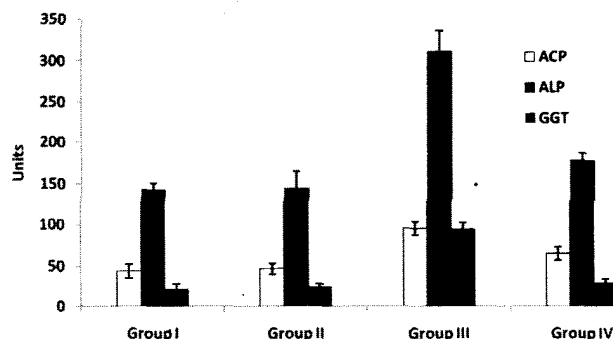


Fig. 2. Levels of alkaline phosphatase (ALP), acid phosphatase (ACP) and gamma glutamyl transferase (GGT) in serum of normal and experimental groups of rats. Group I normal control; Group II, treated with taurine (i.p.) (100 mg kg⁻¹ body wt. day⁻¹ for 21 days), Group III rats fed on commercial pellet diet and fulminant hepatic failure induced by injecting GalN [500 mg (dissolved in physiological saline) 100 mg kg⁻¹ body weight day⁻¹ for 2 days] and Group IV rats treated with taurine prior to fulminant failure induction. Results are mean $\pm$ SD for six animals. Values expressed: ALP and ACP- μ moles phenol/h/l and GGT, μ g nitoraniline liberated /min/l.

serum of rats in which hepatitis was induced by GalN injection when compared to both control and taurine administered groups. In the group where rats were treated with taurine prior to induction of GalN hepatitis, the levels of the above mentioned enzymes reduced substantially.

Antiperoxidative enzymes in liver of experimental rats are given in Fig. 3. CAT, SOD, GPX and GST levels registered significant ($p < 0.001$) decrease in liver of rats induced with GalN hepatitis when compared with control and taurine administered rats. In group IV rats, the level of antiperoxidative enzymes showed substantial rise almost on par with the control values.

Fig. 4 shows the levels of GSH and TBARS in the rats. Taurine administered rats showed slightly higher levels of reduced glutathione that indicate the beneficial effect of taurine on glutathione metabolism in rats. The levels of GSH and TBARS showed significant ($p < 0.001$) decrease and increase respectively in the GalN injected rats indicating the presence of lipid peroxidation.

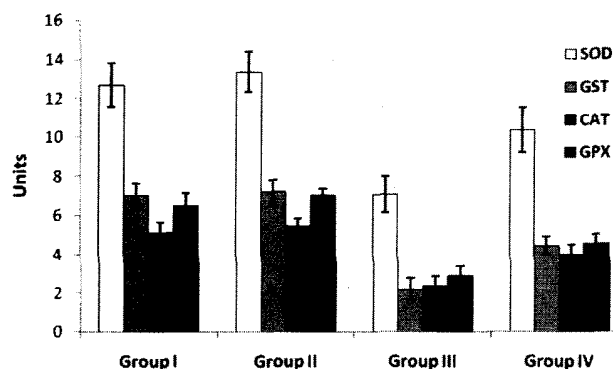


Fig. 3. Activities of catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPX), glutathione S transferase (GST) in liver of normal and experimental rats. Group I normal control; Group II, treated with taurine (i.p.) (100 mg kg^{-1} body wt day^{-1} for 21 days), Group III rats fed on commercial pellet diet and fulminant hepatic failure induced by injecting GalN [500 mg (dissolved in physiological saline) 100 mg kg^{-1} body weight day^{-1} for 2 days and Group IV rats treated with taurine prior to fulminant failure induction. Results are mean $\pm$ SD for six animals. Values expressed- CAT: nmol GSH oxidized/min/mg protein; GST: μmol CDNB conjugate formed/min/mg protein; nmoles H_2O_2 decomposed/min/mg protein; SOD: one unit is the amount of protein required to give 50% inhibition of adrenaline autoxidation.

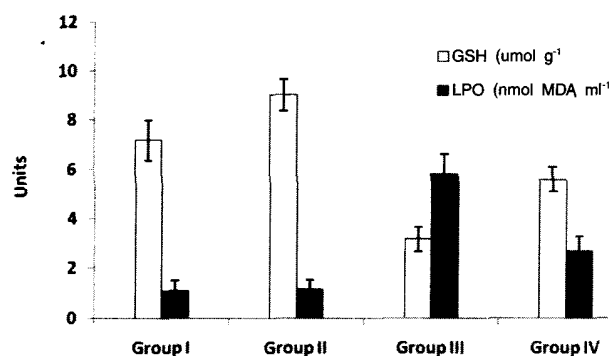


Fig. 4. Concentrations of reduced glutathione (GSH) and thiobarbituric acid reactive substances (TBARS) in liver of normal and experimental rats. Group I normal control; Group II, treated with taurine (i.p.) (100 mg kg^{-1} body wt. day^{-1} for 21 days), Group III rats fed on commercial pellet diet and fulminant hepatic failure induced by injecting GalN [500 mg (dissolved in physiological saline) 100 mg kg^{-1} body weight day^{-1} for 2 days] and Group IV rats treated with taurine prior to fulminant failure induction. Results are mean $\pm$ SD for six animals.

Prior administration of taurine to rats (group IV) has brought the GSH and TBARS to within the level in control rats.

Liver histopathology was evaluated based on sinusoidal congestion, cytoplasmic vacuolization and hepatocellular necrosis. Control and taurine administered rats showed normal histology (Fig. 5, 6) a result which correlates with normal range of liver specific enzymes in serum. GalN-intoxicated rats (Fig. 7.) had livers that showed extensive hepatocellular necrosis and sinusoidal congestion (Fig. 5). In contrast, in taurine-pretreated rats (Fig. 8.) injected with GalN there were only minor patchy spots of mild necrosis signifying effective damage control by taurine.



Fig. 5. The architecture of normal liver tissue in control rats



Fig. 6. The liver tissue in rats administered with taurine indicating no significant changes in architecture in comparison to the normal condition

Liver parenchymal damage results in the liver specific enzymes spilling into the blood stream which explains the rise in their

concentration in serum. GalN injection induces hepatitis and triggers a series of events, which include hepatocellular necrosis and parenchymal cell damage that let the liver enzymes to be released into the blood stream (Sapronov & Gavrovskaya, 1991). In the present study an increase in the concentration of these enzymes following GalN injection was noted and this is in agreement with previous reports (Masano *et al.*, 1985). Taurine alone did not cause any change in the content of liver specific enzymes in serum. However, administration of taurine prior to GalN injection resulted in lower levels of the enzymes in serum, indicating a protective effect of taurine and consequently minimum liver parenchymal damage (Shim *et al.*, 1998). Liver histology of rats of the four groups confirms the above observations.

In the present study, GalN administration increased oxidative stress, suggesting that there is enhanced susceptibility of the membranes to damage. Free radical production and oxidative stress play a key role in the triggering and progression of various pathological states. One of the mechanisms by which GalN brings about its hepatotoxic effect is by destabilizing liver cell membranes by lipid peroxidation (Sakaguchi & Yokota, 1995). Prior treatment with taurine has prevented the GalN-induced elevation in lipid peroxidation products which may be

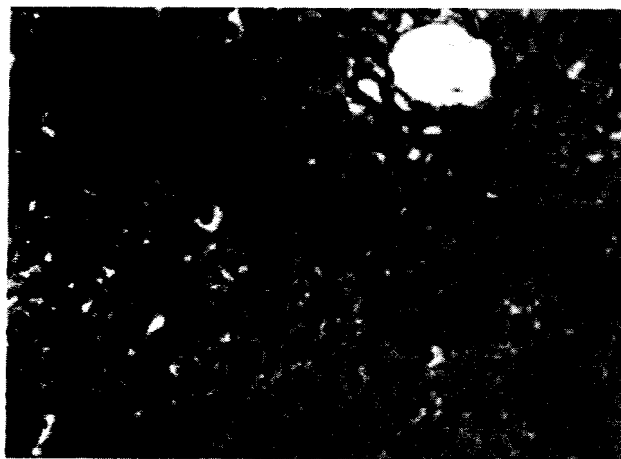


Fig. 7. The architecture of liver tissue in D-galactosamine-administered rats showing necrosis with inflammatory cells



Fig. 8. The architecture of liver tissues in rats treated with taurine and D-galactosamine, showing marked reduction in necrosis and inflammatory cells

due to the direct antioxidant property of taurine (Murakami *et al.*, 2002). Because the potent antioxidant property of taurine may be linked to its sulfur moiety, (Sevier *et al.*, 2002; Woo *et al.*, 2003) it was predicted that taurine may modulate levels of GSH, which is a fundamental defense mechanism in conditions of increased oxidative stress. Interestingly, taurine supplementation completely prevented the GalN-induced decrement in GSH levels ($p < 0.001$). GSH plays an important role in the cellular defense against oxidative stress (Forgione *et al.*, 2002; Li *et al.*, 2003) by regulating the redox status of proteins in the cell membrane (Sole & Jeejeebhoy, 2000).

Taurine can also react directly with a variety of cytotoxic aldehydes, including MDA, suggesting that the protective effects of taurine on liver function may also be related to lowering of aldehyde levels per se (Schuller-Levis & Park, 2003). Moreover, taurine may have a role in mediating anti-inflammatory effects, (Suzuki *et al.*, 2002) and maintaining cellular metabolism via its effect on mitochondria (Inoue *et al.*, 1987).

The antiperoxidative enzymes protect the membranes from free radical attack and prevent lipid peroxidative damage. The system comprising of reduced glutathione, GPX, GST and the cellular NADPH-generat-

ing mechanism together remove hydroperoxides from the cell (Aw & Rhoads, 1994). In detoxification reactions, GST, a scavenging enzyme binds to lipophilic substances and is expected to bind to GalN for GSH conjugation reactions (Homma & Lostowsky, 1985). Therefore, cells depleted of these enzymes cannot fight peroxidation effectively, leading to membrane and cell damage. In the present study, in GalN-induced hepatitis, liver showed a significant decline in the levels of these enzymes, which enhances the susceptibility of the liver for peroxidative damage. Taurine treatment restored the levels of these enzymes in the liver of hepatitis induced rats, an effect that may be a direct consequence of taurine's antioxidant and membrane stabilizing properties.

In summary, GalN induced fulminant hepatic failure model shows that taurine supplementation has unequivocal beneficial effects on hepatic structure and function, with marked reductions in lipid peroxidation products in GalN induced oxidative stress. The role of taurine in preserving reduced glutathione levels provides an important mechanism by which oxidative stress induced hepatic damage can be curtailed. The present study substantiates a hepatoprotective effect of taurine in the experimental animals. Given the impressive benefit and absence of toxicity with taurine supplementation, it is proposed that increased dietary taurine intake represents an important nutritional modification that may prove to be a useful intervention to reduce the oxidative stress related alterations in fulminant hepatic failure.

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