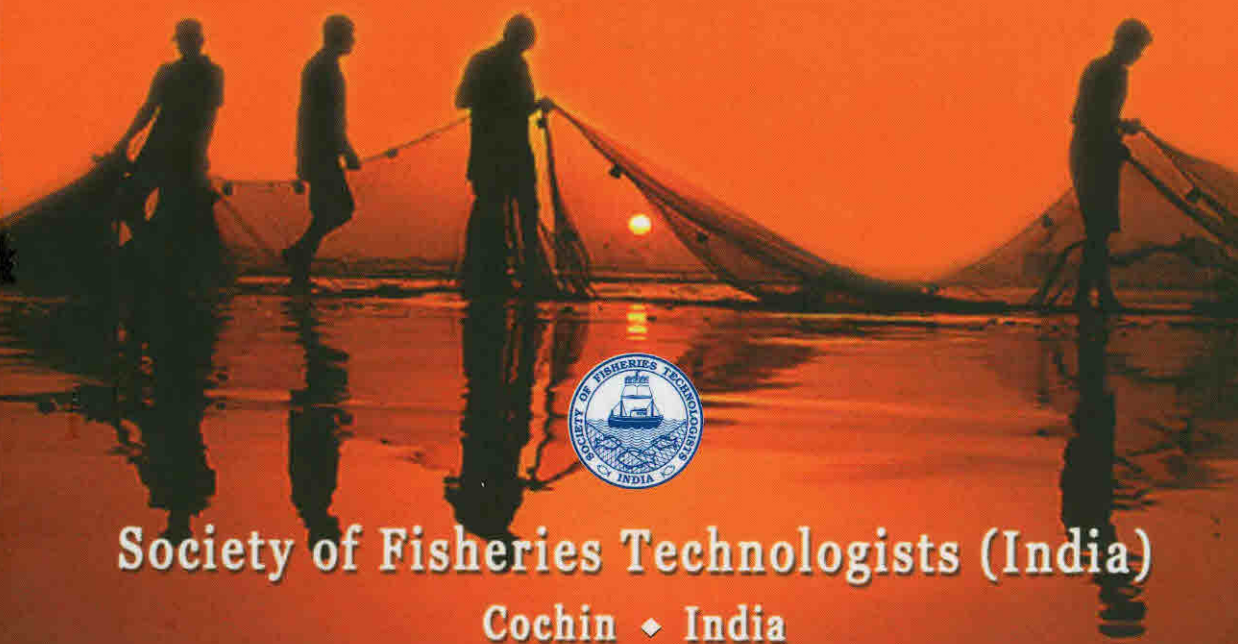
Coastal Fishery Resources of India

Conservation and Sustainable Utilisation



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2010

Effect of Taurine on Glucose Metabolism in Experimentally-induced Fulminant Hepatic Failure in Rats

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Introduction

Fulminant hepatic failure (FHF) is a devastating illness that has a high mortality rate and affects patients with previously healthy livers (Moreno-Gonzalez *et al.* 1995). Although an uncommon disorder, it is usually fatal and is defined as the occurrence of encephalopathy in a previously healthy person, within eight weeks from onset of severe liver disease. Although the etiology of FHF remains unclear, viral hepatitis and drug-induced liver injury account for the majority of causes. FHF caused by viral hepatitis is a national health problem in the developing countries. Hepatitis E causes large-scale epidemics of hepatitis in the Indian subcontinent, involving hundreds of thousands of cases with high mortality (Acharya *et al.,* 2000; Khan *et al.,* 2006) Clinical features of FHF can be divided into two broad groups: (i) manifestations of acute hepatic injury, namely, jaundice, shrunken liver, high liver enzymes, deficiency of clotting factors and other synthetic functions of the liver; and (ii) multi-organ failure and a wide range of metabolic disturbances. All patients should be managed in an intensive care setting pending transfer to a liver transplantation center. Several issues namely selection of patients, appropriate timing of the transplant, the difficulty of making donor liver available within a short period of time, and postoperative course of these sick patients, and the fact that liver transplant should take place before severe irreversible brain damage has made transplantation for FHF a very challenging field (Turchetti, 2003). Despite this complexity, impressive recent progress has been achieved in advancing our understanding and appreciation of the cellular processes and mechanistic bases underlying fulminate hepatic failure. Effective clinical application of hepatoprotective and cytotrophic drugs may offer valuable time to provide a donor liver, or alternatively, to allow the native liver to regenerate.

FHF is associated with a number of metabolic changes among which disturbances in glucose metabolism are significant. Hypoglycemia is common, resulting in precipitous deterioration in mental state (Doria *et al.,* 2006). The hypoglycemia is a consequence of impaired gluconeogenesis (Bernstein and Tripod, 1998) and inability to mobilize glycogen stores (Heneghan, 2007).The major abnormalities noticed in FHF are oxidative free radical damage and loss of plasma membrane integrity apart from defects in protein synthesis. A wide range of chemical agents have been analyzed for possible hepatoprotective effect. Most of these are synthetic and many are known to produce undesirable side effects (Wang *et al.,* 2007). It is appropriate thus to use a biological molecule with antioxidant and membrane stabilizing properties but devoid of adverse side effects, as a therapeutic to effectively counteract the above mentioned aberrations. It could be of great significance if such a molecule was also an integral part of the living system. Increasing attention is being given world wide on therapeutic effects of naturally occurring substances like vitamins, minerals, amino acids, small bioactive peptides commonly referred to as nutraceuticals. A number of researchers have been investigating the association between nutrients and liver disease.

Taurine (2-aminoethanesulfonic acid), a non-protein sulfur containing amino acid, is the most abundant free amino acid and has been shown to play several essential roles in the human body (Lombardini *et al.,*1996)). It is widely distributed in very high concentrations in brain, liver, heart, kidney, lens, and reproductive organs (Huxtable, 1992). It is involved in various important biological and physiological functions, which include cell membrane stabilization (Heller-Stilb *et al.,* 2002)), antioxidation (Atmaca, 2004), detoxification (Birdsall, 1998), osmoregulation (Timbrell *et al.,* 1995), neuromodulation and brain (Huxtable, 1992) and retinal development (Wright *et al.,* 1986). Earlier studies demonstrated that pathology develops if the animal is depleted of taurine stores either through a taurine deficient diet or use of taurine transport antagonists (Heller-Stilb *et al.,* 2002; Warskulat *et al.,* 2004). The protective effect of taurine on glucose metabolism in experimentally–induced FHF in rats was studied. D-galactosamine (D-galN) injection produces hepatic failure in rats that is biochemically and histologically similar to FHF in humans (Newsome *et al.,* 2000).

Materials and Methods

Taurine, tetraethoxy propane and D-galN were obtained from M/s. Sigma Chemical Company, St. Louis. MO, USA. All the other chemicals used were of analytical grade.

Adult male Wistar strain albino rats, weighing 100-120g were selected for the study. The animals were housed individually in polyurethane cages under hygienic conditions and maintained at normal room temperature. The animals were allowed food and water *ad libitum*. The experiment was carried out according to the guidelines of Committee for the Purpose of Control and Supervision of experiments on Animals (CPCSEA), New Delhi, India, and approved by the Institutional Animal Ethics Committee.

Fulminant hepatic failure was induced in experimental rats by injecting D-galN (500 mg/100g body weight/day), i.p. for 2 days (Anandan and Devaki, 1999). Seven days after acclimatization, the animals were further divided into four groups of 6 rats each. Group I and group III animals were fed on commercial feed for 45 days and group II and group IV animals were fed on commercial feed with added taurine at 100 mg/kg body weight level for a period of 45 days. After 45 days feeding, the group III and group IV animals were intraperitoneally (i.p.) injected with D-galN (500 mg/100g body weight $^{-1}$day^{-1}) for 2 days for the induction of fulminant hepatic failure.

At the end of the experimental period, i.e., 24 h after last injection of D-galN, the experimental animals were sacrificed, blood was collected using sodium citrate as anticoagulant and the plasma separated was used for assay of various biochemical parameters. The liver tissue was excised immediately and washed with chilled isotonic saline. Accurately weighed liver tissue was homogenized in ice-cold 0.1 M Tris-HCl buffer, pH 7.2 and centrifuged. The supernatant was used for further biochemical analyses.

Blood glucose (Folin and Wu, 1919) and liver glycogen (Plummer, 1952) content were estimated. The activities of glycolytic enzymes hexokinase (Somogyi, 1952) and glucose-6-phosphate dehydrogenase (Glock and McLean, 1953); gluconeogenic enzymes, glucose-6-phosphatase (Nordlie and Arion, 1966) and fructose-1, 6-bis phosphatase (Pontremoli *et al.,* 1965); and glycogenolytic enzyme glycogen phosphorylase (Suzuki and Hikino, 1989) were assayed in liver of normal, taurine-administered and FHF-induced rats. Protein was estimated by the method of Lowry (Lowry *et al.,* 1951). Results were expressed as means ± SD and Student's *t*-test was used to assess statistical significance.

Results and Discussion

Liver glycogen is a molecule that functions as the secondary long-term energy storage in animal cells. It is made primarily by the liver through

glycogenesis (Saladin, 2007). In the liver hepatocytes, glycogen can comprise up to 8% of the fresh weight and it plays an important role in the glucose cycle (Campbell *et al.,* 2006). Glycogen forms an energy reserve that can be quickly mobilized to meet a sudden need for glucose. In the present study, a significant ($p<0.001$) decrease in the liver content of glycogen was noted in group III rats intoxicated with D-galN when compared to normal group I rats. This is in agreement with similar reports. Hou *et al.* (2008) describe a decrease in hepatic glycogen stores of rats upon D-galN administration in their study. Following D-galN injection, the hepatic carbohydrate metabolism was greatly altered to maintain plasma glucose concentration. Glycogen dropped during the first hours, remaining low for up to 48 h.

Pretreatment of group IV rats with taurine significantly ($p<0.001$) elevated the levels of glycogen (Fig. 1) in liver when compared to group III D-galN-intoxicated rats. Several other reports support this observation. (De Oliveira *et al.,* 1992) The ability of taurine to restore the levels of glycogen in liver may in part be explained by its effect on the activity of the glycogenolytic enzyme glycogen phosphorylase that catalyzes the breakdown of glycogen.

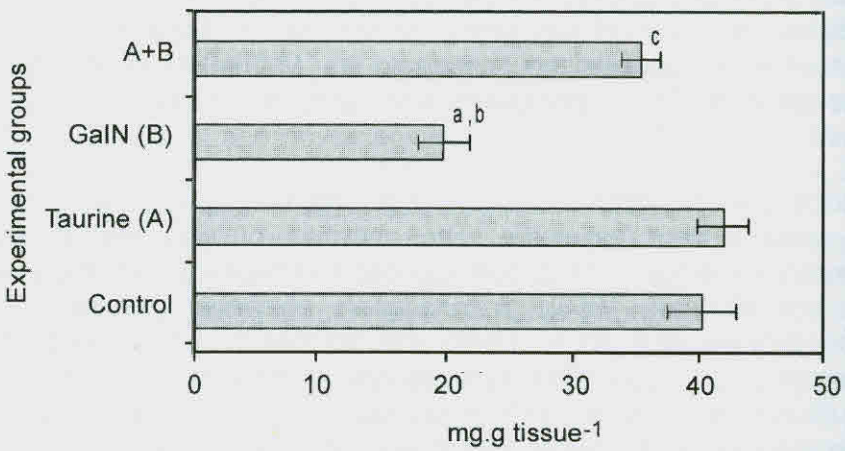

Fig 1. Levels of glycogen in liver of control and experimental groups of rats (A: Taurine, 100mg kg^{-1} body wt day^{-1}, i.p. for 21 days; B: D-galN, 500mg100g^{-1} body weight day^{-1}, i.p. for 2 days. Results are mean ± SD for 6 animals; One way ANOVA; $^{a}p<0.001$ significantly different compared with group I control animals; $^{b}p<0.001$ significantly different compared with group II taurine-administered animals; $^{c}p<0.001$ significantly different compared with group III D-galN -induced hepatic failure rats.)

In the present study D-galN intoxicated group III rats caused a significant ($p<0.001$) rise in the activity of the glycogen phosphorylase (Fig 2) resulting in depletion of the hepatic glycogen stores. This trend may be to compensate for the hypoglyceamia seen after D-galN injection as reported earlier (Mourelle and Meza, 1989). Prior administration of taurine in rats of group IV injected with D-galN has resulted in significant ($p<0.01$) decrease in the hepatic activity of glycogen phosphorylase (Fig 2) when compared to group III D-galN intoxicated rats. This effect of taurine aids in enhancing the glycogen stores in the liver (Anandan et *al.,* 2000). Taurine is reported to cause the stimulation of glycolysis and glycogenesis and the later was shown to be promoted because of the increase in glycogen synthase I and decrease in glycogen phosphorylase a activity. These effects of taurine were shown to be dependent on insulin concentration, suggesting a link between the two substances (Yamamoto *et al.,* 1995).

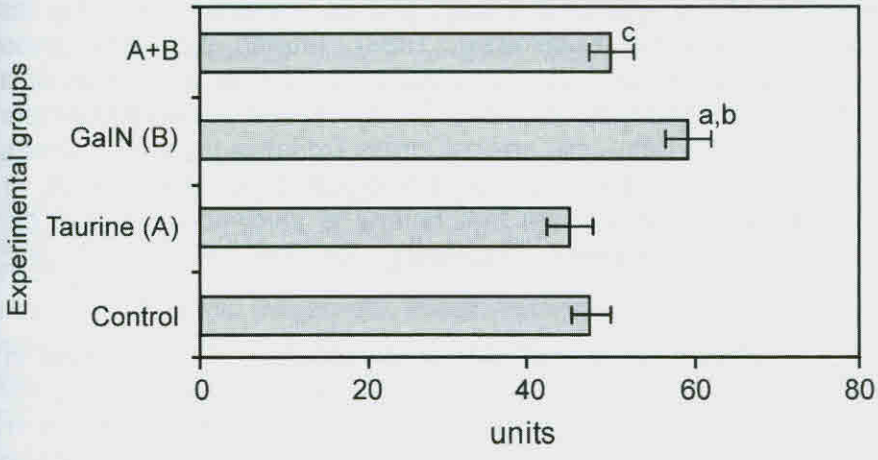

Fig. 2: Activity of glycogen phosphorylase in liver of control and experimental groups of rats

(A: Taurine, 100mg kg^{-1} body wt day^{-1}, i.p. for 21 days; B: D-galN, 500mg100g^{-1} body weight day^{-1}, i.p. for 2 days. Results are mean ± SD for 6 animals; One-way ANOVA; $^{a}p<0.001$ significantly different compared with group I control animals; $^{b}p<0.001$ significantly different compared with group II taurine-administered animals; $^{c}p<0.01$ significantly different compared with group III D-galN -induced hepatic failure rats)

Taurine is involved in many important biological functions including osmoregulation, inhibition of protein phosphorylation and calcium modulation (Yamamoto *et al.,* 1995). It is found at high concentrations

within pancreatic islets (Bustamante *et al.*, 1998). Taurine reduces the rate of apoptosis (Merezak *et al.*, 2001) and acts on DNA synthesis, preventing abnormal development of the endocrine pancreas (Boujendar *et al.*, 2003). Taurine has important effects on insulin secretion. In fetal rat islets, taurine increases glucose-stimulated insulin secretion and enhances the action of some secretagogues, such as leucine or arginine (Cherif *et al.*, 1998). In an animal model of fetal protein malnutrition, taurine supplementation normalized islet cell proliferation and insulin secretion (Kalbe *et al.* 2005).Furthermore, in guinea pigs with hyperglycemia, taurine administration significantly decreased blood glucose levels (Kaplan *et al.*, 2004). Moreover, it has been shown that taurine increases glucose sensitivity cells by enhancing mitochondrial metabolism, at least partially by acting on the mechanism for Ca^{2+} sequestration into the mitochondrial matrix (Han *et al.,* 2004). Finally, taurine inhibits ATP-sensitive K^{+} (KATP) channel activity in adult rat beta cells (Park *et al.*, 2004). In addition, there is evidence indicating that taurine also has hypoglycemic properties due to the potentiation of the effects of insulin and its interaction with the insulin receptor (Maturo and Kulakowski, 1988). Taurine increases glycogen synthesis, glycolysis and glucose uptake in the liver and heart of adult rats (Kulakowski and Maturo, 1984). Finally, taurine antioxidant properties protect pancreatic beta-cells against stress oxidative-induced decrease in function observed in some pathophysiological conditions (Kaniuk *et al.*, 2007). These actions indicate that taurine is involved in distinct central and peripheral processes necessary for the control of glucose homeostasis.

In the present study there was a marked ($p<0.001$) decrease in the levels of plasma glucose (Fig. 3) in group III rats when compared to normal group I rats. This is in agreement with similar published reports. In D-galN -induced hepatic failure hypoglycemia is a marked feature (Anandan et *al.*, 2000). It is attributed to the depletion of glycogen stores in liver injury due to enhanced glycogenolysis. Also there is increase in the rate of glycolysis, the reason being hyperinsulinemic condition brought about by D-galN injection. Ozeki *et al.* (1982) reported that intraperitoneal injection of a single dose of D-galN hydrochloride resulted in remarkable decreases of glycogen and UDPG in severely damaged liver which (Ozeki *et al.*, 1982), which may be the cause of hypoglycemia.

Pretreatment of group IV rats with taurine has resulted in notable ($p<0.001$) rise in blood glucose levels (Fig. 3) to normal levels when compared to group III D-galN -intoxicated rats. Though taurine is reported

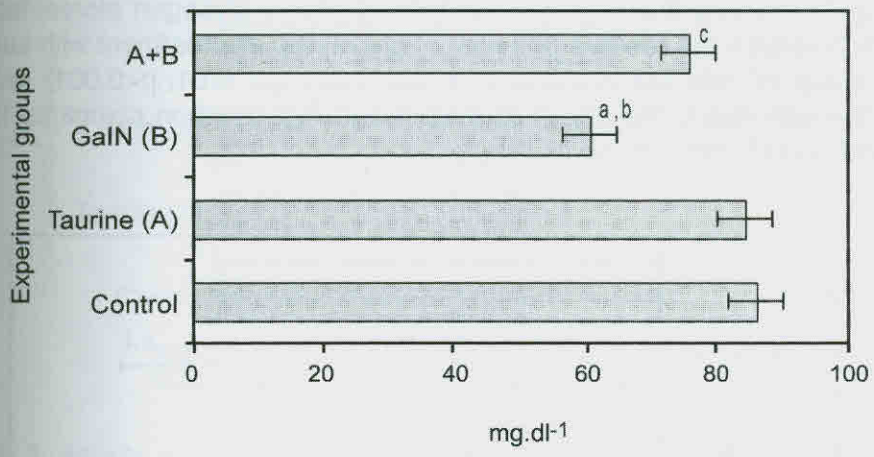

Fig. 3. Levels of glucose in blood of control and experimental groups of rats (A: Taurine, 100mg kg^{-1} body wt day^{-1}, i.p. for 21 days; B: D-galN, , 500mg$100g^{-1}$ body weight day^{-1}, i.p. for 2 days. Results are mean ± SD for 6 animals; One-way ANOVA: $^{a}p<0.001$ significantly different compared with group I control animals; $^{b}p<0.001$ significantly different compared with group II taurine-administered animals; $^{c}p<0.001$ significantly different compared with group III D-galN -induced hepatic failure rats)

to decrease the concentrations of glucose, and increase the contents of insulin, C-peptide, and glycogen in the liver in many studies associated with experimental diabetes mellitus and these effects combine to make taurine hypoglycemic (Miyamoto, 2003), taurine in this study has elevated glucose levels. This may be due to taurine's potential to counteract the galN–induced aberrations and its overall positive effect on glucose homeostasis and its influence on all pathways of glucose metabolism that occur in the liver.

The activities of hexokinase and glucose-6-phosphate dehydrogenase were assayed to delineate the effect of taurine on glycolysis in D-galN induced hepatic failure. The two enzymes catalyze rate limiting reactions in glycolysis and their activities are reported to be increased in D-galN -induced fulminant hepatic failure (Yamamoto *et al.,* 1995). The present study too describes a similar trend. There is a significant ($p<0.001$) rise in the levels of hexokinase (Fig. 4) and glucose-6-phosphate dehydrogenase (Fig. 5) in the group III D-galN -injected rats when compared to normal group I control rats. Topaloglu *et al.* (1996) showed that galactosamine altered glucose transport and induced hypoglycemia and a high mortality in ten-day-old rats treated with a low dose of endotoxin.

D-galN reduces tissue glucose uptake, depletes glycogen stores; factors which reduce the reserve potential of glycolysis. Pretreatment with taurine in group IV rats has resulted in a significant ($p< 0.01$; $p<0.001$) decline in the activities if the enzymes (Fig. 4 and Fig. 5) when compared to D-galN -intoxicated group III rats.

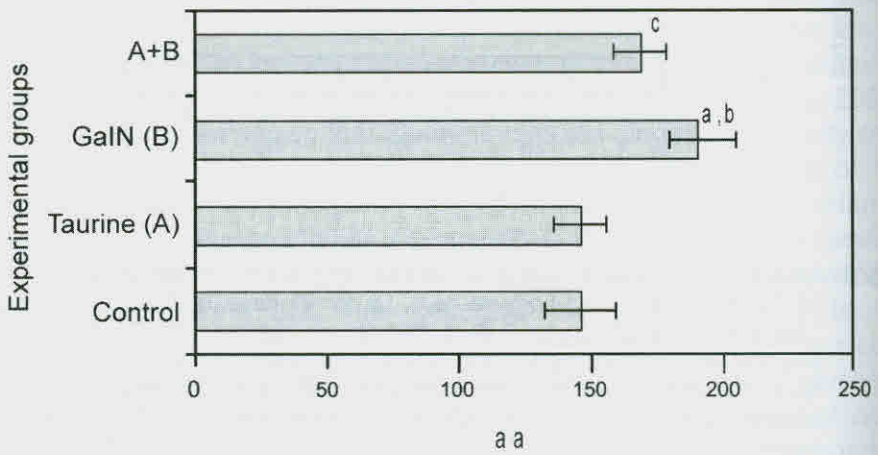

Fig. 4: Activity of hexokinase in liver of control and experimental groups of rats (A: Taurine, 100mg kg^{-1} body wt day^{-1}, i.p. for 21 days; (B): Galactosamine, 500mg100g^{-1} body weight day^{-1}, i.p. for 2 days. Results are mean ± SD for 6 animals; One-way ANOVA: $^{a}p<0.001$ significantly different compared with group I control animals; $^{b}p<0.001$ significantly different compared with group II taurine-administered animals; $^{c}p<0.01$ significantly different compared with group III galactosamine-induced hepatic failure rats.)

Glucose-6-phophatase and fructose-1, 6-bis phospahatase are enzymes catalyzing rate limiting reactions in gluconeogenesis. Their activities were measured to describe the effect of taurine on galN induced hepatic failure. Gluconeogenesis is reported to be taking place at a reduced rate in GalN intoxicated rats. Severe hepatic damage with massive necrosis causes a decrease in the activities of glucose-6-phosphatase and fructose-l, 6-diphosphatase as reported earlier (Kulakowski and Maturo 1984). Therefore, glucose release from liver into the blood stream decreases and the inhibition of gluconeogenesis occurs. The present study also shows similar results. There is a significant ($p<0.001$) decrease in the activity of glucose-6-phosphatase (Fig. 6) and fructose-1,6 bis phosphatase (Fig. 7) in group III rats intoxicated with GalN when compared to normal group I rats. It has been demonstated that in FHF-induced rat

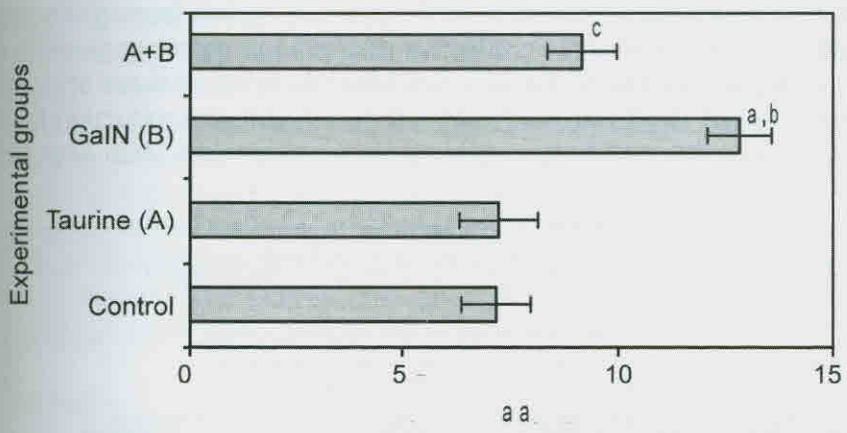

Fig. 5: Activity of glucpse-6-phosphate dehydrogenase in liver of control and experimental groups of rats

(A: Taurine, 100mg kg^{-1} body wt day^{-1}, i.p. for 21 days; (B): Galactosamine, 500mg100g^{-1}.body weight.day^{-1}, i.p. for 2 days. Results are mean ± SD for 6 animals; Oneway ANOVA; SPSS version 10. $^{a}p<0.001$ significantly different compared with group I control animals; $^{b}p<0.001$ significantly different compared with group II taurine-administered animals; $^{c}p<0.001$ significantly different compared with group III D-galN-induced hepatic failure rats.)

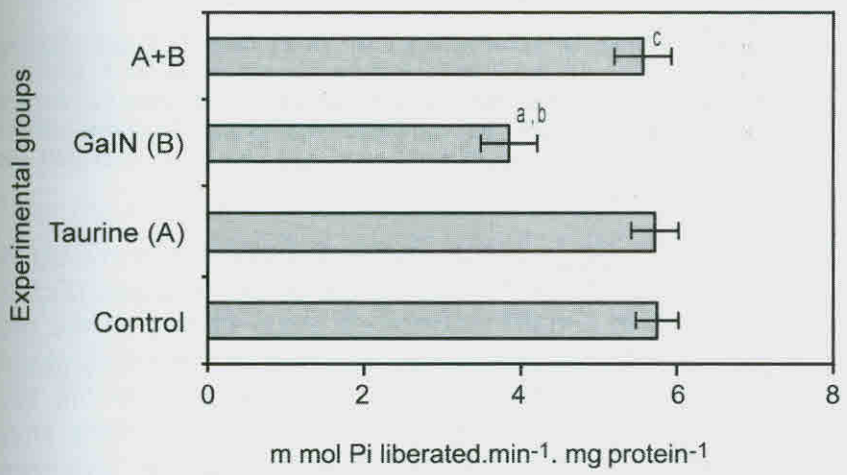

Fig. 6: Activity of glucose-6-phosphatase in liver of control and experimental groups of rats

(A: Taurine, 100mg kg^{-1} body wt day^{-1}, i.p. for 21 days; B: Galactosamine, 500mg100g^{-1}.body weight.day^{-1}, i.p. for 2 days. Results are mean ± SD for 6 animals; One-way ANOVA: $^{a}p<0.001$ significantly different compared with group I control animals; $^{b}p<0.001$ significantly different compared with group II taurine-administered animals; $^{c}p<0.001$ significantly different compared with group III D-galN-induced hepatic failure rats.)

livers there was reduced amino acid uptake, a switch from gluconeogenesis to glycolysis, causing an effective decrease in gluconeogenesis when compared with normal fasted rat livers. Mass-balance analysis showed that hepatic glucose synthesis was inhibited as a result of a reduction in amino acid entry into the tricarboxylic acid cycle by anaplerosis (Arai *et al.*, 2001).

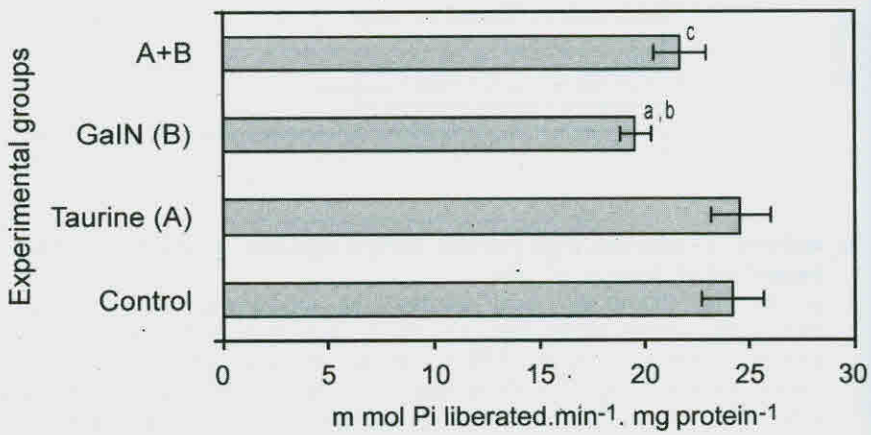

Fig. 7: Activity of fructose 1, 6 bis phosphatase in liver of control and experimental groups of rats
(A: Taurine, 100mg kg^{-1} body wt day^{-1}, i.p. for 21 days; B: D-galN, 500mg100g^{-1}.body weight.day^{-1}, i.p. for 2 days. Results are mean±SD for 6 animals; One-way ANOVA: $^{a}p<0.001$ significantly different compared with group I control animals; $^{b}p<0.001$ significantly different compared with group II taurine-administered animals; $^{c}p<0.01$ significantly different compared with group III D-galN -induced hepatic failure rats.)

Pretreatment with taurine in group IV rats has resulted in a significant ($p< 0.001$; $p<0.01$) increase in the activities of the enzymes (Fig. 6 and 7) when compared to D-galN -intoxicated group III rats. In the present study taurine has restored glucose homeostasis by regulating glycolysis, and gluconeogenic rates and elevated glycogen levels in the liver by inhibiting glycogenolysis. The activities of the rate limiting enzymes (hexokinase and glucose-6-phosphate dehydrogenase) in glycolysis are lowered and that of gluconeogenesis (glycogen phosphorylase) is enhanced to regularize the blood glucose levels. During the last years, several studies have shown that taurine is involved in different central (strict regulation of insulin synthesis and secretion) (Cherif *et al.*, 1998) and peripheral (peripheral metabolic effects of insulin) (Kalbe *et al.*, 2005) processes necessary for the control of glucose homeostasis, however, the key events underlying effects of taurine on blood glucose levels remain

unknown (Nandhini *et al.,* 2004). Taurine supplementation modulates glucose homeostasis via â-cell stimulus–secretion coupling and enhancing peripheral insulin sensitivity. Taurine appears to act by regulation of the expression of genes required for glucose-stimulated insulin secretion depending on the glycemic state (Carneiro *et al.,* 2009). The transcription factor PDX-1 is required for the expression and regulation of insulin and other proteins involved in the stimulus–secretion coupling in beta-cells including Glut-2 and glucokinase (Watada *et al.*, 1996). Carneiro *et al.,* (2009) demonstrated that taurine modulated levels of PDX-1 in response to glycemic state and maintained the blood glucose homeostasis.

Conclusion

Taurine supplementation in diet prior to induction of FHF with D-galN has restored glucose homeostasis. Taurine seemed to affect all the pathways of glucose metabolism, modulating the activities of rate limiting enzymes of key pathways in glucose metabolism like glycolysis, gluconeogenesis and glycogenolysis. Since imbalance in glucose metabolism is one of the key features in FHF, treatment with taurine could present a much required relief from symptoms associated with impaired glucose metabolism.

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