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Taurine modulates kallikrein activity and glucose metabolism in insulin resistant rats

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Summary. Taurine, a potent antioxidant has been reported to show an anti-diabetic effect in streptozotocin-induced diabetes mellitus in which the development of hyperglycemia results from the damage to β cells of pancreas by reactive oxygen species. In addition, taurine also increases the excretion of nitrite and enhances the formation of kinins and would be expected to improve insulin resistance. The effect of taurine on insulin sensitivity was examined in the high fructose-fed rats, an animal model of insulin resistance. Male Wistar rats of body weight 170–190 g were divided into 4 groups: a control group and taurine-supplemented control group, taurine supplemented and unsupplemented fructose-fed group. An intravenous glucose tolerance test (IVGTT) and a steady state plasma glucose level (SSPG) were performed before the sacrifice. The fructose-fed rats displayed hyperglycemia and insulin resistance and they had a greater accumulation of glycogen than did control rats. Hyperglycemia and insulin resistance were significantly lower in the taurine supplemented fructose-fed group than in the unsupplemented fructose-fed group. Urinary kallikrein activity was higher in taurine-treated animals than in the rats fed only fructose. The activity of membrane bound ATPases were significantly lower in fructose-fed rats than in the control rats and were significantly higher in the taurine supplemented group than in the fructose-fed group. Taurine effectively improves glucose metabolism in fructose-fed rats presumably via improved insulin action and glucose tolerance.

Keywords: Taurine – Insulin resistance – Glucose tolerance – Hepatic enzymes-membrane ATPases – Urinary kallikrein

Introduction

Taurine (2 amino ethane sulfonic acid) is the major free amino acid in the plasma and cytosol. It is present at millimolar concentrations in many animal tissues, including nervous tissue, heart, liver, retina and neutrophils

(Yokogoshi, 1999). Taurine has various biological and physiological functions and are extensively reviewed (Huxtable, 1992). Bile salt formation and detoxification of xenobiotics are its firmly established physiological functions. Experimental studies have documented antihypertensive (Dawson et al., 2000), antiatherogenic (Murakami et al., 1996), antioxidant (Green et al., 1991) antiarrhythmic (Nara et al., 1978) and anticonvulsive (Oja and Kontro, 1978) actions of taurine. Taurine is used to treat anxiety, hyperactivity, poor brain function, epilepsy, hypertension and seizures (Yamori et al., 1996).

Taurine has been implicated to affect carbohydrate metabolism. For e.g. the hypoglycemic and antidiabetic actions of taurine have been demonstrated about 20 years ago in experimental animals (Tokunaga et al., 1983). Some observations suggest that taurine in some way affects glucose utilization and interact with insulin receptors. (Kulakowski et al., 1985).

Taurine also exhibits membrane-stabilizing activity. It facilitates the passage of sodium, potassium, and possibly calcium and magnesium ions into and out of cells and electrically stabilizes cell membranes (Gaull, 1989). The cellular mechanism of action of taurine is under investigation and appears to involve the interaction of the sulphonic amino acid with several ion channels.

Kinins including bradykinin are polypeptides liberated from plasma and tissue kininogens by several proteases, including the kallikreins. Several observations indicate that kinins can affect glucose uptake and insulin release and insulin action (Damas et al., 1999). Taurine is reported to activate the renal kallikrein – kinin system since elevation of urinary kallikrein activity as measured by a synthetic substrate was increased after taurine supplementation in normal rats (Kohashi et al., 1989).

Varying the type of carbohydrate in the diet can influence glucose metabolism and insulin action. For e.g, rats consuming a high fructose diet develop insulin insensitivity and glucose intolerance (Bezerra et al., 2000) and are widely used as a non – obese model for studying insulin resistance. Insulin resistance in animals fed a high fructose diet is associated with a decrease in hepatic glucose uptake and glycogen synthesis and increase in hepatic glucose output. Fructose rich diet was also shown to be associated with the reduction of insulin receptor kinase *in vitro* (Boyd et al., 1990). No previous studies are available on the effect of taurine in diet-induced insulin resistance state. In the present work we report the effect of taurine co-administration on the levels of glucose and insulin, hepatic glucose metabolism, glycogen content, glucose tolerance and the ion channels (membrane bound ATPases) in fructose-fed insulin resistant rats. Urinary kallikrein excretion was also determined in these rats to test the involvement of kinins in the action of taurine.

Materials and methods

Animals

Male adult Wistar rats of body weight ranging from (170–190 g) were obtained from the Central Animal House, Rajah Muthiah Medical College, Annamalai University. They were housed two per cage under controlled conditions on a 12 h light/12 h dark cycle. They

all received a standard pellet diet (Karnataka State Agro Corporation Ltd, Agro feeds division, Bangalore, India) and water *ad libitum*.

After acclimatisation the animals were divided into the following groups consisting of 12 rats each.

Experimental groups

Group 1– Control animals (CON) received the commercial diet containing vegetable starch (61%) as the sole source of carbohydrate and tap water *ad libitum*.

Group 2– Fructose-fed animals (FRU) received a fructose-enriched diet containing 60% fructose, 20% casein, 0.7% methionine, 5% groundnut oil, 10.7% wheat bran and 3.5% salt mixture and water *ad libitum*. 0.2 ml of vitamin mixture [Vitamin A concentrate I.P., 2500 I.U; Vitamin D_3 Cholecalciferol, 200 I.U; Thiamine hydrochloride, 0.5 mg; Riboflavin, 0.5 mg; Pyridoxin, 0.5 mg; Sodium pantothenate, 1.5 mg; Nicotinamide, 5 mg; Ascorbic acid, 25 mg. (ABDEC multi vitamin drops, Pharmpak pvt. Ltd., Mumbai)] was added per kg feed. The diet was prepared freshly every day.

Group 3– Fructose-fed animals (FRU-TAU) received the fructose diet and were allowed to drink 2% taurine solution *ad libitum.*

Group 4– Control animals (CON-TAU) received the commercial diet and were given 2% taurine solution *ad libitum.*

The animals were maintained in their respective groups for 30 days. Food intake, fluid intake and body weight changes were measured regularly. 24 h urine samples were collected during the end of the experimental period.

Investigations: Insulin sensitivity

Insulin sensitivity was assessed in 6 animals from each group by the insulin suppression test (Reaven et al., 1983). For this the animals were fasted overnight and were anaesthetized by an intraperitoneal injection of phenobarbitone (40 mg/kg body weight). Rats received continuous infusion of a solution containing epinephrine (0.08 μg/kg/min), propranolol (1.7 μg/kg/min), glucose (8 mg/kg/min) and insulin (2.5 mU/kg/min) for 160 min. Tail blood samples were taken during the last hour at 15-minute intervals. Mean glucose concentrations were then determined by the method of Sasaki and Matsui (1972). An intravenous glucose tolerance tests (IVGTT) was performed two days before the sacrifice of the animals. For this the rats were fasted overnight and glucose (0.5 g/kg) was given from 30% solution through the tail vein. Blood samples were collected sequentially from the tail vein before and 10,30 and 60 min after the glucose load. All the samples were collected in heparinized test tubes and were immediately used for glucose determination. IVGTT curve was prepared by plotting blood glucose (mmol/L) levels against time (minutes).

Biochemical analysis

At the end of 30 days, the animals were anaesthetized using light ether and sacrificed by cervical decaptitation. Blood was collected and processed for the determination of glucose. Liver was cleared of adhering fat, weighed accurately and cut into fragments and homogenized in a known volume of 0.1 M Tris-HCl buffer, pH 7.4 using a Potter-Elvehijiam homogeniser with a Teflon pestle. Aliquots from the homogenate were used for further studies.

Blood glucose was estimated by the method of Dubowski as modified by Sasaki and Matsui (1972). Plasma insulin was determined by the microparticle enzyme immuno assay

method, using a reagent kit obtained from Abbott laboratories, Diagnostic Division Dainabot, Tokyo, Japan. The insulin levels in plasma were expressed as μU/ml. Glycogen content in liver and muscle were estimated by the method of Morales et al. (1973).

Glucose-6-phosphatase activity was assayed by the method of Kumari and Mathew (1995). Hexokinase (Brandstrup et al., 1957) was assayed by determining the μmoles of glucose used up in the reaction system. Glucose-6-phosphate dehydrogenase activity was determined in the tissue homogenate by the method of Ells and Kirkman (1961). Total ATPase activity was estimated in RBC membrane by Evans (1969) with slight modifications. The activity of Ca^{2+} ATPase was measured in RBC membrane by the method of Hjertan and Pan (1983). Na^{+}/K^{+} dependent ATPase activity was estimated in RBC membrane according to the procedure of Bonting (1970). Mg^{2+} ATPase activity was assayed in RBC membrane by the method of Ohinishi et al. (1982). The amount of phosphorus liberated in all these methods was estimated by the method of Fiske and Subbarow (1925). Protein content was assayed by the method of Lowry et al. (1951). Urinary kallikrein activity was assayed using a synthetic substrate benzoyl L-arginine ethyl ester (Trautschold et al., 1974).

Statistical analysis

All the grouped data were statistically evaluated and significance of changes between was determined using student's t-test. The values are expressed as means ± SD of 6 rats from each group and analysis of variance (ANOVA) was done wherever appropriate.

Results

Figure 1 shows the body weights of the rats during the experimental period of 4 weeks. The body weight of the animals increased progressively during the experimental period. The fructose-fed rats (Group 2) showed a higher weight gain, which however was not significant as compared with those of the normal rats (Group 1). Administration of taurine did not significantly alter the body weights of animals (Group 2). Food and fluid intake were similar in all groups.

Figure 2 shows the plasma glucose level in response to an intravenous glucose load. The plasma glucose levels returned to the basal values within

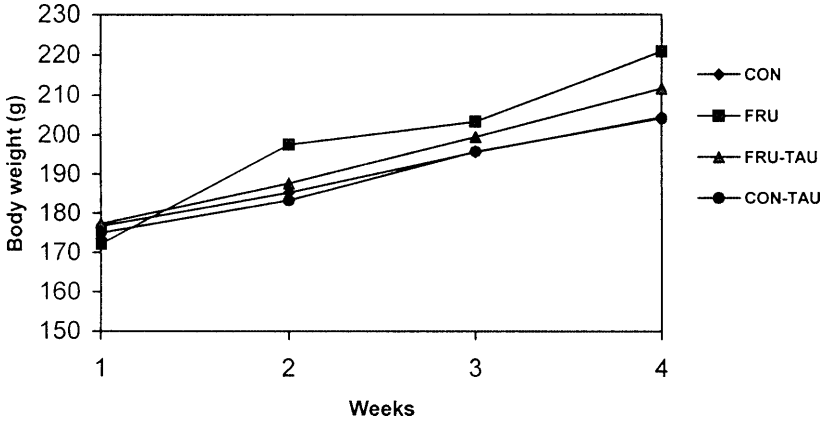

Fig. 1. Body weight changes (g) of control and experimental rats (means ± SD, n = 6). Measurements were taken weekly until the experimental period

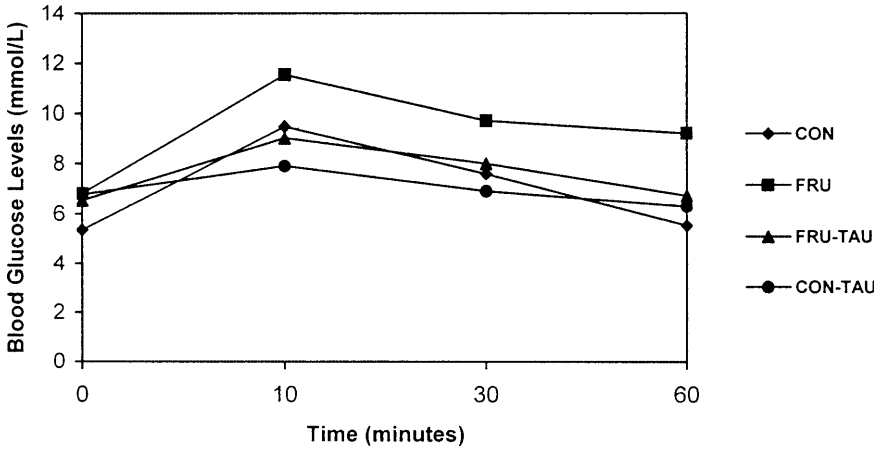

Fig. 2. Blood glucose levels during IVGTT performed in control and experimental rats at 4 weeks after being fed with fructose diet. Glucose was administered at a dosage of 0.5 g/kg. Data are means ± SD of six observations in treated rats and controls

approximately 30 min in normal rats. In rats administered high fructose diet, there was marked glucose intolerance. The glycemic levels attained 11.54 ± 0.04 mmol/L at 10 min after glucose injection decreasing slowly thereafter (at 60 min the glycemia was 9.21 ± 0.20 mmol/L). A substantial improvement of glucose tolerance was observed in Group 3 rats with plasma glucose levels returning to the fasting levels within 60 min. It was also noticed that glucose tolerance in Group 4 rats was comparable with that of the normal rats.

Figure 3 displays the mean ± SD values of steady-state plasma glucose levels for all 4 groups. The SSPG concentration of fructose-fed rats (7.26 ± 0.07 mmol/L) was significantly greater ($p < 0.001$) than that of control rats (5.4 ± 0.04 mmol/L). The supplementation of taurine to fructose-fed animals attenuated the effect of fructose. Thus, Group 3 rats had a significantly lower SSPG value than the Group 2 rats. It is obvious that Group 3 rats were significantly ($p < 0.001$) more insulin resistant than Group 1 animals.

Figure 4 shows the levels of glucose and insulin in plasma and that of glycogen in liver of control and experimental animals. A significant increase in plasma glucose and insulin was observed in fructose-fed rats (Group 2). The levels were not significantly altered in control rats treated with taurine (Group 4) as compared with those of normal rats, whereas administration of taurine to the fructose-fed rats controlled the hyperglycaemia and hyperinsulinemia (Group 3). A significant decrease in the liver glycogen was observed in fructose-fed rats (Group 2) as compared with those of normal rats. The glycogen content in the liver was near normal in taurine – treated fructose-fed rats (Group 3), whereas the glycogen content was not significantly altered in control rats treated with taurine (Group 4).

Figure 5 gives the urinary kallikrein activity in animals at the end of 30 days. Urinary kallikrein levels were significantly lower in fructose-fed rats ($p < 0.05$). Treatment with taurine resulted in increased excretion of kallikrein in groups 3 and 4 animals when compared to the control rats (Group 1).

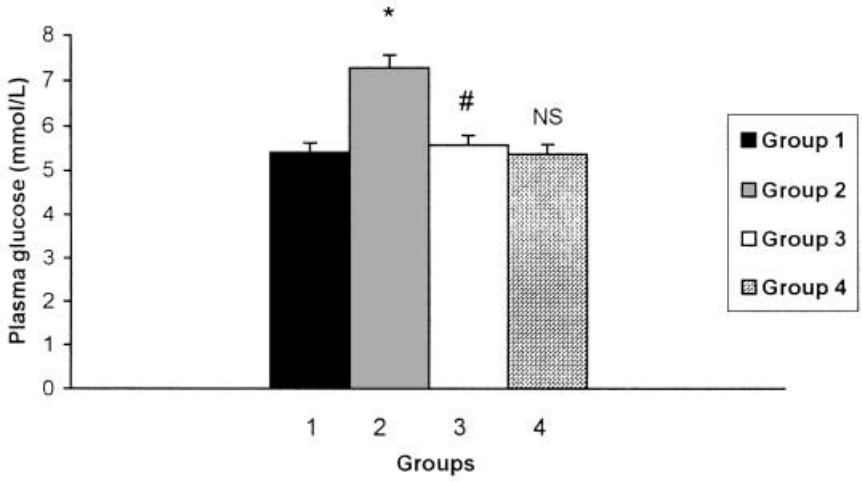

Fig. 3. SSPG concentration during the insulin suppression test in control rats (Group 1), fructose-fed rats (Group 2), fructose-fed rats with taurine (Group 3) and control rats fed with taurine (Group 4). Values are given as means ± SD, n = 6. * – Significant with respect to control ($p < 0.001$); # – significant with respect to fructose-fed rats ($p < 0.001$); *NS* non significant as compared to control

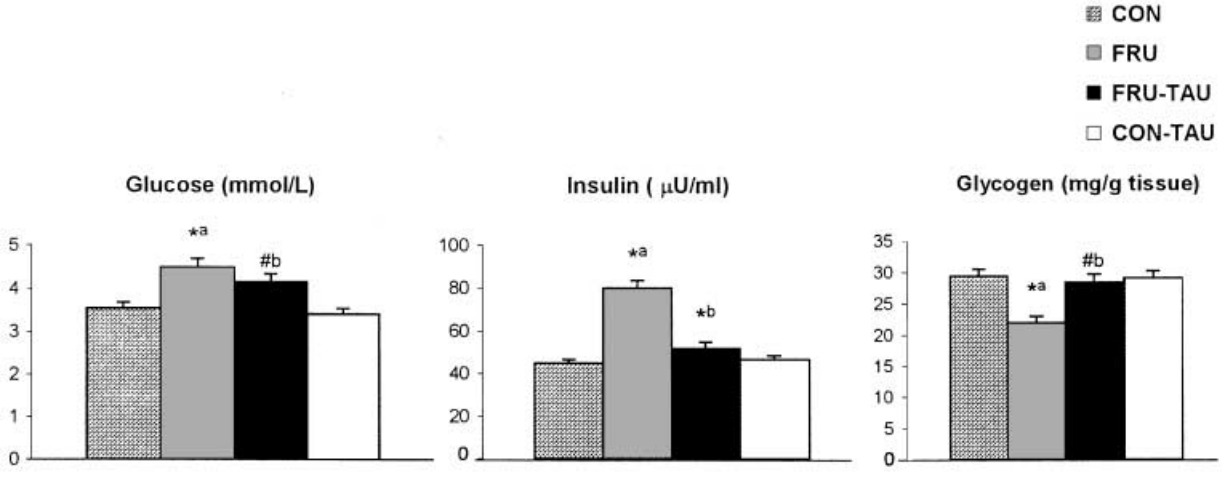

Fig. 4. Levels of plasma glucose and insulin and liver glycogen concentrations of rats (means ± SD, n = 6). [a] – As compared to control rats; [b] – as compared to fructose-fed rats; significant at $*p < 0.001$, $^{\#}p < 0.05$

Table 1 gives the activities of the enzymes hexokinase, glucose-6-phosphatase and glucose-6-phosphate dehydrogenase in the liver tissue of control and experimental animals. The mean value of glucose-6-phosphatase activity was significantly higher ($p < 0.001$) and those of hexokinase ($p < 0.001$) and G6PDH ($p < 0.01$) were significantly lower in fructose-fed rats as compared with those of the normal rats (Group 1). Taurine treatment prevented these alterations and the enzyme activities were near–normal in Group 3 rats. The activity remained unaltered in control rats treated with taurine (Group 4).

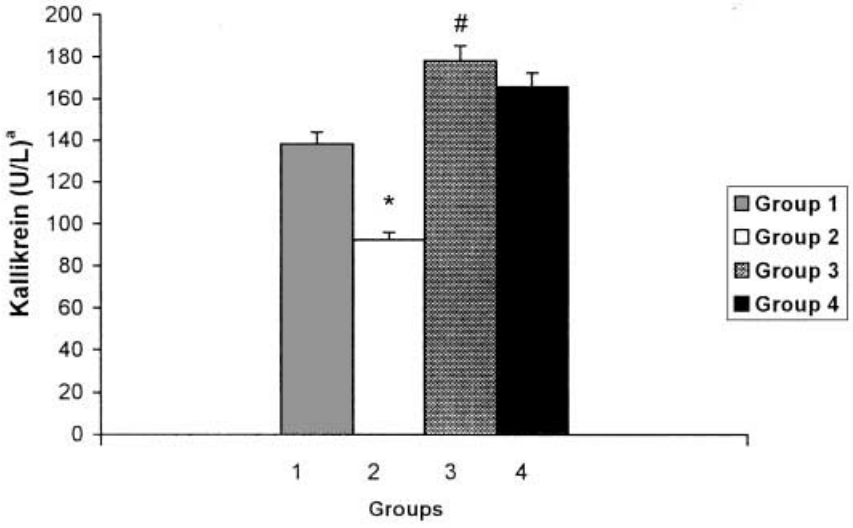

Fig. 5. Urinary kallikrein excretion of control and experimental rats. Values are means ± SD, n = 6

Table 2 gives the activities of membrane bound enzymes in erythrocyte membrane of control and experimental animals. A significant reduction in total, Na^+/K^+-, Ca^{2+}- and Mg^{2+}-ATPases ($p < 0.001$) in the RBC membrane of untreated fructose-fed rats (Group 2) was observed. Fructose- fed rats that were given taurine simultaneously showed significant elevation in the ATPases activities as compared to group 2 rats and were near normal.

Discussion

Increase in plasma glucose levels associated with hyperinsulinemia, in fructose-fed rats suggests impaired insulin action. Further the glucose intolerance and increased SSPG levels indicate the development of insulin resistance. Taurine administration to fructose-fed rats attenuated the rise in plasma glucose and insulin levels. Since taurine controls hyperglycemia without increasing serum insulin levels, it appears that the hypoglycemic action of taurine is unrelated to a direct stimulation of pancreatic insulin release. On the other hand taurine may have a direct action on the cell membrane to enhance glucose transport. Insulin-like actions of taurine have been demonstrated in rat-perfused heart (Lampson et al., 1983). Binding of taurine to isolated rat heart sarcolemma is inhibited by insulin and taurine has been shown to interact with purified insulin receptor *in vitro* (Maturo, 1988).

The changes in the enzyme activities and glycogen content in fructose-fed rats are indicative of the liver being in the gluconeogenic state. Fructose feeding could lower the cellular ATP content, which could be responsible for this. Several studies report that hepatic enzymes in fructose-fed rats are resistant to insulin action. Decreased activity of hexokinase and glycogen synthase (Vaag, 1992), increased glucose-6-phosphatase and L-pyruvate kinase activity

Table 1. Activities of glucose-6-phosphatase, hexokinase and glucose-6-phosphate dehydrogenase in liver of control and experimental animals

	CON	FRU	FRU + TAU	CON + TAU	F-ratio
Glucose-6-phosphatase (μg pi lib/min/mg protein $\times 10^{-2}$)	4.053 ± 0.63	6.151 ± 0.53[a]***	4.330 ± 0.54[b]***	4.061 ± 0.40	4.85♣
Hexokinase (μmoles of glucose phosphorylated/ hour/mg protein)	0.225 ± 0.006	0.187 ± 0.007[a]***	0.212 ± 0.01[b]***	0.220 ± 0.01	5.91♣
Glucose-6-phosphate dehydrogenase (mIU/mg protein $\times 10^{-4}$)	4.618 ± 0.34	3.805 ± 0.27[a]**	4.383 ± 0.30[b]**	4.458 ± 0.26	6.95♣

Values are means ± SD of six rats from each group.
CON control; *FRU* Fructose-fed rats; *FRU + TAU* Fructose-fed rats treated with taurine; *CON + TAU* control rats treated with taurine.
[a] As compared with control rats. [b] As compared with fructose-fed rats. * $p < 0.05$ ** $p < 0.01$ and *** $p < 0.001$ (Student's t-test); ♣ $p < 0.01$ (ANOVA).

Table 2. Membrane bound enzymes in RBC membrane. Values are expressed as μmoles of phosphorus liberated/mg protein/hour

	CON	FRU	FRU + TAU	CON + TAU	F-ratio
Total ATPase	1.71 ± 0.14	1.62 ± 0.07	1.66 ± 0.13	1.79 ± 0.07	17.88♣
Na^+/K^+-ATPase	0.79 ± 0.07	0.62 ± 0.05[a]***	0.78 ± 0.07[b]***	0.81 ± 0.04	5.65♣
Ca^{2+}/ATPase	0.40 ± 0.03	0.22 ± 0.10[a]***	0.35 ± 0.04[b]***	0.45 ± 0.02	1.17
Mg^{2+}/ATPase	0.33 ± 0.02	0.28 ± 0.01[a]***	0.33 ± 0.02[b]***	0.32 ± 0.01	37.45♣

Values are means ± SD of six rats from each group.
CON control; *FRU* Fructose-fed rats, *FRU + TAU* Fructose-fed rats treated with taurine; *CON + TAU* control rats treated with taurine.
[a] As compared with control rats. [b] As compared with fructose-fed rats.
*** $p < 0.001$ (Student's t-test); ♣ $p < 0.01$ (ANOVA).

(Naguchi et al., 1995) are recorded in hepatic insulin resistant states. Further, the decreased glucose utilization causes a slow down of the utilization of glycogen stores. Restoration of enzyme activities in taurine – treated fructose-fed rats could be the consequence of potentiation of insulin action and glucose utilization by taurine. Taurine could reduce basal hepatic glucose output through an effect on hepatic glycogen synthesis (Gandhi and Mulky, 1990). Taurine increases glucose utilization in the rat diaphragm (Donadio and Framageot, 1964). Taurine has potential beneficial effects on diabetic and hypertensive patients. Taurine has been shown to have therapeutic actions in insulin dependent diabetic patients (Franconi et al., 1995) and to lower blood pressure in essential hypertensive patients (Fujita et al., 1987).

The membrane bound enzymes regulate the ion gradient and there by a large number of cellular functions such as cell volume, osmotic pressure, transport of amino acids, monosaccharides and co-transport of many ions which depend on intra- and extra-cellular ion concentration (Vasilets et al., 1993). The stimulation of the transmembrane exchange system by insulin provides an important mechanism for hormonal control of multiple cellular processes. Alterations in membrane composition and functions observed in insulin resistant states are of particular interest in this context. Derangement in the activities of ATPases in fructose-fed rats could be a sequel to defect in insulin action.

Taurine supplementation resulted in normalization of ATPases activities in RBC membrane of fructose-fed rats. Taurine has an important modulatory impact on membrane structure and function. A possible site of action for taurine is Na^+/K^+ ATPase in plasma membrane. Stimulation of Na^+/K^+ ATPase activity produces a decrease in uptake of Ca^{2+} due to the decreased activity of Na^+/Ca^{2+} exchanger (Huxtable, 1992). Taurine was reported to stimulate Na^+/K^+ ATPase activity in hamster brain with half maximal rate of 39 mM (Hastings et al., 1985). Taurine could also influence the Ca^{2+} movements. Taurine stimulates the pumping rate of Ca^{2+}-activated ATPase pump possibly by increasing the turnover rate of the pump secondary to a membrane modification (Sebring and Huxtable, 1985). Taurine modulates Ca^{2+}

channel activity by two means: by an alteration in the properties of Ca^{2+} binding sites on membrane acidic phospholipids (there by modifying Ca^{2+} delivery to the channel) and by a direct effect on a hydrophilic site near or on the channel there by modifying the kinetics of channel opening or closing (Sawamura et al., 1990). The protective effects of taurine against Ca^{2+} overload and the polyvalent actions of taurine on Ca^{2+} movement have been documented (Huxtable, 1992). Taurine attenuates hyperglycemia-induced HUVEC apoptosis through $[Ca^{2+}]i$ stabilization and exerts a beneficial effect in preventing diabetes-associated microangiopathy (Wu et al., 1999). Normalisation of calcium homeostasis and prevention of intracellular calcium overload could have contributed to the beneficial effects of taurine.

The observed effect of taurine could also be due in part to the activation of renal kallikrein-kinin system as taurine-fed rats (both group 3 and group 4) showed increase in urinary kallikrein enzyme activity as compared to control rats. Taurine is reported to increase the kinin availability and to attenuate the salt – induced hypertension in Dahl S – rats (Ideishi et al., 1994). Augmented kinin availability may contribute to increased insulin sensitivity since a role for the kinin system in insulin action has been suggested in rats. (Mayfield et al., 1996).

Oshida et al. (2000) have suggested the possibility that NO donors such as sodium nitroprusside may improve insulin resistance induced by high fructose feeding. Further the stimulatory effect of insulin on peripheral tissue glucose utilization *in vivo* is NO dependent (Roy et al., 1998). Taurine increases urinary excretion of nitrite indicating higher NO secretion in Tokushima fatty rat, a model of spontaneous type II diabetes (Nakaya, 2000). In view of the above findings it could be conceived that taurine could have exerted its beneficial effects through the enhanced release of kinins and/or the messenger molecule, the nitric oxide. However, further studies are required to elucidate the molecular mechanism for the beneficial actions of taurine in fructose-fed rats.

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