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Chronic taurine supplementation ameliorates oxidative stress and Na^+K^+ATPase impairment in the retina of diabetic rats

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Summary. This study evaluates the effect of 4 months supplementation with 2% and 5% taurine (w/w) on the retina of diabetic rats. In non-diabetic rats, taurine does not modify glycemia, body weight, retinal conjugated dienes (CD), lipid hydroperoxide (LP), and Na^+K^+ATPase activity. In diabetic rat, at 2, 4, 8, 16 weeks following the onset of diabetes, retinal CD and LP are significantly and progressively increased, while pump activity is gradually and significantly reduced. In taurine supplemented diabetic rats, glycemia is not affected but lipid peroxidation is significantly decreased. Finally, taurine preserves ATPase activity being 5% more effective than 2% taurine. We conclude that taurine supplementation ameliorates biochemical retinal abnormalities caused by diabetes, thereby suggesting that taurine may have a role in the prevention of retinal changes in diabetes.

Keywords: Diabetes mellitus – Lipid peroxidation – Glycemia – Streptozotocin – Na^+K^+ATPase

Introduction

Diabetes mellitus causes various complications including retinopathy, which affects 90% of diabetics and progresses to blindness in about 5% (Merimee, 1990; Engerman and Kern, 1995). In diabetes and its complications, there is an increased production of oxidants and down regulation of antioxidative defense, which result in an oxidative stress (Bayes et al., 1999; Santini et al., 1997). Thus, the prevention of oxidative stress may have important implications for pharmacological attempts to prevent diabetic complications.

Taurine has been considered a conditionally semiessential amino acid (reviewed in Huxtable, 1992). It is also considered to be a regulatory factor in the maintenance of osmotic pressure, in calcium homeostasis and redox status (Franconi et al., 1982; Pasantes Morales and Cruz, 1985; Huxtable, 1992; Militante and Lombardini, 2000). In cats, in rats, and in monkeys taurine deficiency results in retinal degeneration and blindness (Huxtable, 1992). In addition, humans, feed parentally, present retinal alterations, which is reverted by taurine administration (reviewed in Chesney et al., 1998). This trend suggests a peculiar role of the amino acid in terms of cellular physiology and pathophysiology of the retina.

Clinically, in insulin dependent and insulin independent diabetes mellitus patients, taurine is decreased in plasma and platelets (Franconi et al., 1995; Franconi et al., 1996; De Luca et al., 2001). Moreover, in insulin dependent diabetic patients, taurine supplementation (1.5 g/day for three months) decreases platelet aggregability and restores plasma and platelet levels (Franconi et al., 1995). Furthermore, taurine is decreased in the retina and lens of diabetic rats (Vilchis and Salceda, 1996; Malone et al., 1990). Recently, it has been also found that taurine has some beneficial effects in experimental diabetic models (Goodman and Shihabi, 1990; Stevens et al., 1993; Trachtman et al., 1993; Trachtman et al., 1995; Kamata et al., 1996; Nanami et al., 1996; Lim et al., 1998; You and Chang, 1998; Mochizuki et al., 1999; Ha et al.,

1999; Obrosova et al., 1999; Mitton et al., 1999; Kilic et al., 1999; Wu et al., 1999; Militante et al., 2000; Pop-Busui et al., 2001; Obrosova et al., 2001).

Therefore, in streptozotocin (STZ) diabetic rat, which is an accepted model of insulin dependent diabetes, we studied the effect of chronic taurine supplementations on glycemia and retinal lipid peroxidation. Moreover, it was investigated the retinal Na^+K^+ATPase activity, because the enzyme activity is decreased by diabetes (MacGregor and Matschinski, 1986) and by lipid peroxidation (Elmoselhi et al., 1994; Santini et al., 1996). Preliminary of this study was communicated (Di Leo et al., 1999).

Materials and methods

Animals

Eight weeks-old male Wistar rats were purchased from Harlan-Nossan (Milan, Italy). All rats were individually caged in the Catholic University College of Medicine Animal Facility in accordance with the Guidelines of American Physiology Society. They were allowed to acclimatize for 1 week before starting the project. Throughout the study, animals had free access to water and food or to the same food enriched in 2% or 5% (w/w) taurine. Riefer (Bolzen, Italy) supplied all diets. Rat weight and 24 h-food consume were noted. In each rat, the measure of food intake (about 50 g/day) permits to calculate the actual intake of taurine. This was an average of 0.9 and 1.2 g/day and 2.1 and 2.7/day for the group that received 2% and 5% taurine enriched diets, respectively.

Diabetes was induced by a single (60 mg/kg) intraperitoneal injection of STZ (Sigma, St. Louis, MO, USA). Two days later and at time indicated in the tables and figures, blood samples were taken from the tail vein for glucose measurements. Rats with serum glucose > 16 mmol/L was considered diabetic. Treatments with 2% and 5% taurine diets were started after the induction of diabetes and continuing throughout the day of sacrifice.

Experimental procedure and biochemical determinations

Rats were anesthetized with sodium pentobarbital (85 mg/kg intraperitoneally) and sacrificed (2, 4, 8, 16 weeks after the induction of diabetes) by cervical dislocation. Both retinae were rapidly dissected and immediately frozen in liquid nitrogen and stored at $-80°C$. In the supernatant of retinal homogenates, Na^+K^+ATPase was measured using the coupled assay of Norby (1988) and expressed as μmolP/h/mg protein. Lipid hydroperoxides (LP) and conjugated dienes (CD) were measured in retinal lipids extracted as previously described (Folch, 1957) partially modified. The LP and CD content were determined with the FOX Version II assay for LP (FOX2) (Wolff, 1994) and according to Prior (1984), respectively. Protein concentration was evaluated by the method of the Bradford (1976).

Statistical analysis

Values are given as means ± SD. Comparisons between diabetic and control groups were made using one-way ANOVA. P values corrected for multiple comparisons by the Fisher method.

Results

Animal general data

In non-diabetic rats, both dietary taurine supplementations (data not shown) did not alter growth, glycemia and food intake. In diabetic rats, dietary taurine did not modify the elevation in serum glucose and did not change the body weight (Table 1).

Retinal LP and CD

In non-diabetic rats, taurine supplementations did not modify retinal LP and CD (Table 2). In diabetic rats, Fig. 1 shows CD and LP were significantly and

Table 1. Effect of chronic dietary taurine on body weight and serum glucose in diabetic rats

Groups	Body weight (g)				
	Duration of illness (weeks)				
	Baseline	2	4	8	16
Non diabetic-rat	236.2 ± 14.6 (7)	295 ± 18.7 (6)	390.0 ± 35.2 (6)	411.7 ± 19.4 (6)	455.0 ± 16.0 (5)
Diabetic rat	240.1 ± 20.0 (7)	266.7 ± 19.0 (9)	264.2 ± 55.0* (6)	224.2 ± 62.3* (6)	199.5 ± 14.3* (8)
2% Taurine diabetic rat	228.0 ± 13.5 (7)	271.5 ± 20.4 (8)	267.6 ± 41.2* (5)	261.2 ± 27.2* (6)	231.6 ± 31.4* (5)
5% Taurine diabetic rat	217.7 ± 16.3 (7)	282.5 ± 48.1 (6)	302.5 ± 41.3* (8)	285 ± 91.8* (10)	262.1 ± 3.4* (6)
	Serum glucose (mmol/L)				
Non diabetic-rat	5.3 ± 0.7 (12)	5.1 ± 0.4 (6)	5.3 ± 0.4 (6)	5.6 ± 0.6 (6)	5.7 ± 0.7 (5)
Diabetic rat		23.1 ± 2.5* (9)	23.8 ± 1.5* (6)	22.6 ± 1.8* (6)	26.4 ± 2.3* (8)
2% Taurine diabetic rat		21.5 ± 1.7* (8)	21.9 ± 1.4* (5)	21.4 ± 1.7* (6)	22.2 ± 1.9* (5)
5% Taurine diabetic rat		20.1 ± 1.7* (6)	20.9 ± 1.7* (8)	20.7 ± 1.6* (10)	22.5 ± 1.7* (6)

Data are given means ± SD in brackets the number of experiments. *$P < 0.001$ vs ND-rat

Table 2. Effects of 16 weeks dietary taurine supplementations on retinal CD (μmol/mg protein), LP (nmol/mg protein) and sodium pump (μmolP/h/mg protein) activity in non-diabetic rats

Groups	CD	LP	Na^+K^+ATPase
Non diabetic rat	5.6 ± 0.6 (5)	4.0 ± 0.3 (5)	78.2 ± 10.6 (5)
2% Taurine non diabetic rat	6.1 ± 0.7 (5)	3.9 ± 0.8 (5)	80.9 ± 23.1 (5)
5% Taurine non diabetic rat	5.5 ± 0.8 (5)	3.8 ± 0.5 (5)	84.5 ± 21.4 (5)

Data are given means ± SD; in brackets the number of experiments

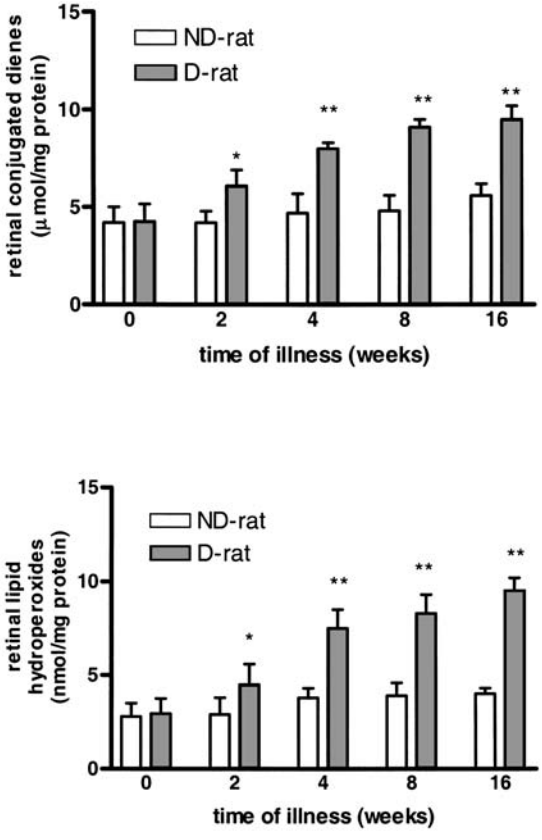

Fig. 1. CD (upper panel) and LP (lowel panel) levels measured in retina of STZ rat at different time from the induction of diabetes. Data are mean ± SD of at least 5 experiments. Diabetic rat versus non diabetic-rat at the same intervals *0.05 < P < 0.01; **P < 0.001

progressively increased during experimental time. Both taurine supplementations significantly attenuated the increase in CD induced by diabetes (Fig. 2). The elevation of LP triggered by diabetes was also attenuated by taurine supplementantions, being 5% taurine more effective than 2% taurine.

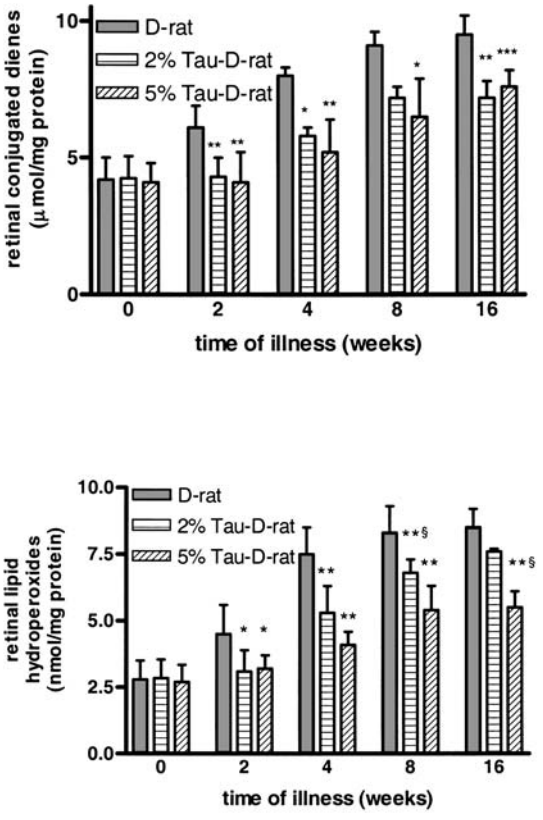

Fig. 2. Effect of chronic taurine supplementations on the increase in CD (upper panel) and LP (lower panel) in the retina of diabetic rats. Data are mean ± SD of at least 5 experiments. Statistical significance was compared with diabetic rat versus diabetic taurine supplemented animals *0.05 < P < 0.01; **0.01 < P < 0.001; and between the two taurine groups §P < 0.001

Retinal Na^+K^+ATPase

In non-diabetic rat, enzymatic activity progressively decreased with age (Fig. 3). The reduction was statistically significant when the value of 16 week was compared with baseline. In non-diabetic rats, both taurine supplementations did not alter the function of pump (Table 2).

Diabetes accelerated and raised the decrease in pump activity (Fig. 3). In diabetic rats, taurine enriched diets ameliorated the pump activity. The effect was more marked in 5% taurine supplemented rats and the difference between the two taurine groups was significant at 8, 16 weeks of disease.

Discussion

This study shows that STZ diabetes decreases sodium pump activity and increase oxidative stress in rat

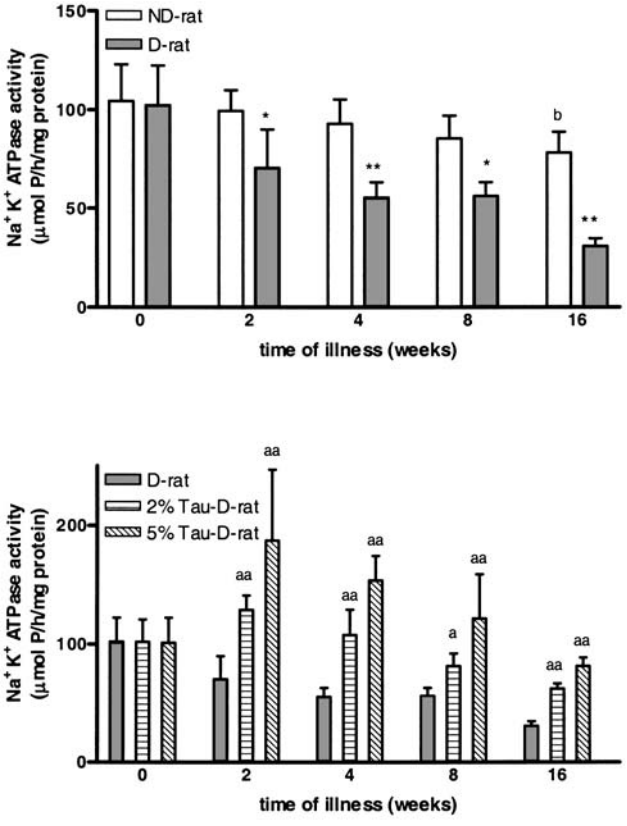

Fig. 3. The effect of diabetes (upper panel) and of 2% and 5% taurine enriched diets on retinal Na^+K^+ATPase in diabetic animals. Data are mean ± SD of at least 5 experiments. Statistical significance (upper panel) was compared: in non-diabetic rat at 2, 4, 8, 16 weeks versus zero time $^b0.05 < P < 0.01$; non-diabetic rat versus diabetic-rat $*0.05 < P < 0.01$, $**0.01 < P < 0.001$. Statistical significance (lower panel) was compared diabetic 5% taurine supplemented rat versus unsupplemented diabetic rat $^aP < 0.001$; 2% taurine supplemented diabetic rat versus unsupplemented $^a0.05 < P < 0.01$; $^{aa}0.01 < P < 0.001$; 5% taurine supplemented diabetic rat versus 2% taurine supplemented diabetic rat $0.01 < P < 0.001$

retina as previously described (MacGregor and Matschinski, 1986; Ansari et al., 1998; Agardh et al., 2000). The biochemical changes are time-dependent and more importantly, taurine supplementations reduce them. The effects of taurine are not linked to a decrease in glycemia. The lack of effect of taurine supplementation on serum glucose levels is consistent with previous results (Goodman and Shihabi, 1990). Interestingly, taurine effects are present only in the retina of diabetic animals. At this regard, it is important to underlie that taurine levels are reduced in retina, retinal pigment epithelium and lens of STZ rats (Vilchis and Salceda, 1996; Malone et al., 1990). As suggested by Vilchis and Salceda (1996), these changes in amino acid concentrations could contribute to retinal diabetic alterations. In this contest, it is likely that taurine supplementation might counteract the decrease in taurine levels reducing the hyperglycemic alterations.

In diabetes, as previously described (Trachtman et al., 1995; Lim et al., 1998; Obrosova et al., 2001) chronic taurine intake decreases lipid peroxidation. The mechanism(s) of antioxidant effect of taurine is/are not clear understood. It scavenges hypochlorite (Huxtable, 1992); preserves intracellular redox state enhancing the antioxidant activity of other molecules (Keys and Zimmerman, 1999). Moreover, it may prevent additional activation of lipid peroxidation due to its membrane stabilizing activity and to its regolatory activity on calcium homeostasis including the retina (Huxtable, 1992; Militante and Lombardini, 2000). In our system, it is likely that taurine hypochlorite scavenging activity is important because the retina contains hypochlorite producing enzyme (Ambati et al., 2000). Hypochlorite is the most effective oxidant in reducing the pump activity (Kurella et al., 1997) and Na^+K^+ATPase is well preserved by taurine supplementations. The preservation of this enzymatic activity is very important because it plays a key role in cellular homeostasis. A vicious circle may be depicted between the profound reduction in pump activity and lipid peroxidation. In fact, the decrease in ATPase activity could generate calcium overload which in turn induces lipid peroxidation and lipid peroxidation decreases the ATPase activity. Taurine, scavenging HCIO (Huxtable, 1992) and modulating intracellular calcium (Franconi et al., 1982; Huxtable, 1992; Militante and Lombardini, 2000) may interrupt the vicious circle between lipid peroxidation and pump activity. The possibility of this circle is suggested by the comparison of the time-coarse of sodium pump activity with time-courses of CD and LP.

Besides, taurine effects could be mediated by other mechanisms. In vivo and in vitro, taurine is antihypoxic (Franconi et al., 1985; Malcangio et al., 1989; Huxtable, 1992) and this activity may contributes to its beneficial effect in STZ diabetes. In fact, in the pathogenesis of diabetic retinopathy, ischemia-reperfusion injury in the boundaries of perfused and nonperfused retina seems to play a role (Dorey et al., 1996). Furthermore, we do not study the osmotic change in the retina; but taurine participates to osmotic regulation (Huxtable, 1992) and that could influence other biochemical changes.

Finally, we cannot deny the possibility that dietary taurine could exert an influence on cell different from retinal ones. It has been reported that taurine reduces platelet aggregation in diabetic patients (Franconi et al., 1995; Franconi et al., 1996) and microthrombi are important in the development of retinopathy (Boeri et al., 2000). In this contest, it is important to underlie that taurine supplementation in STZ rats reduce plasma cholesterol (Goodman and Shihabi, 1990; Nanami et al., 1996; You and Chang, 1998; Mochizuki et al., 1999). Although, the link between cholesterol and diabetic retinopathy is not established; this taurine effect could be important in preventing other diabetic complications. Thus, it would be safe to conclude that taurine has beneficial effects on preservation of retinal function, although the effects may be not exerted totally through their direct action on retinal cells.

In conclusion, the results of our study demonstrate the ability of chronic dietary taurine to preserve retinal integrity in diabetes in bad metabolic control without influencing glycemia.

Considering, that taurine has been found beneficial in inhibiting the development of other diabetic complications (Trachtman et al., 1995; Pop-Bausi et al., 2001) and hypercholesterolemia (Goodman and Shihabi, 1990; Nanami et al., 1996; You and Chang, 1998; Mochizuki et al., 1999) and platelet hyperaggregability (Franconi et al., 1995; Franconi et al., 1996) it could be useful to use taurine supplementation in diabetic patients. Thus, these findings encourage new investigations to evaluate the efficacy of taurine as an adjunctive agent to ameliorate the course of diabetic complications considering the low cost and the low toxicity (Huxtable, 1992) of this amino acid and the importance of disease.

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