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ORIGINAL ARTICLE

Taurine transporter gene expression in peripheral mononuclear blood cells of type 2 diabetic patients

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Abstract Taurine acts as antioxidant, cell osmolyte, modulator of glucose metabolism, and plays a role in the retinal function. It is 10^3-fold more concentrated in the intracellular than in the extracellular milieu due to a specific taurine-Na-dependent transporter (TauT), which is upregulated by hypertonicity, low extracellular taurine, or oxidative stress and acutely downregulated 'in vitro' by high glucose concentrations. Aim of this study was to investigate whether TauT expression was modified in mononuclear peripheral blood cells (MPC) of type 2 diabetic patients with or without micro/macrovascular complications. Plasma taurine, as well as other sulphur-containing aminoacids (assayed by HPLC) and TauT gene expression (assayed by real-time PCR analysis) were measured in MPC of 45 controls and of 81 age-and-sex matched type 2 diabetic patients with or without micro/macrovascular complications. Median value (interquartile range) of plasma taurine was significantly lower in diabetic patients than in controls [28.7 (13.7) μmol/l vs. 46.5 (20.3) μmol/l; $P < 0.05$], while median TauT expression, in arbitrary units, was significantly higher in diabetics than in controls [3.8 (3.9) vs. 1 (1.3); $P < 0.05$) and was related to HbA1c only in controls ($r = 0.34$; $P < 0.05$). Patients with retinopathy ($n = 25$) had lower TauT expression than those who were unaffected [3.1 (2.8) vs. 4.1 (3.4); $P < 0.05$], while persistent micro/macroalbuminuria was associated with unchanged TauT expression. A trend toward reduction in TauT expression was observed in patients with macroangiopathy [$n = 27$; 3.3 (2.5) vs. 4 [3.7]; $P =$ NS]. In conclusion, TauT gene is overexpressed in MPC of type 2 diabetic patients, while presence of retinopathy is specifically associated with a drop in TauT overexpression, suggesting its possible involvement in this microangiopathic lesion.

Keywords Taurine · Taurine transporter · Type 2 diabetes · Retinopathy · Mononuclear peripheral blood cells

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Introduction

The semi-essential amino acid taurine has numerous functions (Huxtable 1992; Schaffer et al. 2000) playing also a role in glucose metabolism (Franconi et al. 1996; Schaffer et al. 2009). Taurine deficiency has been observed in experimental and in clinical models of both type 1 and type 2 diabetes mellitus, or in clinical situations of insulin resistance (De Luca et al. 2001; Franconi et al. 1995, 2006; Merheb et al. 2007) and has been associated with the pathogenesis of diabetic complications (Ha et al. 1999; Vilchis and Salceda 1996). Next, taurine administration seems to prevent several alterations induced by hyperglycaemia 'in vitro' (Franconi et al. 2006; Schaffer et al. 2009; Verzola et al. 2002; Wu et al. 1999) and by diabetes in animal models (Franconi et al. 2003, 2006) or in humans (Franconi et al. 1995; Xiao et al. 2008; Schaffer et al. 2009; Ito et al. 2011).

The mechanisms that underlie taurine deficiency in diabetes mellitus are, nevertheless, still unknown, even if it has been suggested that diabetes-specific taurine deficiency could be due, at least in part, to the impairment in net intestinal and/or renal taurine absorption (Merheb et al. 2007), or to disruption of trans-membrane Na-dependent amino acid taurine transporter (TauT) (Stevens et al. 1999).

TauT is present in many cells, working against a concentration gradient since taurine is more concentrated (about 10^3-fold) in the intracellular compartment than in the extracellular milieu, and has, so far, been both morphologically and functionally well characterized (Tappaz 2004; Han et al. 2006). TauT is regulated by hypertonicity through the TonE (tonicity-responsive element)/TonB (TonE-binding protein) pathway (Uchida et al. 1992; Han et al. 2006; Ito et al. 2004). Acute hyperglycaemia, moreover, reduces the expression of Taut mRNA and protein 'in vitro' in different cellular models (Stevens et al. 1999; Askwith et al. 2009) and, interestingly, oxidation, DNA damage, or dietary manipulation, also affect TauT expression (Matsell et al. 1997; Han et al. 2009; Han and Chesney 2010).

Since no study has ever investigated whether TauT expression is varied 'in vivo' in patients with type 2 diabetes mellitus, we conceived this study to test whether TauT gene expression is modified in blood mononuclear peripheral cells (MPC) of patients with type 2 diabetes with or without micro/macrovascular complications.

Materials and methods

Patients and controls

Patients were chosen among diabetic subjects who consecutively attended the Diabetes Outpatient Clinic of our hospital and were classified as affected by type 2 diabetes since the diagnosis was done after the age of 40 years and did not require insulin therapy at the onset of their illness. Thirty-nine patients were on oral therapy, 16 on insulin, 17 on oral therapy + insulin, and 9 on diet alone. In diabetic patients, presence of retinopathy was ascertained by retinal fluorescein angiography as previously described (Di Simplicio et al. 1995) and nephropathy was diagnosed if 24-h-urinary albumin excretion rate (AER), evaluated as the mean value of three samples during the last 6 months, was $\geq$20 μg/min. Plasma creatinine was <124 μmol/l in all cases. Presence of macroangiopathy was ascertained by anamnestic and clinical–instrumental criteria (clinical evaluation as well as history of previous cardiovascular disease, presence of altered ST-T in ECG and/or presence of atherosclerotic lesions in carotids or lower limbs' vessels evaluated by Echo-Color-Doppler technique).

Age-and-sex matched controls were recruited among hospital personnel or their relatives, without direct evidence or history of diabetes.

This study has been approved by the Ethical Committee of our Hospital and all subjects gave their written informed consent prior to their inclusion in the study.

Biochemical assays

All biochemical assays were obtained in the morning in fasting condition. In both patients and controls we measured fasting plasma glucose and glycated hemoglobin (HbA1c) by routine methods. In both patients and controls we also assayed plasma levels of taurine and methionine by separation followed by fluorimetric detection of their *p*-orthophtalaldehyde (OPA) derivatives (Bianchi et al. 1999) and homocysteine by using fluorescence polarization immunoassay (FPIA, Abbott, Italy).

Taurine transport gene expression

In each subject blood mononuclear peripheral cells (MPC, lymphocytes and monocytes) were separated from 4 ml of whole blood by Accuspin System-Histopaque-1077 (Sigma-Aldrich, Italy) and stored in RNA later solution (Qiagen, Italy) at −20°C.

Each sample contained a median count of 2.53×10^6 (interquartile range: 1.1×10^6) cells/ml, of which 2.05×10^6 (interquartile range: 0.92×10^6) lymphocytes/ml and 0.44×10^6 (interquartile range: 0.19×10^6) monocytes/ml. Total RNA was purified through Rneasy-Plus-Mini-kit (Qiagen, Italy); its concentration was determined by measuring absorbance at 260 nm and its purity was provided by readings' ratios of 260/280 nm. First-strand cDNA was synthesized from 1 μl of RNA by random examers and SuperScript III reverse transcriptase (Invitrogen, Italy). The amount of c-DNA was quantified by a Qubit spectrophotometer (Invitrogen, Italy). TauT and GAPDH (housekeeping gene) mRNA were quantified by real time RT-PCR (Rotorgene 6000, Corbett, UK), using intercalation of SYBR Green. Primers' sequences for TAUT were: 5′-GAAATCTTCATCGCCTTCG-3′ (forward) and 5′-TAGCCAATCATGTCCTCA-3′ (reverse), while for GAPDH were: 5′-GAAGGTGAAGGTCGGAGT-3′ (forward) and 5′-GAAGATGGTGATGGGATTTA-3′ (reverse) (Schöndorf et al. 2002; Mochizuki et al. 2005). To quantify mRNA expression a standard curve was constructed from cDNA generated from human reference RNA (1 μg/1 μl; Stratagene) and standard curves were used for estimation PCR efficiency and as a calibration curve to estimate the starting concentrations of unknown samples (Ramarkers et al. 2003). Amplification was performed in triplicate by the following thermal cycling conditions: 2 min at 52°C,

activation at 95°C for 10 min, followed by 45 cycles of 15 s at 95°C and 60 s at 60°C. Dissociation analysis of the PCR products was performed by running a gradient from 95 to 55°C (gradient 0.1°C) to confirm the presence of single PCR products.

Changes in mRNA gene expression levels were reported, after normalization to GAPDH, as fold changes relative to controls and values of fold changes in the control sample versus target samples represent averages from triplicate measurements. Relative quantification was performed using the comparative cycle threshold (Ct) method after determining the Ct values for reference (GAPDH) and target gene (TauT) in each sample according to the $2^{-\Delta\Delta Ct}$ method. In short, ΔCt was obtained by subtracting the Ct of target gene (TauT) from the Ct of the reference gene (GAPDH), and then it was calculated $\Delta\Delta Ct = \Delta Ct - \Delta Ct\_Mean$. Finally, gene expression level was expressed as $2^{-\Delta\Delta Ct}$ (Pfaffl 2006).

Statistical methods

Data were analyzed by ANOVA (after log transformation for abnormally distributed variables) or via Wilcoxon rank-sum-test to check for statistically significant differences among groups. Relations among variables were tested by univariate analysis, expressing Spearman's correlation coefficients. Values of abnormally distributed variables were expressed as median (interquartile ranges). Significance of P value was set at <0.05.

All statistical analyses were carried out by means of SAS software for Windows, version 8.2 (SAS Institute Inc., Cary, NC, USA).

Results

The median values (interquartile range) of both plasma methionine and homocysteine were higher while, on the contrary, median plasma taurine was significantly reduced in type 2 diabetic patients than in controls (Table 1) and because there was no significant gender difference as to plasma aminoacid levels and to TauT gene expression, data of men and women were pooled in all analyses.

In presence of similar numbers of both lymphocytes and monocytes collected in blood samples (Table 1) diabetes mellitus greatly affected TauT gene expression inducing an increase in its expression about fourfold higher in diabetic patients in comparison with healthy volunteers (Table 1; Fig. 1).

After stratifying diabetic patients according to micro and macroangiopathic complications, patients with retinopathy had significantly lower median TauT gene expression when compared to other non retinopathic diabetic patients, even if it was still higher when compared with the expression of healthy volunteers [3.1 (2.7) AU vs. 1 (1.3) AU; $P < 0.05$ (Table 2; Fig. 2a)].

TauT gene expression was unaffected by presence of persistent micro/macroalbuminuria (Table 2; Fig. 2b), whereas a trend toward a decrease was observed in patients with macroangioapthy.

Lymphocyte and monocyte counts were unchanged in diabetic patients with or without micro/macroangiopathic complications (data not shown).

Plasma levels of taurine, homocysteine, and methionine were not varied in diabetic groups with or without evidence of micro and macroangiopathic complications (Table 2).

Table 1 Main characteristics of diabetic patients and of control subjects

	Controls	Type 2 diabetes	P*
No.	45	81	
Age (years)	58.8 ± 9.3	63 ± 10	NS
Sex (% of males)	46	49	NS
BMI (kg/m^2)	23.9 ± 3	29.4 ± 5	<0.05
Duration of diabetes (years)	–	10.8 ± 8	–
Plasma glucose (mmol/l)	5.1 ± 0.7	8.8 ± 2.9	<0.05
HbA1c (%)	5.2 ± 0.6	7.7 ± 1.3	<0.05
Plasma taurine (μmol/l)	46.5 (20.3)[a]	28.7 (13.7)[a]	<0.05
Plasma methionine (μmol/l)	14.9 (4.4)[a]	17 (8.4)[a]	<0.05
Plasma homocysteine (μmol/l)	10.4 (4.4)[a]	13.6 (6.5)[a]	<0.05
Lymphocites (cells × 10^6/ml)	2.10 (0.77)	2.19 (1.22)	NS
Monocytes (cells × 10^6/ml)	0.43 (0.16)	0.45 (0.21)	NS
Taurine Transporter gene expression[b]	1 (1.3)[a]	3.8 (3.9)[a]	<0.05
Retinopathy (no.)	–	25	–
Micro-macroalbuminuria (no.)	–	12	–
Macroangiopathy (no.)	–	27	–

* Calculated by Wilcoxon rank-sums-test

[a] Median (interquartile range)

[b] Expressed in arbitrary units (AU)

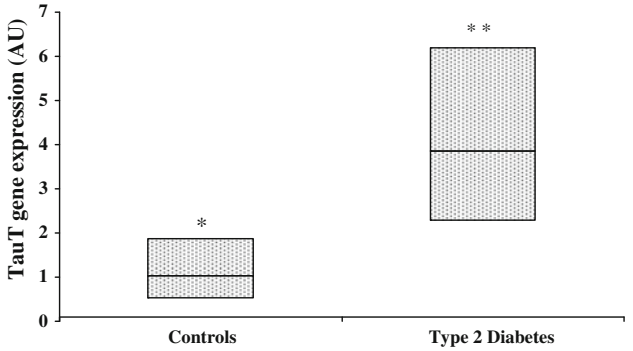

Fig. 1 Median with 1st and 3rd quartile values of TauT gene expression in arbitrary units (*AU*) in MPC of controls and of type 2 diabetic patients. * versus $**P < 0.05**$

Finally, we also investigated the correlations among TauT gene expression and age, BMI, duration of diabetes fasting plasma glucose, HbA1c, plasma taurine, methionine, and homocysteine (Table 3). Significant correlations have been found only in controls: in these, latter TauT gene expression was positively related with HbA1c and inversely associated with fasting plasma glucose whereas plasma taurine was negatively related with HbA1c ($r = -0.44$; $P < 0.05$). Additionally, in controls, taurine/methionine ratio was inversely related with HbA1c ($r = -0.38$; $P < 0.05$) and, reciprocally, methionine/taurine ratio and HbA1c were each other positively related ($r = 0.40$; $P < 0.05$).

Discussion

This study evidences that TauT gene is expressed in adult human MPC. These results are in line with previous data that described TauT gene expression in foetal peripheral lymphocytes and platelets (Iruloh et al. 2007). Indeed, here we show that TauT expression: (1) is not sexual dimorphic, and (2) in normal subjects is inversely related with fasting plasma glucose ($r = -0.36$; $P < 0.05$) and positively associated with Hba1c ($r = 0.34$; $P < 0.05$). This speculatively suggests that TauT gene is acutely downregulated by incremental variations of plasma glucose in its physiological range (3.7–6.8 mmol/l), and, on the contrary, seems chronically upregulated at plateau by higher daily glycemic milieu in the non diabetic HbA1c range: 3.6–6.5%. These findings could tentatively indicate a dimorphic glucose behaviour suggesting a fine acute adjustment of MPC TauT, associated with its upregulation at chronic glycemic plateau.

The most important novelty of this paper, however, resides in the fact that TauT gene is overexpressed in the MPC derived from type 2 diabetic patients indicating that it is associated with an alteration of TauT expression

Table 2 Median plasma values (interquartile range) of taurine, homocysteine, methionine as well as of TauT gene expression in MPC of control subjects, compared to diabetic patients with or without micro-macroangiopathic lesions

	Taurine (μmol/l)			Homocysteine (μmol/l)			Methionine (μmol/l)			TauT (AU)[a]		
	Presence	Absence	*P*	Presence	Absence	*P*	Presence	Absence	*P*	Presence	Absence	*P*
Retinopathy	27.3 (15.4)	28.9 (13.6)	NS	14 (9.5)	13.5 (6.4)	NS	16.8 (5.9)	16.9 (9.2)	NS	3.1 (2.7)	4.1 (3.4)	<0.05
Micro-macroalbuminuria	25.8 (8.6)	29.1 (13.8)	NS	14.5 (7.3)	8.9 (6.4)	NS	16.8 (9.9)	16.9 (8.7)	NS	4.2 (5.8)	3.8 (3.4)	NS
Macroangioapthy	30.6 (13.4)	28.4 (14.4)	NS	13.4 (10.1)	13.6 (6.3)	NS	16.1 (4.4)	17.1 (9.9)	NS	3.3 (2.5)	4 (3.7)	NS

[a] Expressed as arbitrary units (AU)

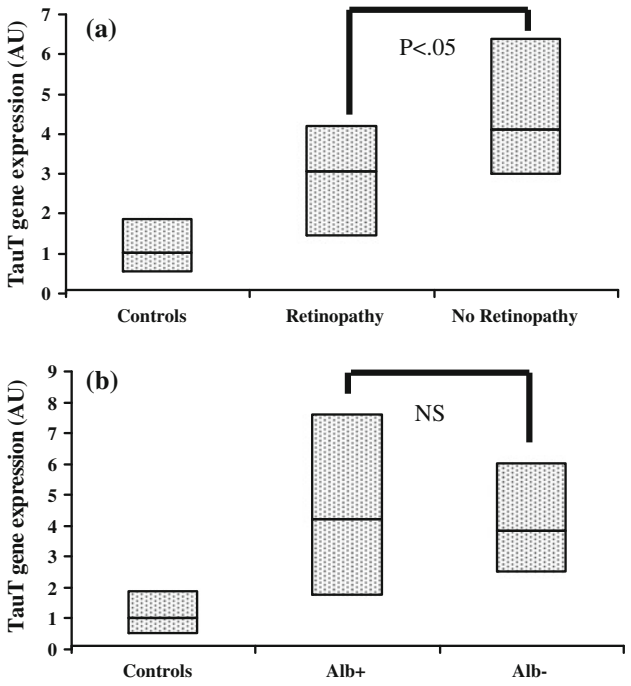

Fig. 2 Median with 1st and 3rd quartile values of TauT gene expression in arbitrary units (*AU*) in MPC of controls and of type 2 diabetic patients with or without retinopathy (**a**) or micro-macroalbuminuria (Alb+ and Alb−) (**b**)

Table 3 Correlation coefficients between TauT expression in MPC and other variables in controls and in type 2 diabetic patients

	Controls ($n = 45$)	*P*	Type 2 Diabetes ($n = 81$)	*P*
	r		*r*	
Age	0.24	NS	0.005	NS
BMI	−0.04	NS	0.12	NS
Duration of diabetes	–	NS	−0.13	NS
Plasma glucose	−0.36	0.02	0.03	NS
HbA1c	0.34	0.02	0.06	NS
Plasma taurine	0.16	NS	−0.10	NS
Plasma methionine	−0.12	NS	−0.02	NS
Plasma homocysteine	0.19	NS	−0.16	NS

'in vivo', at least in these cells. It is known that TauT expression is adaptively upregulated by low extracellular taurine (Tappaz 2004; Han et al. 2006; Uchida et al. 1992) and taurine levels are indeed decreased in the group of diabetic patients, in agreement with most previous observations (De Luca et al. 2001; Franconi et al. 1995; Merheb et al. 2007). Low plasma taurine in diabetes has been ascribed to reduced taurine reabsorption at renal or intestinal level due to the impairment of cell TauT expression (Merheb et al. 2007). In this context, however, increased MPC TauT expression, as we observed, cannot automatically mirror an equal TauT upregulation at renal tubular cells, where taurine handling seems to be a complex mechanism controlled by adaptive regulation of TauT in response to taurine availability as well as by its upregulation due to increased osmolality (Satake et al. 2010).

Finally, although mammals placed on taurine-restricted diet markedly reduce taurine urinary excretion enhancing renal TauT (Han et al. 2006), here the lack of correlation between TauT expression and plasma taurine suggests that the decrease in plasma taurine levels has a scarce effect on the adapting mechanisms that produce TauT upregulation.

Acute hyperglycemia in vitro downregulates TauT in cultured rat cardiomyocytes (Shi et al. 2003), in cultured retinal pigment epithelial cells (Stevens et al. 1999; Nakashima et al. 2005) and in human Schwann cells (Askwith et al. 2009). Glucose-induced TauT downregulation in human Schwann cells is reversed by inhibition of aldose reductase as well as by protein kinase C (PKC) inhibitors indicating the importance in the process of both osmolality (Askwith et al. 2009) and of glucose-driven intracellular pathways (Stevens et al. 1999; Shi et al. 2003). All this could be viewed as deeply conflicting with our results obtained in vivo. To explain this apparent contradiction, however, we should consider some points.

The first point is that in almost every study the inhibitory effect exerted by high glucose 'in vitro' on cell TauT expression is obtained with glucose medium concentrations equal to or above 20 mmol, which largely exceed the glucose concentrations observed in our patients (7–16 mmol/l). As to this aspect it is to note, moreover, that no studies have, so far, specifically investigated TauT cell expression and/or function 'in vitro' in such a lower range of glucose concentrations.

The second point is the deeply different time length of high glucose exposure in these two different situations: relatively short (from 24 h to a maximum of 7 days) in previous studies 'in vitro', as compared to a much longer chronical high glucose exposure as happens in diabetic patients.

The third point is characterized by the fact that when we consider diabetic patients we must take into account that diabetes is just not only hyperglycemia: in other words increased TauT expression which we have observed could be related with other constitutive aspects of the diabetic 'milieu' such as, for instance, the presence of various degrees of insulin resistance or the presence of increased concentration of other metabolites such as, for instance, lipids, free radicals, etc. In this context, previous studies concerning retinal pigment epithelial cells obtained from diabetic rats showed that cell taurine uptake was elevated, rather than decreased, suggesting that diabetes is able to stimulate 'in vivo', at least in some cell lines, the activity of the taurine transporter (Vilchis and Salceda 1996).

Furthermore raised TauT gene expression by MPC can, additionally, be explained by an increase in MPC overall activation in type 2 diabetes, since, as recently described, peripheral B cells contribute to insulin resistance by producing pathogenic IgG antibodies (Winer et al. 2011), suggesting that these circulating cells can be activated by diabetic-related mechanisms.

A further factor possibly implicated in stimulating TauT expression could be insulin itself, even if there are no evidences in this sense from previous reports, and, in the present study, no difference in TauT expression was noted between patients on insulin therapy, when compared with those on other treatments (data not shown).

Finally TauT promoter contains an antioxidant response element (ARE), activated in response to prooxidants (Nakashima et al. 2005) and oxidants, whose production is raised in diabetes, increase TauT expression in human Schwann cells 'in vitro' (Askwith et al. 2009). It is also interesting to note that nitric oxide, which is a promoter of TauT expression in cultured human retinal pigment epithelial cells, is increased in diabetes and its action can be amplified by the presence of oxidative stress (Bridges et al. 2001).

A separate consideration should be done about the relation linking high glucose with hypertonicity and TauT expression. It is indeed also known that TauT is generally upregulated by hypertonicity through the TonE/TonEBP signalling pathway (Ito et al. 2004, 2009). Nevertheless conflicting results have been described when different cells have been acutely challenged with high glucose concentrations 'in vitro': under such a circumstance extracellular and intracellular hypertonicity seem to have a sort of 'paradoxical' inhibitory effect on TauT expression and function, both restored, even if in not all cases, by treatment with aldose reductase inhibitors (Stevens et al. 1999; Askwith et al. 2009). This represents a further piece of evidence for possible discrepancies between what observed 'in vitro' and the effect of chronic exposure to higher glucose levels 'in vivo': proving that hypertonicity cannot be assumed to be the sole or most important mechanism involved in the regulation of TauT expression (Han et al. 2006).

In summary, considering that taurine is an osmolyte and an antioxidant and that its intracellular content is mainly regulated by TauT, the hypothesis stemming by our data is that cells chronically exposed to diabetic milieu might attempt to improve their homeostasis increasing TauT gene expression.

Furthermore, it is of interest to note that TauT overexpression is significantly reduced in patients with retinopathy while nephropathy and macroangiopathic complications do not affect TauT, thus suggesting that retinopathic patients have a minor capacity to counteract the retinal damage jointly related to both chronically increased plasma glucose exposure and reduced levels of taurine, which, coupled together with TauT, have a well known protective role for retinal cells (Timbrell et al. 1995; Warskulat et al. 2007).

Finally, plasma levels of other sulphur-containing aminoacids such as methionine and homocysteine were elevated in diabetic patients. Increased levels of homocysteine in diabetes have previously been described (Hoogeveen et al. 2000). And, notably, the increase in homocysteine observed in diabetic patients could decrease the substrate for taurine biosynthesis decreasing the availability of cysteine (Wu 2009). Previous data on plasma methionine are scarce and one paper (Tessari et al. 2005) shows that it is not changed in diabetic patients, while we found a significant increase in methionine. However, considering that taurine inhibits methionine uptake in some cell models such as intestinal Caco-2 cells (Martin-Venegas et al. 2009) the observed increase in methionine could be biologically plausible.

In conclusion, this study describes, for the first time, a raised TauT gene expression in MPC of type 2 diabetic patients. Whether this specific upregulation is the response to a number of diabetes-associated factors such as increase in circulating oxidants, hypertonicity, chronic hyperglycemia, reduction in plasma taurine or eventually other unidentified factors remains to be further elucidated. The increment of TauT expression is reduced in MPC of patients with retinopathy, suggesting a possible role for TauT in the protective mechanisms against the retinal damage of diabetes. In any case, even if these data have some limitations and warrant further confirmation, they indicate TauT as another candidate target of diabetic illness, further confirming the role of taurine in glucose homeostasis both in normoglycemic subjects and diabetic patients.

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Conflict of interest The authors declare that they have no conflict of interest.

References

Askwith T, Zeng W, Eggo MC, Stevens MJ (2009) Oxidative stress and dysregulation of the taurine transporter in high-glucose-exposed human Schwann cells: implications for pathogenesis of diabetic neuropathy. Am J Physiol Endocrinol Metab 297:E620–E628. doi:1152/ajpendo.00287.2009

Bianchi L, Della Corte L, Tipton KF (1999) Simultaneous determination of basal and evoked output levels of aspartate, glutamate, taurine and 4-aminobutyric acid during microdialysis and from perfusated brain slices. J Chromatogr B Biomed Sci Appl 723:47–59

Bridges CC, Ola MS, Prasad PD, El-Sherbeny A, Ganapathy V, Smith SB (2001) Regulation of taurine transporter expression by NO in cultured human retinal pigment epithelial cells. Am J Physiol Cell Physiol 281:1825–1836

De Luca G, Calpona PR, Caponetti A, Romano G, Di Benedetto A, Cucinotta D, Di Giorgio RM (2001) Taurine and osmoregulation: platelet taurine content, uptake, and release in type 2 diabetic patients. Metabolism 50:60–64

Di Simplicio P, De Giorgio LA, Cardaioli E, Lecis R, Miceli M, Rossi R, Anichini R, Mian M, Franconi F (1995) Glutathione, glutathione enzyme and thioltransferase in platelet of insulin-dependent diabetic patients: relation with aggregation and with microangiopathic complications. Eur J Clin Invest 25:665–669

Franconi F, Bennardini F, Mattana A, Miceli M, Ciuti M, Mian M, Gironi A, Anichini R, Seghieri G (1995) Plasma and platelet taurine are reduced in subjects with insulin-dependent diabetes mellitus: effects of taurine supplementation. Am J Clin Nutr 61:1115–1119

Franconi F, Loizzo A, Ghirlanda G, Seghieri G (2006) Taurine supplementation and diabetes mellitus. Curr Opin Clin Nutr Metab Care 9:32–36

Franconi F, Loizzo A, Ghirlanda G, Seghieri G (1996) Taurine and diabetes. Humans and experimental models. Adv Exp Med Biol 403:579–582

Franconi F, Santini SA, Gentiloni Silveri N, Caputo S, Giardina B, Ghirlanda G, Di Leo MA (2003) Taurine reduces mortality in diabetic rats: taurine and experimental diabetes mellitus. Adv Exp Med Biol 526:67–73

Ha H, Yu MR, Kim KH (1999) Melatonin and taurine reduce early glomerulopathy in diabetic rats. Free Radic Biol Med 26:944–950. doi:10.1016/S0891-5849(98)00276-7

Han X, Chesney RW (2010) Stress-responsive gene +TauT and acute kidney injury. J Biomed Sci 17(Suppl 1):S28. doi:10.1186/1423-0127-17-S1-S28

Han X, Patters AB, Jones DP, Zelikovic I, Chesney RW (2006) The taurine transporter: mechanisms of regulation. Acta Physiol (Oxf) 187:61–73

Han X, Yue J, Chesney RW (2009) Functional TauT protects against acute kidney injury. J Am Soc Nephrol 20:1323–1332

Hoogeveen EK, Kostense PJ, Eysink PE, Polak BC, Beks PJ, Jakobs C, Dekker JM, Nijpels G, Heine RJ, Bouter LM, Stehouwer CD (2000) Hyperhomocysteinemia is associated with the presence of retinopathy in type 2 diabetes mellitus: the Hoorn study. Arch Intern Med 160:2984–2990

Huxtable RJ (1992) Physiological actions of taurine. Physiol Rev 72:101–163

Iruloh CG, D'Souza SW, Speake PF, Crocker I, Fergusson W, Baker PN, Sibley CP, Glazier JD (2007) Taurine transporter in fetal T lymphocytes and platelets: differential expression and functional activity. Am J Physiol Cell Physiol 292:C332–C341

Ito T, Fujio Y, Hirata M, Takatani T, Matsuda T, Muraoka S, Takahashi K, Azuma J (2004) Expression of taurine transporter is regulated through the TonE (tonicity-responsive element)/TonEBP (TonE-binding protein) pathway and contributes to cytoprotection in HepG2 cells. Biochem J 382:177–182. doi:10.1042/BJ20031838

Ito T, Fujio Y, Schaffer SW, Azuma J (2009) Involvement of transcriptional factor TonEBP in the regulation of the taurine transporter in the cardiomyocyte. Adv Exp Med Biol 643:523–532. doi:10.1007/978-0-387-75681-3_54

Ito T, Schaffer SW, Azuma J (2011) The potential usefulness of taurine on diabetes mellitus and its complications. Amino Acids. doi:10.1007/s00726-011-0883-5 (Epub ahead of print)

Martin-Venegas R, Rodriguez-Lagunas MJ, Mercier Y, Geraert PA, Ferrer R (2009) Effect of pH on L- and D-methionine uptake across the apical membrane of Caco-2 cells. Am J Physiol Cell Physiol 296:C632–C638

Matsell DG, Bennett T, Han X, Budreau AM, Chesney RW (1997) Regulation of the taurine transporter gene in the S3 segment of the proximal tubule. Kidney Int 52:748–754

Merheb M, Daher RT, Nasrallah M, Sabra R, Ziyadeh FN, Barada K (2007) Taurine intestinal absorption and renal excretion test in diabetic patients: a pilot study. Diabetes Care 30:2652–2654

Mochizuki T, Satsu H, Shimizu M (2005) Signaling pathways involved in tumor necrosis factor alpha-induced upregulation of the taurine transporter in Caco-2 cells. FEBS Lett 579:3069–3074

Nakashima E, Pop-Busui R, Towns R, Thomas TP, Hosaka Y, Nakamura J, Greene DA, Killen PD, Schroeder J, Larkin DD, Ho YL, Stevens MJ (2005) Regulation of the human taurine transporter by oxidative stress in retinal pigment epithelial cells stably transformed to overexpress aldose reductase. Antioxid Redox Signal 7:1530–1542. doi:10.1089/ars.2005.7.1530

Pfaffl MW (2006) Relative quantification. In: Dorak T (ed) Real TIME PCR (BIOS advanced methods). Taylor & Francis, Oxford, pp 63–82

Ramarkers C, Ruijter JM, Deprez RHL, Moorman AFM (2003) Assumption free analysis of quantitative real-time polymerase chain reaction (PCR) data. Neurosci Lett 339:62–66

Satake M, Ikarashi N, Kagami M, Ogiue N, Toda T, Kobayashi Y, Ochiai W, Sugiyama K (2010) Increases in the expression levels of aquaporin-2 and aquaporin-3 in the renal collecting tubules alleviate dehydration associated with polyuria in diabetes mellitus. Biol Pharm Bull 33:1965–1970. doi:10.1248/bpb.33.1965

Schaffer SW, Azuma J, Mozaffari M (2009) Role of antioxidant activity of taurine in diabetes. Can J Physiol Pharmacol 87:91–99

Schaffer S, Takahashi K, Azuma J (2000) Role of osmoregulation in the actions of taurine. Amino Acids 19:527–546

Schöndorf T, Kurbacher CM, Göhring UJ, Benz C, Becker M, Sartorius J, KolhagenH MallmanP, Neumann R (2002) Induction of MDR1-gene expression by antineoplastic agents in ovarian cancer cell lines. Anticancer Res 22:2199–2203

Shi YR, Gao L, Wang SH, Bu DF, Zhang BH, Jiang HF, Pang YZ, Tang CS (2003) Inhibition of taurine transport by high concentration of glucose in cultured rat cardiomyocytes. Metabolism 52:827–833

Stevens MJ, Hosaka Y, Masterson JA, Jones SM, Thomas TP, Larkin DD (1999) Downregulation of the human taurine transporter by glucose in cultured retinal pigment epithelial cells. Am J Physiol 277:E760–E771

Tappaz ML (2004) Taurine biosynthetic enzymes and taurine transporter: molecular identification and regulations. Neurochem Res 29:83–96

Tessari P, Coracina A, Kiwanuka E, Vedovato M, Vettore M, Valerio A, Caramella M, Garibotto G (2005) Effects of insulin on methionine and homocysteine kinetics in type 2 diabetes with nephropathy. Diabetes 54:2968–2976

Timbrell JA, Seabra V, Waterfield CJ (1995) The in vivo and in vitro protective properties of taurine. Gen Pharmacol 26:453–462

Uchida S, Kwon HM, Yamauchi A, Preston AS, Marumo F, Handler JS (1992) Molecular cloning of the cDNA for an MDCK cell Na(+)- and Cl (−)-dependent taurine transporter that is regulated by hypertonicity. Proc Natl Acad Sci 89:8230–8234

Verzola D, Bertolotto MB, Villaggio B, Ottonello L, Dallegri F, Frumento G, Berruti V, Gandolfo MT, Garibotto G, Deferran G (2002) Taurine prevents apoptosis induced by high ambient glucose in human tubule renal cells. J Invest Med 50:443–451

Vilchis C, Salceda R (1996) Effect of diabetes on levels and uptake of putative amino acid neurotransmitters in rat retina and retinal pigment epithelium. Neurochem Res Int 21:1167–1171

Warskulat U, Heller-Stilb B, Oermann E, Zilles K, Haas H, Lang F, Häussinger D (2007) Phenotype of the taurine transporter knockout mouse. Methods Enzymol 428:439–458. doi:10.1016/S0076-6879(07)28025-5

Winer DA, Winer S, Shen L, Wadia PP, Yantha J, Paltser G, Tsui H, Wu P, Davidson MG, Alonso MN, Leong HX, Glassford A, Caimol M, Kenkel JA, Tedder TF, McLaughlin T, Miklos DB, Dosch HM, Engleman EG (2011) B cells promote insulin resistance through modulation of T cells and production of pathogenic IgG antibodies. Nat Med 17:610–617. doi:10.1038/nm.2353

Wu G (2009) Amino acids: metabolism, functions, and nutrition. Amino Acids 37:1–17. doi:10.1007/s00726-009-0269-0

Wu QD, Wang JH, Fennessy F, Redmond HP, Bouchier-Hayes D (1999) Taurine prevents high-glucose-induced human vascular endothelial cell apoptosis. Am J Physiol 277:C1229–C1238

Xiao C, Giacca A, Lewis GF (2008) Oral taurine but not N-acetyl-cysteine ameliorates NEFA-induced impairment in insulin sensitivity and beta cell function in obese and overweight, non-diabetic men. Diabetologia 51:139–146. doi:10.1007/s00125-006-0211-x