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ORIGINAL ARTICLE

Taurine prevents fat deposition and ameliorates plasma lipid profile in monosodium glutamate-obese rats

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Abstract The aim of the present study was to evaluate the preventive effects of taurine (TAU) supplementation upon monosodium glutamate (MSG)-induced obesity. Rats treated during the first 5 days of life with MSG or saline were distributed into the following groups: control (CTL), CTL-treated with TAU (CTAU), MSG and MSG-supplemented with TAU (MTAU). CTAU and MTAU received 2.5% of TAU in their drinking water from 21 to 90 days of life. At the end of treatment, MSG and MTAU rats were hyperinsulinemic, glucose intolerant and insulin resistant, as judged by the HOMA index. MSG and MTAU rat islets secreted more insulin at 16.7 mM glucose compared to CTL. MSG rats also showed higher triglycerides (TG) and non-esterified fatty acids (NEFA) plasma levels, Lee Index, retroperitoneal and periepidydimal fat pads, compared with CTL, whereas plasma lipid concentrations and fat depots were lower in MTAU, compared with MSG rats. In addition, MSG rats had a higher liver TG content compared with CTL. TAU decreased liver TG content in both supplemented groups, but fat content only in MTAU rats. TAU supplementation did not change glucose homeostasis, insulin secretion and action, but reduced plasma and liver lipid levels in MSG rats.

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Keywords NEFA · MSG · Obesity · TG · Taurine supplementation

Abbreviations

apoB	Apolipoprotein B100
CHOL	Cholesterol
CTL	Control
CTAU	Control rats supplemented with TAU
HOMA-IR	Homeostasis model assessment of insulin resistance
ipGTT	Intraperitoneal glucose tolerance test
LDL	Low-density lipoprotein
MSG	Monosodium glutamate
MTAU	MSG rats supplemented with TAU
NEFA	Non-esterified fatty acids
TAU	Taurine
TG	Triglyceride
VLDL	Very low-density lipoprotein

Introduction

Type II diabetes mellitus has extended worldwide and, while insulin resistance is an early phenomenon partly related to obesity, pancreas beta-cell function declines gradually over time before the onset of clinical hyperglycemia. As such, alternative therapies able to stimulate or enhance insulin secretion, as well as their action, may be important to moderate hyperglycemia and, in turn, reduce the occurrence of beta-cell dysfunction (Kahn et al. 2001).

Experimental animal models are used to understand the mechanisms involved in the development of obesity and co-morbidities associated with this syndrome, such as type

II diabetes. Early postnatal administration of MSG in rodents produces selective neuronal necrosis within the preoptic and arcuate nuclei of the hypothalamus as well as median eminence; animals consequently present obesity in adulthood (Olney 1969, 1971). MSG-induced obesity is not accompanied by hyperphagia (Martins et al. 2004) and, compared to non-treated animals, these animals are shorter and lighter (Dawson 1983). Similar to other experimental obesity models, MSG-obese rodents present a massive amount of accumulated fat tissues, glucose intolerance, hyperinsulinemia and insulin resistance (Balbo et al. 2007).

Several treatments and preventive strategies have been used in an attempt to reverse or prevent obesity. TAU (2-aminoethanesulphonic acid), a naturally occurring sulfur-containing amino acid, which is not incorporated into protein and not used for energy (Huxtable 1992), has a potential role in glucose homeostasis (Kulakowski and Maturo 1984; Maturo and Kulakowski 1988; Kaplan et al. 2004), improving insulin actions by the interaction with the insulin receptor and increasing insulin secretion (Carneiro et al. 2009; Ribeiro et al. 2009, 2010). A relationship between low concentrations of TAU in the plasma and a possible disruption in glucose homeostasis has also been suggested in obesity (Nandhini et al. 2005; Tsuboyama-Kasaoka et al. 2006). The maintenance of physiological plasma TAU concentrations seems to be an important factor for adequate β-cell function and insulin action (Cherif et al. 1996, 1998; Boujendar et al. 2002; Nandhini et al. 2005; Kaniuk et al. 2007; Tas et al. 2007; Xiao et al. 2008). In this study, we found that TAU supplementation decreases body fat depots, total fat and triglycerides (TG) accumulation in the liver, non-esterified fatty acids (NEFA) and TG plasma concentrations without altering glucose tolerance and insulin sensitivity in MSG-obese rats.

Materials and methods

Materials

^{125}I human insulin was purchased from Amersham International (Little Chalfont, Bucks, UK). Routine reagents were purchased from Sigma Chemical (St Louis, MO, USA).

Animals, MSG treatment and TAU supplementation

All experiments were approved by the University's Committee on Ethics in Animal Experimentation (CEEAAP/UNIOESTE). Male newborn *Wistar* rats received a subcutaneous injection of MSG (4 g/kg body weight per day, MSG group), or hyperosmotic saline solution (1.25 g/kg body weight per day, CTL group) which have same osmolarity of MSG solution, during the first 5 days of life (Balbo et al. 2000). Pups were weaned on the 21st day of life and had free access to standard rodent chow (Nuvital, Colombo, Brazil) and water; they were housed in standard cages and maintained on a 12 h light/dark cycle (lights on 06:00–18:00 h) and controlled temperature (22 ± 1°C). The rats were distributed into four groups: CTL; CTAU that received 2.5% TAU in their drinking water from 21 to 90 days of life; MSG; and MTAU, MSG rats supplemented with TAU.

General nutritional parameters

Body weight and food intake were measured during the experimental period (from 21 to 90 days of life). Food intake was expressed by feed efficiency (food intake/body weight) (Duivenvoorden et al. 2005). At the end of the supplementation period, the final body weight and naso-anal length were measured in all groups for calculation of the Lee Index [from the ratio of body weight $(g)^{1/3}$/naso-anal length (cm) × 1,000] used as predictor of obesity in rodents (Bernardis and Patterson 1968). In addition, fasted and fed rats were decapitated, their blood collected and plasma was stored at −20°C. Plasma glucose was measured using a glucose analyzer (Accu-Chek Advantage, Roche Diagnostic, Switzerland) and insulin was measured by radioimmunoassay (RIA), as previously reported (Ribeiro et al. 2010). Total cholesterol (CHOL), TG and NEFA were measured using standard commercial kits, according to the manufacturer's instructions (Boehringer Mannhein®, Germany; Merck®, Germany and Wako®, Germany, respectively).

TAU plasma levels

To measure fed TAU plasma concentrations, 200 µL of plasma were deproteinized by adding 200 µL of 25% trichloroacetic acid solution and were then centrifuged at 21,000*g* for 10 min. Supernatant (100 µL) was collected and mixed with sample loading buffer (100 µL) (Biochrom 20 reagent kit, Cambridge, UK). An aliquot of 25 µL of the mixture was then resolved by liquid chromatography on a Biochrom 20 plus amino acid analyzer (Amersham Pharmacia, Piscataway, NJ, USA). Amino acid standards were analyzed first, followed by the samples. Amino acids were quantified using Biochrom 20 control software, version 3.05.

Intraperitoneal glucose tolerance test (ipGTT)

Blood glucose concentrations (time 0) were measured (as previous described) in overnight fasted rats. A glucose load of 2 g/kg body weight was then administered by ip injection and additional blood samples were collected at 15, 30, 60 and 120 min.

HOMA index

Tissue insulin sensitivity was also evaluated by the previously validated (Bonora et al. 2000) homeostasis model assessment (HOMA) using the HOMA index of insulin resistance (HOMA-IR) = fasting insulin (μU/mL) × fasting glucose (mM)/22.5 described by (Matthews et al. 1985).

Islet isolation, static insulin secretion and total islet insulin content

Islets were isolated by collagenase digestion of the pancreas. For static incubations, groups of four islets were first incubated for 30 min at 37°C in Krebs–Ringer bicarbonate (KRB) buffer with 5.6 mM glucose and 3 g of BSA/L, and equilibrated with a mixture of 95% O_2/5% CO_2 to give pH 7.4. This medium was then replaced with fresh buffer and the islets incubated for 1 h under the following conditions: 2.8 or 16.7 mM glucose. At the end of the incubation period, the insulin content of the medium was measured by RIA. For total insulin content measurement, groups of four islets were collected and transferred to tubes containing deionized water (1 mL), pancreatic cells were disrupted using a Polytron PT 1200 C homogenizer (Brinkmann Instruments, NY, USA), employing three 10-s pulses and the islet insulin content was measured by RIA.

Glucose oxidation

Glucose oxidation were measured by the rate of formation of $^{14}CO_2$ from D-[U-^{14}C]glucose (20 μCi/mL) by the islets. Groups of 25 islets were incubated for 2 h at 37°C in 30 μL of KRB supplemented with 16.7 mM of glucose. After incubation, oxidation was stopped with 1 N HCl for cell cleavage. Released $^{14}CO_2$ was absorbed by 1 M NaOH and the $NaH^{14}CO_3$ obtained was measured by liquid scintillation in a β radiation counter.

Lipids and TG content of liver

Liver lipids were extracted by the method of Folch et al. (1957). The extract was evaporated to dryness under N_2 and weighted by gravimetry for measured total fat content. Then it was diluted in isopropanol for determination of the TG content in the liver using enzymatic colorimetric methods according to the manufacturer instructions (Merck®, Germany).

Statistical analysis

The results are presented as means ± SEM for the number of determinations (n) indicated. The statistical analyses were carried out using one-way analysis of variance (ANOVA) followed by the Newman–Keuls post-test ($P < 0.05$). Tests were performed using GraphPad Prism version 4.00 for Windows (GraphPad Software®).

Results

Animal features

Figure 1a shows that the body weight of MSG rats was significantly different to that of CTL rats at 59 days of age. This effect was not due to any alteration in food intake, since MSG rats presented similar food efficiency to that of CTL rats (Fig. 1b). Furthermore, TAU supplementation of MSG-treated rats did not prevent body weight alteration.

At 90 days of age, MSG-treated rats demonstrated a decreased body size and weight compared with CTL rats (19.6 ± 0.4 cm and 268 ± 9.9 g vs. 23 ± 0.2 cm and 348 ± 13 g, respectively; $P < 0.001$). TAU supplementation did not alter these parameters (MTAU 19.3 ± 0.4 cm and 270 ± 11 g vs. CTAU 23 ± 0.3 cm and 343 ± 8 g, respectively). As shown in Figure 1, MSG rats had a higher Lee index (Fig. 1c) and fat accumulation, as demonstrated by their increased retroperitoneal and periepididymal fat pad weights when compared with CTL rats ($P < 0.001$; Fig. 1d and e, respectively). TAU supplementation attenuated the fat accumulation with decreases of 18 and 20% in retroperitoneal and periepididymal fat pad weights, respectively, in MTAU rats when compared with MSG rats ($P < 0.01$). However, the Lee index was not altered by supplementation in the MTAU group, where rats demonstrated similar values to those of the MSG rats (Fig. 1c).

Table 1 shows that plasma glucose and CHOL were not altered by MSG treatment or supplementation. In contrast, MSG rats presented higher insulin, TG and NEFA plasma levels when compared with CTL rats ($P < 0.001$). TAU ameliorated plasma lipids in MSG-supplemented rats. However, hyperinsulinemia was observed in MTAU rats (Table. 1). Fed TAU plasma levels were 150 and 47% higher in the CTAU and MTAU groups, respectively, compared with CTL rats ($P < 0.05$).

Glucose homeostasis

At the end of the experimental period, rats of both experimental groups were submitted to an ipGTT. After glucose loading, the plasma glucose concentration reached maximal levels at 15 min in both groups. MSG and MTAU rats presented higher glucose values at 60 and 120 min, compared with control rats ($P < 0.05$ and $P < 0.01$, respectively; Fig. 2a). The area under the curve (AUC) of the glucose plasma levels during the ipGTT in MSG group was 31% higher than for the CTL group ($P < 0.01$; Fig. 2b).

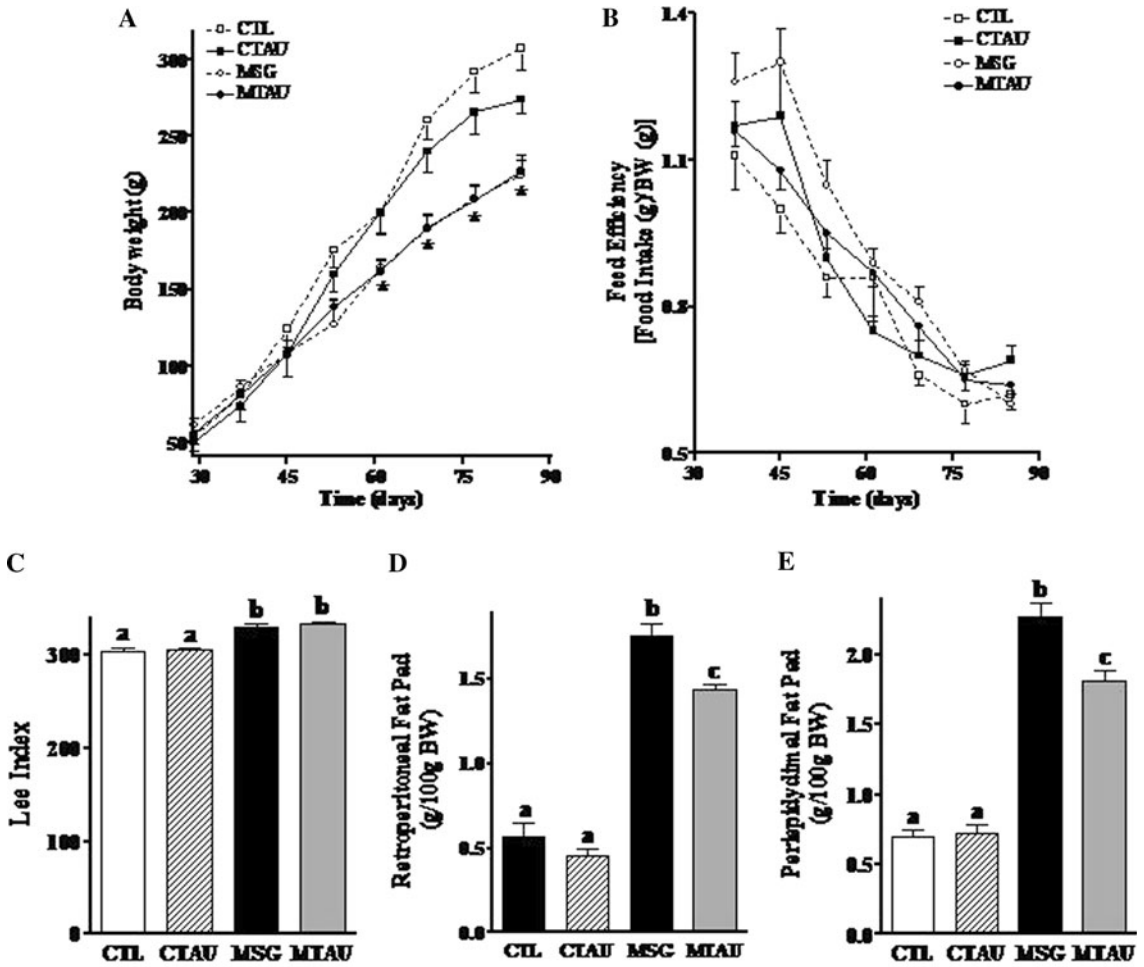

Fig. 1 Body weight (**a**), food efficiency (**b**), Lee index [body weight $(g)^{1/3}$/naso-anal length (cm) × 1,000] (**c**), and, fat accumulation in retroperitoneal (**d**) and periepididymal (**e**) pads of 90-day-old CTL, CTAU, MSG and MTAU rats. Data are means ± SEM obtained from 6–11 rats for each group. *Significant difference between MSG and MTAU groups, compared to controls. The *letters over the bars* represent significant differences ($P < 0.05$)

Table 1 Fasting plasma glucose, insulin, NEFA, TG and CHOL concentrations, and, fed TAU plasma levels in 90-day-old CTL, CTAU, MSG and MTAU rats

	CTL	CTAU	MSG	MTAU
Glucose (mg/dL)	65 ± 4.5	66 ± 2.8	78 ± 2.2	71 ± 2.8
Insulin (ng/mL)	0.46 ± 0.1a	0.62 ± 0.09a	1.39 ± 0.16b	1.47 ± 0.18b
NEFA (mM)	0.86 ± 0.28a	0.70 ± 0.15a	1.27 ± 0.36b	0.93 ± 0.14a
TG (mg/dL)	75 ± 18a	52 ± 5a	320 ± 48b	180 ± 17c
CHOL (mg/dL)	86 ± 10	101 ± 11	117 ± 13	110 ± 6
TAU (μmol/mL)	0.36 ± 0.06a	0.91 ± 0.09b	0.44 ± 0.02a	0.66 ± 0.06c

Data are means ± SEM ($n = 6$–11). Different letters indicate significant difference ($P < 0.05$)

This impairment in glucose tolerance was in accordance with a lower insulin action, demonstrated by a 2.5-fold higher HOMA index in the MSG rats, when compared with CTL rats ($P < 0.001$; Fig. 2c). TAU supplementation did not prevent the impairment in glucose tolerance and insulin sensitivity in the MTAU group (Fig. 2).

Insulin secretion and glucose oxidation by the islets

Figure 3 shows glucose-induced insulin secretion in islets isolated from CTL, CTAU, MSG and MTAU rats. Basal insulin release at 2.8 mM glucose was similar between the groups. However, at 16.7 mM glucose, insulin secretion was

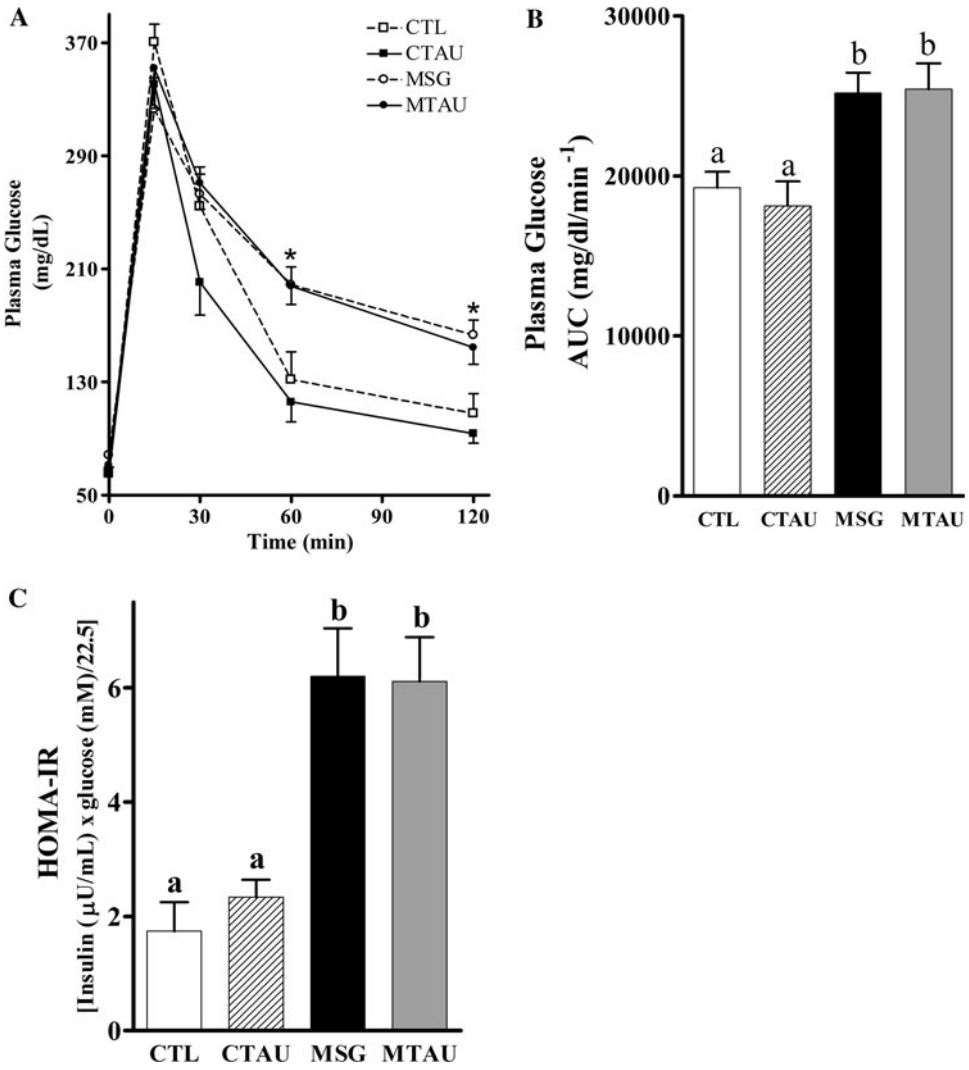

Fig. 2 Intraperitoneal glucose tolerance test (**a** and **b**) and HOMA index (**c**) in MSG-treated rats, supplemented or not, with TAU. Data are means ± SEM obtained from 7–8 rats for each group. *$P < 0.05$ indicates significant different between MSG and MTAU rats, as compared to controls. The *letters over the bars* represent significant differences, $P < 0.05$

significantly higher in islets from MSG rats, compared with CTL islets ($P < 0.001$). The hypersecretion verified in islets from the obese rats was not prevented by TAU supplementation. D-[U-^{14}C]glucose oxidation in response to 16.7 mM glucose was reduced in MSG islets, compared with CTL islets (27 ± 2 vs. 35 ± 2 pmol/islet/2 h^{-1}, respectively; $P < 0.05$), whereas glucose oxidation in MTAU islets was similar to that of CTL islets (32 ± 2 pmol/islet/2 h^{-1}). In addition, total insulin content was similar in both groups of islets (MSG 47 ± 7, MTAU 48 ± 7, CTL 44 ± 5 and CTAU 48 ± 9 ng/islet, respectively).

Hepatic fat content

Figure 4a shows that total liver fat content was not different in MSG rats, compared to CTL rats. However, TAU supplementation significantly decreased total fat accumulation in the MTAU group, compared to the CTL group ($P < 0.05$). MSG rats presented a 21% higher TG liver content, compared with CTL rats ($P < 0.05$; Fig. 4b). Interestingly, TAU decreased TG liver content in both groups of supplemented rats with a 67% lower TG content in both supplemented groups compared with the CTL group ($P < 0.001$; Fig. 4b).

Discussion

In agreement with previous reports (Balbo et al. 2000; Macho et al. 2000), neonatal treatment with MSG caused obesity in 90-day-old adult rats. The MSG-treated rats demonstrated low body weight, normal food intake, a higher fat pad weight, fasting hyperinsulinemia, glucose intolerance, and higher NEFA and TG plasma levels. In contrast, TAU supplementation of MSG-treated rats prevented tissue fat accumulation, decreased hepatic and

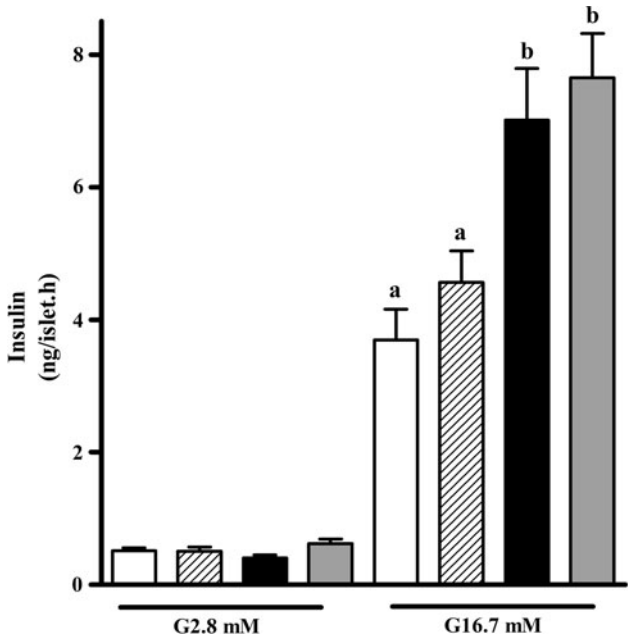

Fig. 3 Glucose-induced insulin secretion in isolated islets from 90-day-old CTL, CTAU, MSG and MTAU rats. For static insulin secretion, islets were incubated for 1 h with 2.8 or 16.7 mM glucose (*G*). Data are means ± SEM obtained from 14–20 groups of islets. *Different letters over the bars* indicate a significant difference, $P < 0.05$

plasma lipid concentrations, without changes in glucose tolerance and glucose-induced insulin secretion by isolated islets.

Several reports have described the involvement of TAU in glucose homeostasis. In experimental models, and in humans, TAU supplementation improved glucose tolerance and insulin sensitivity (Anuradha and Balakrishnan 1999; Nakaya et al. 2000; Nandhini et al. 2005; Tsuboyama-Kasaoka et al. 2006; Xiao et al. 2008; Carneiro et al. 2009; Ribeiro et al. 2009). In addition, the possible effect of TAU upon pancreatic beta-cell function was extensively studied (Cherif et al. 1996, 1998; Carneiro et al. 2009; Ribeiro et al. 2009, 2010). Although TAU supplementation did not ameliorate glucose tolerance and insulin sensitivity, or prevent the increase in insulin secretion and hyperinsulinemia in MSG-treated rats, TAU exerted a positive effect upon islet glucose oxidation, associated with an improvement in body lipid metabolism without modification in weight gain, food intake and Lee index (Fig. 1; Table 1).

The beneficial effects of TAU upon lipid metabolism have been previously documented. TAU decreased plasma CHOL concentrations in *Goto Kakisaki* diabetic rats that received a high CHOL diet (Nishimura et al. 2002) and, in high CHOL fed rats, TAU supplementation reduced the content of CHOL and TG in the liver (Choi et al. 2006). In *Otsuka Long-Evans Tokushima Fatty* rats TAU decreased plasma TG and CHOL plasma levels, fat and TG liver content and abdominal fat pads (Nakaya et al. 2000). In addition, a lower CHOL content in the plasma and liver was observed in high-fat diet mice supplemented with TAU (Murakami et al. 2000). This effect was reported to be due to a higher CHOL 7α-hydroxylase activity in the liver of these rodents, improving the conversion of CHOL to bile acid formation (Murakami et al. 2002). In accordance with data obtained in animal models, Zhang et al. (2004) demonstrated decreased TG plasma levels in overweight and obese non-diabetic subjects supplemented with TAU (3 g/day per 7 weeks). Lower TG plasma levels, observed in subjects taking TAU, were probably due to suppression in TG secretion by the liver (Chen et al. 2004). In addition, in healthy men submitted to a high CHOL diet,

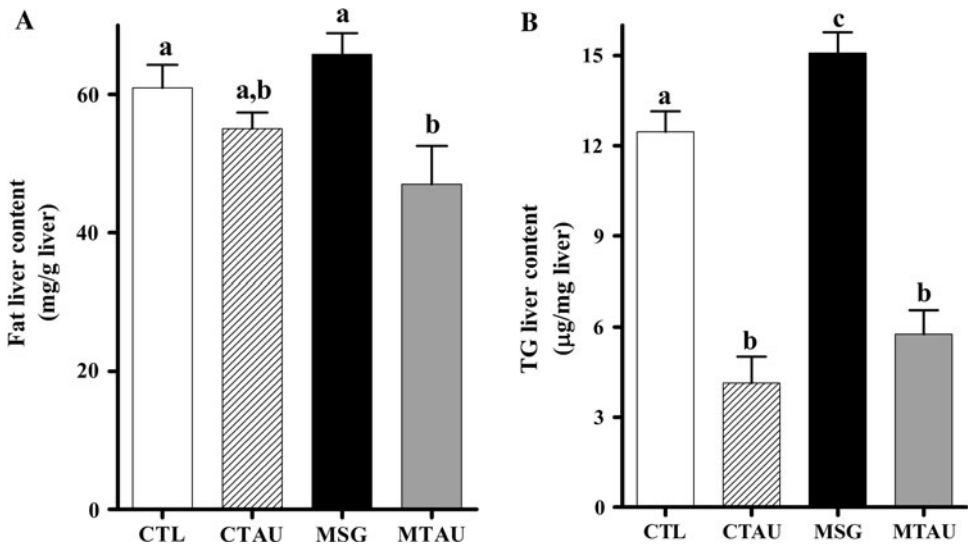

Fig. 4 Fat content (**a**) and TG concentration (**b**) in the liver of 90-day-old CTL, CTAU, MSG and MTAU rats. Data are means ± SEM obtained from 6–10 rats for each group. *Different letters* indicate significant difference, $P < 0.05$

TAU attenuated increases in total CHOL and low-density lipoprotein (LDL) levels (Mizushima et al. 1996).

In view of the above observations, we suggest that TAU supplementation reduced plasma lipid concentrations in MSG-treated rats decreasing hepatic lipid synthesis and secretion as well as lipid transport to the tissues. It is known that the liver synthesizes and secretes the lipoproteins containing apolipoprotein B100 (apoB) that is required for the intracellular assembly and secretion of very low-density lipoprotein (VLDL) and LDL (Dashti 1992; Olofsson and Boren 2005). VLDL is linked to TG and CHOL transport to the tissues. In human hepatoblastoma cells (HepG2) treated with TAU oleate incorporation was decreased resulting in lower TG synthesis and secretion. TAU also had an inhibitory effect upon CHOL metabolism, since HepG2 cells treated with TAU decreased CHOL content and [^{14}C]oleoylcholesterol incorporation. The latter effect seems to be due to an inhibition in Acyl-coenzyme A: CHOL acyltransferase that catalyzes CHOL ester synthesis in the cells. In addition, TAU significantly decreased apoB secretion by HepG2 cells incubated with oleate, this action may be dependent on lower TG synthesis induced by TAU and may influence lipid availability to the body (Yanagita et al. 2008).

A relationship between increased TAU plasma concentration by supplementation and prevention of the development of obesity was also reported (Tsuboyama-Kasaoka et al. 2006). Decreased TAU biosynthesis by the adipose tissue reduced plasma TAU levels in different experimental models of obesity. Lower TAU plasma levels correlate with increased fat tissue depots and create a vicious cycle with increased lipid accumulation in the tissues. Restoring plasma TAU concentrations by supplementation prevented diet and genetic-obesity development. This effect was due to increased mRNA levels of transcription factors and cofactors involved in energy expenditure in adipose tissue, as well as by increased mRNA levels of fatty acid β-oxidation enzymes and mitochondrial respiration components (Tsuboyama-Kasaoka et al. 2006).

In contrast to that referred by Tsuboyama-Kasaoka et al. (2006), we did not observe differences in plasma TAU concentrations between in obese MSG and CTL that was significantly higher in MTAU rats. Thus, we assume that the lower fat accumulation in MTAU rats may be a consequence of the higher levels of this amino acid during the progression of obesity.

In conclusion, we demonstrate that TAU supplementation in MSG-treated rats did not improve glucose tolerance and insulin sensitivity, but ameliorated plasma and liver lipid content and metabolism, without modification in CHOL values. This effect culminated in decreased lipid deposition, as seen in the retroperitoneal and periepididymal fat pads.

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