Effects of Paternal Hypothalamic Obesity and Taurine Supplementation on Adiposity and Vascular Reactivity in Rat Offspring

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Abbreviations

Ach	Acetylcholine
AUC	Area under curve
BW	Body weight
CHOL	Cholesterol
CTAU	CTL supplemented with Tau
CTL	Control
ipGTT	Intraperitoneal glucose tolerance test
MSG	Monosodium glutamate
MTAU	MSG supplemented with Tau
NO	Nitric oxide
Phe	Phenylephrine
RIA	Radioimmunoassay
Tau	Taurine
TG	Triglycerides

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1 Introduction

Obesity is characterized by excessive fat accumulation, due to an imbalance between calories consumed and expended. This syndrome is associated with an increased risk of type 2 diabetes and cardiovascular diseases (Meigs 2010). Genetic, neuroendocrine, metabolic, behavioral and environmental factors contribute to the manifestation and maintenance of obesity (Soubry et al. 2013; Sominsky and Spencer 2014; Chavey et al. 2014).

Several reports have demonstrated that the intrauterine milieu and changes in maternal metabolism may program the metabolic phenotype of the offspring through physiological and/or epigenetic mechanisms (Cherif et al. 1996; Kalbe et al. 2005; Catalano et al. 2009; Chavey et al. 2014). Maternal diabetes and/or obesity were also associated with cardiovascular dysfunction in adult offspring and increased mortality from cardiovascular events (Dabelea 2007; Reynolds et al. 2013). However, while paternal metabolic conditions are often not considered, paternal metabolism can alter DNA and histone methylation and acetylation profiles, leading to alterations in gene expression. These epigenetic modifications are propagated through the gametes to the offspring and may contribute to the development of metabolic dysfunctions and its associated comorbidities in later life (Ng et al. 2010; Soubry et al. 2013; Fullston et al. 2013).

Neonatal administration of monosodium glutamate (MSG) in rodents causes lesions in different hypothalamic areas, resulting in metabolic and neuroendocrine changes that lead to obesity (Olney 1969). MSG obese rodents show massive fat accumulation (Balbo et al. 2000), hyperleptinemia (Kim et al. 2005), hyperinsulinemia, insulin resistance and hypertriglyceridemia (Hirata et al. 1997; Nardelli et al. 2011). In addition, MSG hypothalamic obesity also causes vascular dysfunction with lower nitric oxide (NO) bioavailability and increased reactive oxygen species production in vascular beds (Lobato et al. 2011).

The amino acid taurine (Tau) is present in high levels in mammalian tissues and plays a role in the regulation of fat metabolism, in body glucose control and in cardiovascular function (Ribeiro et al. 2009; Xu et al. 2008; Nardelli et al. 2011; Abebe and Mozaffari 2011). In the former process, Tau demonstrates antihypertensive actions (Abebe and Mozaffari 2011), vasorelaxation properties (Ristori and Verdetti 1991; Niu et al. 2008; Abebe and Mozaffari 2011) and retards the initiation and progression of atherosclerosis (Murakami 2014). Here, we analyzed whether paternal MSG hypothalamic obesity may influence adiposity, glucose tolerance and vascular reactivity in later life in offspring. We also verified whether Tau supplementation given to fathers modulates these effects.

2 Methods

2.1 MSG Treatment, Tau Supplementation and Offspring Groups

All protocols were approved by the local Animal Care and Use Committee (CEUA *Campus UFRJ-Macaé*, license n°.: MACAE01). Male *Wistar* rats received subcutaneous injections of MSG [4 g/kg body weight (BW); MSG group] or hyperosmotic saline solution [1.25 g/kg BW; control (CTL) group] during the first 5 days of life (Balbo et al. 2000). At weaning (21 days), the rats were distributed into the following groups: CTL, MSG, and CTL and MSG supplemented with 2.5 % Tau in their drinking water (CTAU and MTAU, respectively). At 90 days of age, all male rat groups were mated with 90-day-old female CTL rats to obtain offspring that were designed according to their fathers' treatment as: CTL, CTAU, MSG and MTAU. During mating, one male and three females were housed together for 8 consecutive days. Litter sizes were standardized to eight pups at postnatal day 1 to control nutrition during the lactation period.

All rat groups were maintained on a 12 h light/dark cycle (lights on 07:00–19:00 h), controlled temperature (21 ± 2 °C) and allowed free access to food and water. All experimental procedures listed below were developed in the male founders at 90 days of age. For female and male offspring groups, the experimental protocols were evaluated at 150 days of age. During the entire experimental period, offspring groups only consumed standard food and water.

2.2 General Nutrition Parameters

Body weight and food intake were measured once a week during the entire experimental period in all offspring groups. At the end of the experimental period, all rats were weighed and nasoanal lengths were measured to calculate the Lee index [BW $(g)^{1/3}$/nasoanal length (cm) × 1,000] (Bernardis and Patterson 1968). Subsequently, rats were euthanized by cervical dislocation and perigonadal and retroperitoneal fat pads were collected and weighed. Blood samples were collected from the tip of the tail and the plasma was used for insulin measurement by radioimmunoassay (Ribeiro et al. 2010), and total cholesterol (CHOL) and triglyceride (TG) levels using standard commercial kits, according to the manufacturer's instructions (Boehringer Mannhein®, Germany; Merck®, Germany and Wako®, Germany, respectively). Plasma glucose was measured using a glucose analyzer (Accu-Chek Performa, Roche Diagnostic, USA).

2.3   *Intraperitoneal Glucose Tolerance Test (ipGTT)*

After a 12 h of fasting, blood samples were collected from the tip of tail from all rats in the offspring groups to measure glycemia using a glucose analyzer (Accu-Chek Performa, Roche Diagnostic, USA), before (0 min) and at 15, 30, 60 and 120 min after an i.p. injection of glucose (2 g/kg BW).

2.4   *Vascular Reactivity in Thoracic Aorta*

At 150 days of age, male offspring were euthanized by cervical dislocation and the thoracic aorta was immediately dissected. Adherent fat and connective tissues were carefully removed, and the aorta was cut into rings of 2–3 mm in length. The aortic rings were placed in a 10 mL vertical chamber containing Krebs Henseleit solution (118 mM NaCl, 4.7 mM KCl, 1.2 mM KH_2PO_4, 1.2 mM $MgSO_4$, 2.5 mM $CaCl_2$, 25 mM $NaHCO_3$ and 11 mM glucose) maintained at 37 °C, pH 7.4, and continuously gassed with carbogen (95 % O_2/5 % CO_2). Isometric tension was measured for each aorta ring mounted between two hooks, one of which was attached to a force transducer (MLT0201; ADInstruments, Bella Vista, New South Wales, Australia). Signals were conditioned (Power Lab 4/30, ADInstruments, Bella Vista, New South Wales, Australia), displayed, and stored on a computer for analysis using LabChart Pro software (ADInstruments, Bella Vista, New South Wales, Australia). After a 90 min equilibration period, concentration-response curves to phenylephrine (Phe; 0.001–10 μM) or acetylcholine (Ach; 0.001–10 μM) were recorded. Relaxations were plotted as percentages of the contraction induced by 10 μM Phe (Raimundo et al. 2006).

2.5   *Statistical Analysis*

Data are presented as means ± SEM, with the number of determinations (n) indicated. The pEC50 ($-\log^{EC50}$) was calculated by non-linear regression analysis. Statistical analyses were carried out using two-way analysis of variance (ANOVA) followed by the Duncan's posttest (P < 0.05) with the Statistica® Software version 7.0 (Statsoft, Tulsa, OK, USA) and graphs were performed using GraphPad Prism® version 5.00 (GraphPad Software, San Diego, CA, USA).

3 Results

3.1 Obesity Evaluation and General Nutritional Features in Paternal Groups

Final BW and length in MSG-treated rats were lower than those of the CTL group (P<0.05 and P<0.03; Table 1). MSG treatment efficiently induced obesity, since the perigonadal and retroperitoneal fat stores were 104 and 178 % larger in the MSG group compared to the CTL rats (P<0.0005 and P<0.0001, respectively; Table 1). Tau-supplemented MSG rats exhibited a reduction of 20 % in the perigonadal fat pads, when compared with non-supplemented MSG rats (P<0.02). However, Tau treatment did not alter other obesity parameters such as BW and the retroperitoneal fat depots (Table 1). In addition, despite no difference in glycemia at fasting and in a fed state between MSG and CTL rats (Table 2), normoglycemia was maintained in the MSG group by hyperinsulinemia under both conditions (P<0.02 and P<0.005). MSG rats also showed hypertriglyceridemia under these nutritional conditions (P<0.004), but presented normal plasma CHOL levels (Table 2). Tau supplementation normalized TG plasma levels in the fed state, without altering the other plasma biochemical parameters (Table 2).

3.2 Obesity Evaluation and General Nutritional Features in Offspring Groups

Body weight in female and male offspring groups was measured weekly, as illustrated in Fig. 1a, c, respectively. No differences between MSG and CTL offspring were observed in total BW, expressed by the area under the growth curve (AUC), as registered during the experimental period (Fig. 1b, d). Total food consumption was also similar in female and male MSG offspring ($2,478 \pm 16$ and $2,742 \pm 71$ g weeks^{-1}) and in CTL offspring ($2,599 \pm 64$ and $2,924 \pm 97$ g weeks^{-1}, respectively). At 150 days of age, final BW and length, and Lee index did not differ between female and male MSG and CTL offspring (Table 3).

Table 1 Obesity parameters evaluated in 90-day-old male CTL, CTAU, MSG and MTAU rats
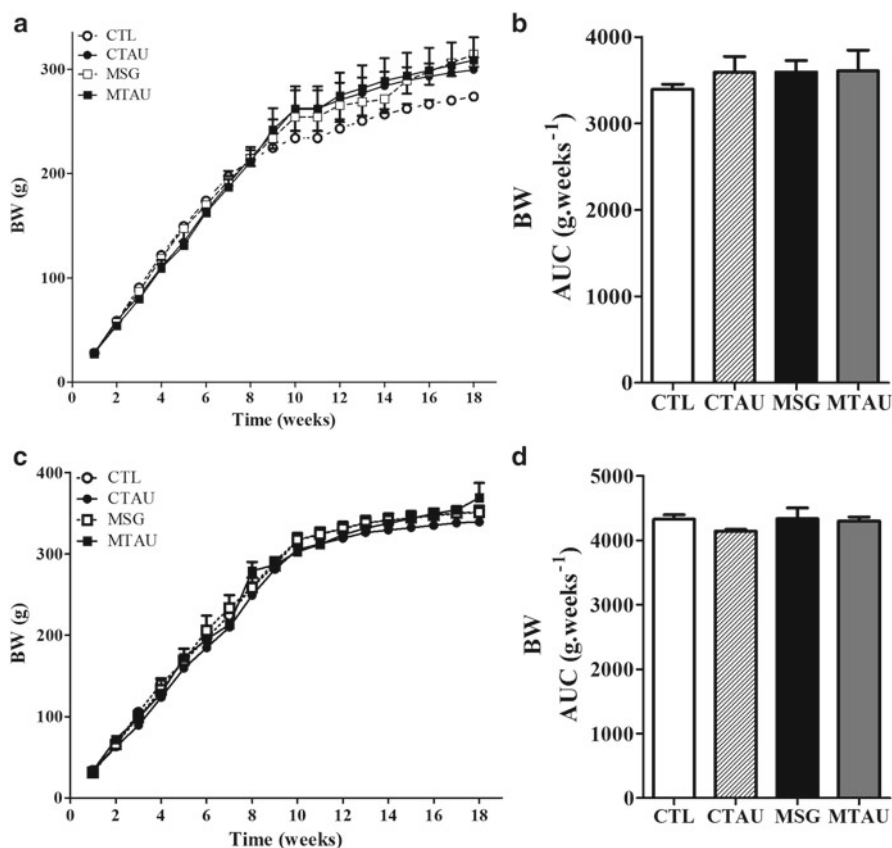
	CTL	CTAU	MSG	MTAU
BW (g)	371 ± 13^a	384 ± 12^a	298 ± 37^b	307 ± 19^b
Nasoanal length (cm)	24 ± 0.7^a	24 ± 0.3^a	22 ± 0.6^b	22 ± 0.4^b
Lee index	300 ± 7	300 ± 1	313 ± 3	303 ± 5
Perigonadal fat pad (mg/g BW)	15.4 ± 0.6^a	14.3 ± 0.9^a	31.5 ± 2.1^b	25.1 ± 1.6^c
Retroperitoneal fat pad (mg/g BW)	12.1 ± 1.4^a	12.8 ± 1.4^a	33.7 ± 1.7^b	31.1 ± 1.7^b

Data are means $\pm$ SEM (n=3–4 rats). Different letters represent significant differences (P<0.05)

Table 2 Plasma biochemical parameters in 12 h-fasted and fed 90-day-old male CTL, CTAU, MSG and MTAU rats

		CTL	CTAU	MSG	MTAU
Glycemia (mg/dL)	Fasting	105±3	113±1	97±4	95±3
	Fed	130±2	136±5	145±10	121±5
Insulinemia (ng/mL)	Fasting	0.52±0.1[a]	0.75±0.1[a,b]	1.18±0.3[b]	1.34±0.2[b]
	Fed	1.15±0.3[a]	1.68±0.3[a,c]	4.61±0.7[b]	3.2±0.9[b,c]
TG (mg/dL)	Fasting	75±6[a]	75±7[a]	143±21[b]	116±19[b]
	Fed	97±7[a]	87±6[a]	158±7[b]	97±9[a]
CHOL (mg/dL)	Fasting	50±4	60±6	62±5	63±6
	Fed	45±5	53±10	53±3	56±6

Data are means±SEM (n=5–7 rats). Different letters represent significant differences ($P < 0.05$)

Fig. 1 Changes in body weight (BW) in female (**a**) and male (**b**) offspring from male MSG and CTL rats supplemented or not with Tau. Means±SEM (n=3–10) of total BW registered during 18 weeks in female (**c**) and male (**d**) offspring from male CTL, CTAU, MSG and MTAU rats

Table 3 Obesity parameters in 150-day-old female and male offspring from male CTL, CTAU, MSG and MTAU rats

		CTL	CTAU	MSG	MTAU
BW (g)	Female	232±4	233±4	244±6	226±4
	Male	382±12	397±6	357±12	423±7
Nasoanal length (cm)	Female	21±0.3	22±0.3	21±0.2	21±0.2
	Male	24±0.4	25±0.4	24±0.3	25±0.4
Lee index	Female	295±4	290±3	299±3	295±1
	Male	295±2	286±4	296±3	299±4
Perigonadal fat pad (mg/g BW)	Female	10.7 ± 2.2^a	24.1 ± 1.8^b	$21.6\pm1.2^{b,c}$	17.0 ± 2.2^c
	Male	12.2±0.8	12.7±1.1	14.5±1.6	13.9±2.0
Retroperitoneal fat pad (mg/g BW)	Female	9.8 ± 2.1^a	24.7 ± 1.6^b	24.2 ± 2.8^b	17.0 ± 2.2^b
	Male	8.2±0.5	8.1±1.2	8.7±0.9	9.7±2.2

Data are means±SEM (n=3–10 rats). Different letters represent significant differences ($P<0.05$)

Table 4 Biochemical parameters in 12 h-fasted 150-day-old female and male offspring from male CTL, CTAU, MSG and MTAU

		CTL	CTAU	MSG	MTAU
Glycemia (mg/dL)	Female	105±2	111±4	114±2	104±4
	Male	104±3	102±3	113±3	110±1
Insulinemia (ng/mL)	Female	0.53±0.08	0.57±0.15	0.65±0.09	0.37±0.05
	Male	1.3±0.2	1.0±0.2	0.9±0.2	1.13±0.2
TG (mg/dL)	Female	98±13	101±14	104±18	97±10
	Male	64±7	84±20	71±14	64±3
CHOL (mg/dL)	Female	85±7	71±7	84±7	61±4
	Male	96±6	99±11	88±5	92±10

Data are means±SEM (n=3–10 rats)

In contrast, perigonadal and retroperitoneal fat pads were 50 % and 60 % higher, respectively, in female MSG offspring, when compared with CTL offspring ($P<0.002$ and $P<0.005$, respectively). No difference between fat stores was observed between male MSG and CTL offspring (Table 3). In addition, both female MTAU and CTAU offspring from fathers that were supplemented with Tau presented higher perigonadal and retroperitoneal fat weights than the CTL group ($P<0.04$ and $P<0.005$; Table 3). In addition, plasma glucose, insulin, TG and CHOL levels were similar between offspring from MSG and CTL fathers that were supplemented or not with Tau (Table 4).

Figure 2 shows an ipGTT in 150-day-old female and male offspring from MSG and CTL fathers that were supplemented or not with Tau. Fasting glucose levels did not differ between the groups. After a glucose load, plasma glucose reached a peak at 15 min of the ipGTT in all female (Fig. 2a) and male (Fig. 2c) offspring rat groups and returns to basal glucose conditions after 120 min. No alterations in glucose
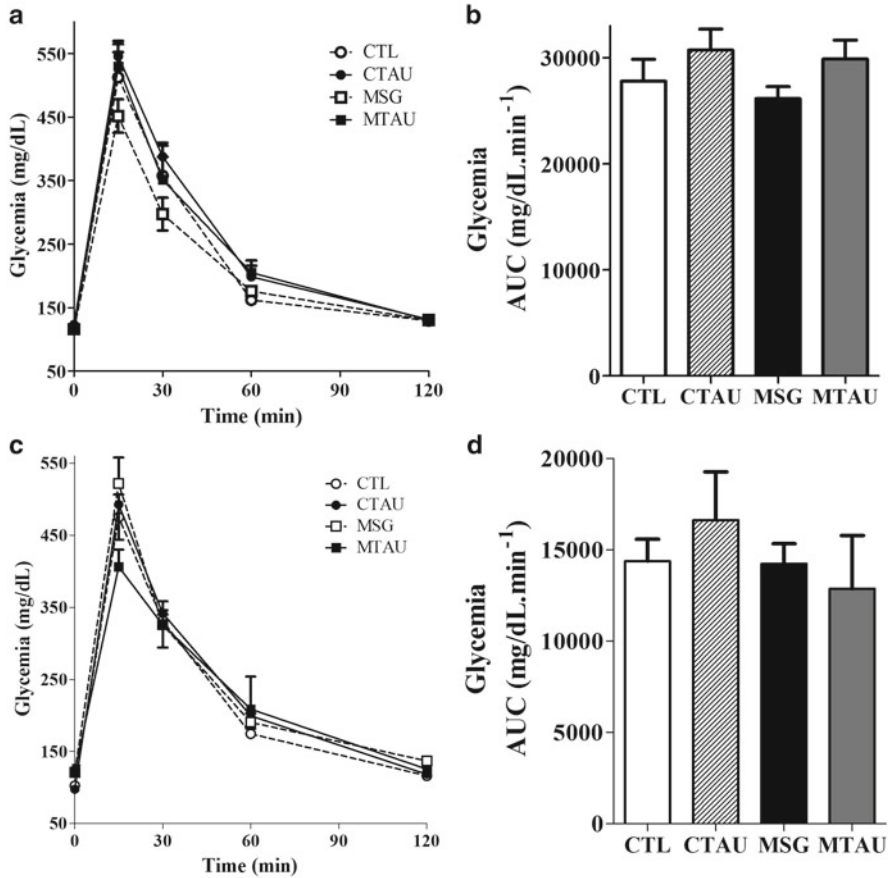
Fig. 2 Plasma glucose concentrations during an ipGTT in 150-day-old female (**a**) and male (**b**) offspring from male MSG and CTL rats supplemented or not with Tau. The figures show blood glucose levels before and after an i.p. injection of glucose (2 g/kg BW). Means ± SEM (n = 3–10) of total glycemia during ipGTT in female (**c**) and male (**d**) offspring from male CTL, CTAU, MSG and MTAU rats

levels during ipGTT or total glycemia expressed by the area under glucose curves (AUC) were observed between the groups (Fig. 2b, d).

3.3   Vascular Reactivity in Thoracic Aorta from Male Offspring

Figure 3a shows that the maximal vasoconstrictor response to Phe was similar in aortas from MSG (1.8 ± 0.1 g) and CTL male offspring (1.7 ± 0.1 g), and Tau supplementation did not alter this parameter in MTAU and CTAU offspring (1.7 ± 0.2 and
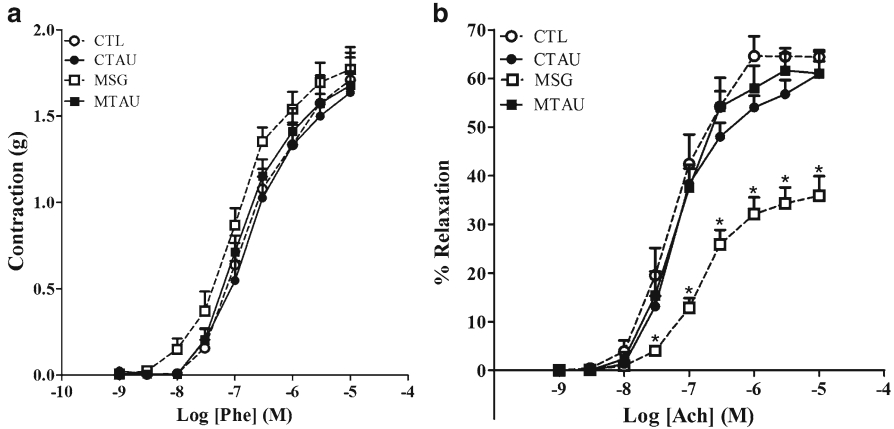
Fig. 3 Dose-response curves for Phe (**a**) and Ach (**b**) in isolated rat thoracic aortas from 150-day-old male offspring from CTL, CTAU, MSG and MTAU rats. Data are means ± SEM (n = 7–14 independent experiments). *MSG offspring is different from CTL under the same [Ach] evaluated (P < 0.05)

1.6 ± 0.1 g, respectively). Also, the potency of Phe was not significantly altered in aortas from MSG (pEC$_{50}$, MSG 7.1 ± 0.1 and CTL 6.7 ± 0.1), and after Tau supplementation (pEC$_{50}$, MTAU 6.9 ± 0.1 and CTAU 6.7 ± 0.1).

The dose-response relaxation curves in response to Ach (0.001–10 μM) are presented in Fig. 3b. Ach-induced maximum relaxation was significantly reduced in aortas from MSG male offspring (36 ± 4 %) in comparison with CTL aortas (64 ± 1 %; P < 0.03), although pEC50 was not significantly altered (pEC$_{50}$, MSG 4.4 ± 0.3 vs. CTL 6.4 ± 0.2; Fig. 3b). Tau supplementation in MSG fathers prevented endothelium dysfunction in their offspring, since MTAU descendants showed similar maximal relaxation (61 ± 4 %) and pEC$_{50}$ (6.1 ± 0.2) in response to Ach as observed in CTL offspring (Fig. 3b).

Vascular reactivity of aortas from the female offspring did not differ between the groups (data not shown).

4   Discussion

Our data show that Tau supplementation prevented fat deposition and hypertriglyceridemia in male MSG obese rats. In addition, we demonstrate that MSG hypothalamic obesity in fathers may program metabolic and vascular dysfunction in their progeny. As such, higher body fat accumulation in female offspring and reduced endothelium-dependent vasodilatation were observed in MSG descendants. Tau treatment in male founders did not prevent fat deposition in female MTAU offspring, whereas male MTAU progeny showed similar Ach-induced vasodilatation in

the thoracic aorta, indicating, for the first time, that this amino acid, when administered to MSG-hypothalamic obese fathers, may prevent vascular dysfunction in their offspring.

As expected, neonatal treatment with MSG efficiently increased perigonadal and retroperitoneal fat depots and induced hyperinsulinemia and hypertriglyceridemia, but lowered BW and body length in the paternal group. All these hypothalamic obesity characteristics have been reported previously (Balbo et al. 2000; Nardelli et al. 2011; Ribeiro et al. 2013, 2014). Although the mechanism of action that leads to obesity in MSG rodents is not completely understood, some reports suggest that neuroendocrine dysfunction and impaired fat metabolism may contribute to the manifestation of obesity (Hirata et al. 1997; Dolnikoff et al. 2001; Kim et al. 2005; Scomparin et al. 2009).

Several potential therapeutic and preventive actions of Tau against obesity development and its comorbidities have been reported (Nakaya et al. 2000; Nandhini et al. 2005; Tsuboyama-Kasaoka et al. 2006; Xiao et al. 2008; Ribeiro et al. 2012; Batista et al. 2013). Here, we confirm data regarding the preventive effect of Tau supplementation against body fat accumulation and hypertriglyceridemia in MSG rats (Nardelli et al. 2011). This effect may be related to the actions of Tau on lipid metabolism, as Tau supplementation is known to decrease circulating and hepatic levels of CHOL and TG in high-CHOL fed rats (Choi et al. 2006; Fukuda et al. 2011), and prevents adiposity in high-fat diet mice (Tsuboyama-Kasaoka et al. 2006; Batista et al. 2013) and in *Otsuka Long-Evans Tokushima Fatty* rats (Nakaya et al. 2000). Accordingly, overweight and obese non-diabetic subjects supplemented with 3 g Tau per day for 7 weeks exhibited decreased TG plasma levels (Zhang et al. 2004). These lower circulating TG levels were probably due to a suppression in hepatic TG secretion (Chen et al. 2004) and higher hepatic fatty acid oxidation, since Tau increases carnitine palmitoyltransferase 1 activity in the liver of high CHOL fed rats (Fukuda et al. 2011). The "antiobesity" effects of Tau may also occur in adipose tissue, since Tau enhances gene expression of several factors involved in energy expenditure in white adipose tissue (Tsuboyama-Kasaoka et al. 2006). This amino acid increases protein-kinase A activity in this tissue, enhancing lipolysis and decreasing the inhibitory action of insulin upon this process (Pina-Zentella et al. 2012).

The maternal metabolic condition as a determinant of the metabolic status in offspring has been extensively investigated (Cherif et al. 1996; Kalbe et al. 2005; de Campos et al. 2007; Catalano et al. 2009; Chavey et al. 2014). However, few studies have looked at the father's role in such a process (Ng et al. 2010; Soubry et al. 2013; Fullston et al. 2013). Here, we verified that female MSG offspring showed larger fat depots (Table 3), despite demonstrating no modifications in BW, food consumption and glucose tolerance (Figs. 1 and 2 and Table 3). These findings are similar to those of a previous study in which female offspring from MSG mothers manifest obesity at 7 months of age (Campos et al. 2008), indicating that both male and female MSG parents may program fat accumulation in their progeny. Another report showed that offspring from fathers that were fed a high-fat diet did not show alterations in adiposity or plasma lipid levels, but rather demonstrated disruption of glucose homeostasis due to lower insulin secretion (Ng et al. 2010). As such, we suggest

that glucose intolerance and fat metabolism disruption can be observed in both male and female offspring from MSG fathers.

As discussed above, Tau has several actions that may prevent body fat accumulation; however, we observed that female MTAU offspring exhibit higher perigonadal and retroperitoneal fat stores (Table 3). These data suggest that although this amino acid improves lipid metabolism in MSG fathers, the effect is not propagated to the female progeny. Additionally, we demonstrated that Tau can impair fat metabolism in offspring, since female CTAU descendants also have larger fat stores (Table 3). Similar deleterious actions of Tau upon adiposity in progeny have been reported. Greater BW gain, body fat deposition and insulin resistance were evidenced in female offspring from dams supplemented with Tau (Hultman et al. 2007). Li et al. (2013) reported that, while Tau supplementation in pregnant rats submitted to an obesogenic diet normalized some hepatic inflammatory markers in female offspring, greater mortality was observed in neonates from control dams supplemented with Tau. These observations together with our results suggest that high Tau levels may have adverse effects on the preconceptional period and in normal pregnancy, changing fat metabolism in the offspring. It is possible that Tau modulates gene expression by epigenetic mechanisms.

In humans, maternal obesity and/or diabetes may predispose to cardiovascular dysfunction in offspring (Dabelea 2007; Reynolds et al. 2013; Marco et al. 2012; Gaillard et al. 2014). This metabolic imprinting in offspring has also been replicated in experimental models (Torrens et al. 2012; Turdi et al. 2013; Fan et al. 2013). Here, isolated thoracic aorta from male offspring of MSG-hypothalamic obese rats showed a clear impaired relaxation in response to Ach (Fig. 3). Remarkably, a decreased cholinergic action in mesenteric vascular beds from MSG-treated rats has been described (Lobato et al. 2011). Therefore, our results demonstrate that obesity and vascular dysfunction in MSG fathers involves an intergenerational mechanism. Previously, only the influence of maternal obesity on vascular dysfunction was reported. Male mice offspring from obese dams and those fed on a high-fat diet after weaning, showed lower Ach-induced relaxation in femoral arteries due to lower NO but higher superoxide production (Torrens et al. 2012). Similarly, isolated abdominal aorta from non-human primate (*Macaca fuscata*) offspring of obese mothers that consumed an obesogenic diet after weaning exhibited a decrease in Ach-induced relaxation, enhanced intima thickness and pro-inflammatory markers in the abdominal aortic wall (Fan et al. 2013).

We also evaluated in MSG offspring the effect of Tau supplementation given to the fathers on vascular reactivity. We verified that relaxation in aortas from MTAU offspring was similar to that observed in the CTL group (Fig. 3). Tau supplementation has several known benefits for cardiovascular function (Xu et al. 2008; Abebe and Mozaffari 2011). Tau supplementation decreases arterial blood pressure in experimental models of hypertension (Abebe and Mozaffari 2011). The amino acid also decreases basal contractile tone and induces relaxation in preconstricted arteries in an endothelium-dependent pathway (Ristori and Verdetti 1991). This Tau-mediated effect may occur due to activation of K^+ channels, since Tau-induced relaxation in renal and mesenteric arteries was abolished in the presence of tetraethylammonium, a non-selective K^+ channel blocker (Niu et al. 2008).

Tau may also contribute to vascular function in utero. Tau supplementation during gestation reduces blood arterial pressure in offspring of stroke-prone spontaneously hypertensive rats (Horie et al. 1987); this prenatal effect was associated with the antioxidant action of the amino acid (Lerdweeraphon et al. 2013). However, the ability of Tau supplementation during the preconception period to prevent vascular dysfunction in offspring was not observed. Thus, obesity is associated with changes in the gamete milieu, leading to alterations in spermatozoa viability, gene expression and DNA methylation (Ghanayem et al. 2010; Fullston et al. 2013). In addition, an altered imprint outcome was observed in neonatal children from obese fathers, indicating that epigenetic alterations during the preconceptional period, induced by life-style, malnutrition or obesity, may reprogram imprint marks during gametogenesis and early development (Soubry et al. 2013). Consequently, as Tau regulates the oxidative stress, motility and survival of the spermatozoa (Yang et al. 2010), we suggest that the high Tau milieu in MSG fathers may prevent epigenetic alterations in their gametes, possibly protecting against vascular dysfunction in the next generation of rats. However, an adverse effect on adiposity in female offspring may occur.

5   Conclusion

This study is the first report to demonstrate that MSG-hypothalamic obese fathers may determine body fat accumulation and vascular dysfunction in the next generation. Tau supplementation given to MSG-treated rats prevented the development of obesity, but this benefit was not propagated to female offspring. Normal aortic relaxation, in response to Ach, was present in MTAU offspring, indicating that this amino acid can prevent the intergeneration inheritance of cardiovascular dysfunction. Tau may act by regulating different epigenetic pathways in gametes, an effect that warrants further investigation.

References

Abebe W, Mozaffari MS (2011) Role of taurine in the vasculature: an overview of experimental and human studies. Am J Cardiovasc Dis 1:293

Balbo SL, Mathias PC, Bonfleur ML, Alves HF, Siroti FJ, Monteiro OG, Ribeiro FB, Souza AC (2000) Vagotomy reduces obesity in MSG-treated rats. Res Commun Mol Pathol Pharmacol 108:291

Batista TM, Ribeiro RA, da Silva PM, Camargo RL, Lollo PC, Boschero AC, Carneiro EM (2013) Taurine supplementation improves liver glucose control in normal protein and malnourished mice fed a high-fat diet. Mol Nutr Food Res 57:423

Bernardis LL, Patterson BD (1968) Correlation between 'Lee index' and carcass fat content in weanling and adult female rats with hypothalamic lesions. J Endocrinol 40:527

Campos KE, Volpato GT, Calderon IM, Rudge MV, Damasceno DC (2008) Effect of obesity on rat reproduction and on the development of their adult offspring. Braz J Med Biol Res 41:122

Catalano PM, Presley L, Minium J, Hauguel-de Mouzon S (2009) Fetuses of obese mothers develop insulin resistance in utero. Diabetes Care 32:1076

Chavey A, Ah Kioon MD, Bailbe D, Movassat J, Portha B (2014) Maternal diabetes, programming of beta-cell disorders and intergenerational risk of type 2 diabetes. Diabetes Metab 40(5):323–330

Chen W, Matuda K, Nishimura N, Yokogoshi H (2004) The effect of taurine on cholesterol degradation in mice fed a high-cholesterol diet. Life Sci 74:1889

Cherif H, Reusens B, Dahri S, Remacle C, Hoet JJ (1996) Stimulatory effects of taurine on insulin secretion by fetal rat islets cultured in vitro. J Endocrinol 151:501

Choi MJ, Kim JH, Chang KJ (2006) The effect of dietary taurine supplementation on plasma and liver lipid concentrations and free amino acid concentrations in rats fed a high-cholesterol diet. Adv Exp Med Biol 583:235

Dabelea D (2007) The predisposition to obesity and diabetes in offspring of diabetic mothers. Diabetes Care 30(Suppl 2):S169

de Campos KE, Sinzato YK, Pimenta Wde P, Rudge MV, Damasceno DC (2007) Effect of maternal obesity on diabetes development in adult rat offspring. Life Sci 81:1473

Dolnikoff M, Martin-Hidalgo A, Machado UF, Lima FB, Herrera E (2001) Decreased lipolysis and enhanced glycerol and glucose utilization by adipose tissue prior to development of obesity in monosodium glutamate (MSG) treated-rats. Int J Obes Relat Metab Disord 25:426

Fan L, Lindsley SR, Comstock SM, Takahashi DL, Evans AE, He GW, Thornburg KL, Grove KL (2013) Maternal high-fat diet impacts endothelial function in nonhuman primate offspring. Int J Obes (Lond) 37:254

Fukuda N, Yoshitama A, Sugita S, Fujita M, Murakami S (2011) Dietary taurine reduces hepatic secretion of cholesteryl ester and enhances fatty acid oxidation in rats fed a high-cholesterol diet. J Nutr Sci Vitaminol (Tokyo) 57:144

Fullston T, Ohlsson Teague EM, Palmer NO, DeBlasio MJ, Mitchell M, Corbett M, Print CG, Owens JA, Lane M (2013) Paternal obesity initiates metabolic disturbances in two generations of mice with incomplete penetrance to the F2 generation and alters the transcriptional profile of testis and sperm microRNA content. FASEB J 27:4226

Gaillard R, Steegers EA, Duijts L, Felix JF, Hofman A, Franco OH, Jaddoe VW (2014) Childhood cardiometabolic outcomes of maternal obesity during pregnancy: the Generation R Study. Hypertension 63:683

Ghanayem BI, Bai R, Kissling GE, Travlos G, Hoffler U (2010) Diet-induced obesity in male mice is associated with reduced fertility and potentiation of acrylamide-induced reproductive toxicity. Biol Reprod 82:96

Hirata AE, Andrade IS, Vaskevicius P, Dolnikoff MS (1997) Monosodium glutamate (MSG)-obese rats develop glucose intolerance and insulin resistance to peripheral glucose uptake. Braz J Med Biol Res 30:671

Horie R, Yamori Y, Nara Y, Sawamura M, Mano M (1987) Effects of sulphur amino acids on the development of hypertension and atherosclerosis in stroke-prone spontaneously hypertensive rats. J Hypertens Suppl 5:S223

Hultman K, Alexanderson C, Manneras L, Sandberg M, Holmang A, Jansson T (2007) Maternal taurine supplementation in the late pregnant rat stimulates postnatal growth and induces obesity and insulin resistance in adult offspring. J Physiol 579:823

Kalbe L, Leunda A, Sparre T, Meulemans C, Ahn MT, Orntoft T, Kruhoffer M, Reusens B, Nerup J, Remacle C (2005) Nutritional regulation of proteases involved in fetal rat insulin secretion and islet cell proliferation. Br J Nutr 93:309

Kim YW, Choi DW, Park YH, Huh JY, Won KC, Choi KH, Park SY, Kim JY, Lee SK (2005) Leptin-like effects of MTII are augmented in MSG-obese rats. Regul Pept 127:63

Lerdweeraphon W, Wyss JM, Boonmars T, Roysommuti S (2013) Perinatal taurine exposure affects adult oxidative stress. Am J Physiol Regul Integr Comp Physiol 305:R95

Li M, Reynolds CM, Sloboda DM, Gray C, Vickers MH (2013) Effects of taurine supplementation on hepatic markers of inflammation and lipid metabolism in mothers and offspring in the setting of maternal obesity. PLoS One 8:e76961

Lobato NS, Filgueira FP, Akamine EH, Davel AP, Rossoni LV, Tostes RC, Carvalho MH, Fortes ZB (2011) Obesity induced by neonatal treatment with monosodium glutamate impairs microvascular reactivity in adult rats: role of NO and prostanoids. Nutr Metab Cardiovasc Dis 21:808

Marco LJ, McCloskey K, Vuillermin PJ, Burgner D, Said J, Ponsonby AL (2012) Cardiovascular disease risk in the offspring of diabetic women: the impact of the intrauterine environment. Exp Diabetes Res 2012:565160

Meigs JB (2010) Epidemiology of type 2 diabetes and cardiovascular disease: translation from population to prevention: the Kelly West award lecture 2009. Diabetes Care 33:1865

Murakami S (2014) Taurine and atherosclerosis. Amino Acids 46:73

Nakaya Y, Minami A, Harada N, Sakamoto S, Niwa Y, Ohnaka M (2000) Taurine improves insulin sensitivity in the Otsuka Long-Evans Tokushima Fatty rat, a model of spontaneous type 2 diabetes. Am J Clin Nutr 71:54

Nandhini AT, Thirunavukkarasu V, Anuradha CV (2005) Taurine modifies insulin signaling enzymes in the fructose-fed insulin resistant rats. Diabetes Metab 31:337

Nardelli TR, Ribeiro RA, Balbo SL, Vanzela EC, Carneiro EM, Boschero AC, Bonfleur ML (2011) Taurine prevents fat deposition and ameliorates plasma lipid profile in monosodium glutamate-obese rats. Amino Acids 41:901

Ng SF, Lin RC, Laybutt DR, Barres R, Owens JA, Morris MJ (2010) Chronic high-fat diet in fathers programs beta-cell dysfunction in female rat offspring. Nature 467:963

Niu LG, Zhang MS, Liu Y, Xue WX, Liu DB, Zhang J, Liang YQ (2008) Vasorelaxant effect of taurine is diminished by tetraethylammonium in rat isolated arteries. Eur J Pharmacol 580:169

Olney JW (1969) Brain lesions, obesity, and other disturbances in mice treated with monosodium glutamate. Science 164:719

Pina-Zentella G, de la Rosa-Cuevas G, Vazquez-Meza H, Pina E, de Pina MZ (2012) Taurine in adipocytes prevents insulin-mediated H_2O_2 generation and activates Pka and lipolysis. Amino Acids 42:1927

Raimundo JM, Sudo RT, Pontes LB, Antunes F, Trachez MM, Zapata-Sudo G (2006) In vitro and in vivo vasodilator activity of racemic tramadol and its enantiomers in Wistar rats. Eur J Pharmacol 530:117

Reynolds RM, Allan KM, Raja EA, Bhattacharya S, McNeill G, Hannaford PC, Sarwar N, Lee AJ, Bhattacharya S, Norman JE (2013) Maternal obesity during pregnancy and premature mortality from cardiovascular event in adult offspring: follow-up of 1 323 275 person years. BMJ 347:f4539

Ribeiro RA, Bonfleur ML, Amaral AG, Vanzela EC, Rocco SA, Boschero AC, Carneiro EM (2009) Taurine supplementation enhances nutrient-induced insulin secretion in pancreatic mice islets. Diabetes Metab Res Rev 25:370

Ribeiro RA, Vanzela EC, Oliveira CA, Bonfleur ML, Boschero AC, Carneiro EM (2010) Taurine supplementation: involvement of cholinergic/phospholipase C and protein kinase A pathways in potentiation of insulin secretion and Ca2+ handling in mouse pancreatic islets. Br J Nutr 104:1148

Ribeiro RA, Santos-Silva JC, Vettorazzi JF, Cotrim BB, Mobiolli DD, Boschero AC, Carneiro EM (2012) Taurine supplementation prevents morpho-physiological alterations in high-fat diet mice pancreatic beta-cells. Amino Acids 43:1791

Ribeiro RA, Balbo SL, Roma LP, Camargo RL, Barella LF, Vanzela EC, de Freitas Mathias PC, Carneiro EM, Boschero AC, Bonfleur ML (2013) Impaired muscarinic type 3 (M3) receptor/PKC and PKA pathways in islets from MSG-obese rats. Mol Biol Rep 40:4521

Ribeiro RA, Bonfleur ML, Vanzela EC, Zotti AI, Scomparin DX, Boschero AC, Balbo SL (2014) Physical exercise introduced after weaning enhances pancreatic islet responsiveness to glucose and potentiating agents in adult MSG-obese rats. Horm Metab Res 46(9):609–614

Ristori MT, Verdetti J (1991) Effects of taurine on rat aorta in vitro. Fundam Clin Pharmacol 5:245

Scomparin DX, Gomes RM, Grassiolli S, Rinaldi W, Martins AG, de Oliveira JC, Gravena C, de Freitas Mathias PC (2009) Autonomic activity and glycemic homeostasis are maintained by precocious and low intensity training exercises in MSG-programmed obese mice. Endocrine 36:510

Sominsky L, Spencer SJ (2014) Eating behavior and stress: a pathway to obesity. Front Psychol 5:434

Soubry A, Murphy SK, Wang F, Huang Z, Vidal AC, Fuemmeler BF, Kurtzberg J, Murtha A, Jirtle RL, Schildkraut JM, Hoyo C (2013). Newborns of obese parents have altered DNA methylation patterns at imprinted genes. Int J Obes (Lond). doi: 10.1038/ijo.2013.193

Torrens C, Ethirajan P, Bruce KD, Cagampang FR, Siow RC, Hanson MA, Byrne CD, Mann GE, Clough GF (2012) Interaction between maternal and offspring diet to impair vascular function and oxidative balance in high fat fed male mice. PLoS One 7:e50671

Tsuboyama-Kasaoka N, Shozawa C, Sano K, Kamei Y, Kasaoka S, Hosokawa Y, Ezaki O (2006) Taurine (2-aminoethanesulfonic acid) deficiency creates a vicious circle promoting obesity. Endocrinology 147:3276

Turdi S, Ge W, Hu N, Bradley KM, Wang X, Ren J (2013) Interaction between maternal and post-natal high fat diet leads to a greater risk of myocardial dysfunction in offspring via enhanced lipotoxicity, IRS-1 serine phosphorylation and mitochondrial defects. J Mol Cell Cardiol 55:117

Xiao C, Giacca A, Lewis GF (2008) Oral taurine but not N-acetylcysteine ameliorates NEFA-induced impairment in insulin sensitivity and beta cell function in obese and overweight, non-diabetic men. Diabetologia 51:139

Xu YJ, Arneja AS, Tappia PS, Dhalla NS (2008) The potential health benefits of taurine in cardio-vascular disease. Exp Clin Cardiol 13:57

Yang J, Wu G, Feng Y, Lv Q, Lin S, Hu J (2010) Effects of taurine on male reproduction in rats of different ages. J Biomed Sci 17(Suppl 1):S9

Zhang M, Bi LF, Fang JH, Su XL, Da GL, Kuwamori T, Kagamimori S (2004) Beneficial effects of taurine on serum lipids in overweight or obese non-diabetic subjects. Amino Acids 26:267