



Effects of taurine supplementation and swimming, associated or not, on obesity and glucose homeostasis in mice

Iris Cheng¹, Maria Lúcia Bonfleur^{1*}, Leonardo Eduardo Ferreira¹, Rosane Aparecida Ribeiro² and Sandra Lucinei Balbo¹

¹Centro de Ciências Biológicas e da Saúde, Universidade Estadual do Oeste do Paraná, Rua Universitária, 1619, 85819-110, Campus Cascavel, Cascavel, Paraná, Brazil. ²Laboratório Integrado de Bioquímica Hatisaburo Masuda, Núcleo em Ecologia e Desenvolvimento Sócio-Ambiental, Universidade Federal do Rio de Janeiro, Campus Macaé, Macaé, Rio de Janeiro, Brazil. *Author for correspondence. E-mail: mlbonfleur@hotmail.com

ABSTRACT. Studies show that physical exercise (PE) is associated with a reduced fat accumulation and increased insulin sensitivity, and taurine (TAU) improves glucose homeostasis in lean rodents. The aim in this work was evaluate the effects of supplementing TAU and practice of PE, associated or not, on obesity and glucose homeostasis on obese MSG-mice. Neonate male *Swiss* mice received injections of monosodium glutamate (MSG group) or saline (CON group). From the 30th to the 90th day of life, one group of animals received TAU in drinking water (MSG TAU group), another was subjected to PE (MSG PE group) and a third group underwent both procedures (MSG PE TAU group). Mice treated with MSG become obese, hypertriglyceridemic, glucose intolerant and insulin resistant. The supplementation with TAU and the PE, isolated or associated, reduced the triglycerides (38%), glucose intolerance (around 30%) and KITT (79%) in MSG-obese animals, but did not influence the accumulation of fat. Interestingly, the combination of both strategies significantly reduced the insulin resistance, compared to animals subjected to isolated strategies. In conclusion, the supplementation with TAU and PE, isolated or associated, did not influence the accumulation of fat in MSG-obese mice, however, reduce the triglycerides and insulin resistance.

Keywords: glycaemia, insulin resistance, physical exercise, amino acid taurine.

Efeito da suplementação com taurina e da natação, associadas ou não, sobre a obesidade e homeostase glicêmica em camundongos

RESUMO. O exercício físico (EF) está associado à redução do acúmulo de gordura e aumento na sensibilidade à insulina e a taurina (TAU) melhora a homeostase glicêmica em roedores magros. Objetivou-se avaliar os efeitos da suplementação com TAU e do EF, associados ou não, sobre a obesidade e a homeostase glicêmica em camundongos obesos-MSG. Camundongos *Swiss* machos neonatos receberam injeções de glutamato monossódico (grupo MSG) ou salina (grupo CON). Do 30º ao 90º dia de vida, um grupo de animais MSG recebeu TAU na água de beber (MSG TAU); outro foi submetido ao EF (MSG EX) e um terceiro grupo foi submetido aos dois procedimentos (MSG EX TAU). Camundongos -MSG tornaram-se obesos, hipertrigliceridêmicos, intolerantes à glicose e resistentes à insulina. A suplementação com TAU e o EF, associados ou isolados, reduziram a trigliceridemia (38%), a intolerância à glicose (30%) e o K_{ITT} (79%) nos animais obesos-MSG, porém, não influenciaram o acúmulo de gordura. A associação das duas estratégias diminuiu significativamente a resistência à insulina, comparado aos animais submetidos às estratégias isoladas. Conclui-se que a suplementação com TAU e o EF, associados ou isolados, não influenciam no acúmulo de gordura dos camundongos obesos-MSG, porém, diminuem a trigliceridemia e a resistência à insulina.

Palavras-chave: glicemia, resistência à insulina, exercício físico, aminoácido taurina.

Introduction

Obesity is a worldwide epidemic (JAMES et al., 2001; HASLAM; JAMES, 2005) associated with increased morbidity and mortality, which are results of several chronic diseases like type 2 diabetes mellitus, hypertension, cardiovascular disease, dyslipidemia and several types of cancer (BOWMAN et al., 2007; FRANCO et al., 2007). This syndrome results from a chronic energy imbalance, whereby the energy intake

exceed expenditure, and the excess is stored as fat in adipose tissue (FONSECA-ALANIZ et al., 2007). Environmental factors, physical inactivity, improper eating habits, heredity, neuroendocrine and metabolic changes contribute to the establishment and development of obesity (BARSH et al., 2000; MARTINEZ, 2000; BOUCHARD, 2001; FLEGAL et al., 2002; PI-SUNYER, 2002).

Several experimental models of animal obesity are studied to try to reverse or prevent undesirable

effects that accompany this syndrome. Among them are the obese animals induced by neonatal treatment with monosodium glutamate (MSG). This substance injures the arcuate nucleus and median eminence, causing metabolic and neuroendocrine changes that lead to obesity. The animals are characterized by presenting normal or hypophagia, reduced body growth, massive accumulation of fat and hyperinsulinemia, gradually developing to insulin resistance (DOLNIKOFF et al., 2001; GOBATTO et al., 2002; BALBO et al., 2007).

Different methods are used in an attempt for prevention and prophylaxis of obesity, as for example, the use of drugs, energy-restricted diet, regular physical exercise (PE), diet rich in taurine (TAU), among others. The PE is associated to a reduction in weight gain and fat accumulation in rats fed high-fat diet, MSG-obese mice (SCOMPARIN et al., 2006), genetically obese Zucker rats (HSIEH et al., 2008). Physical training also seem to have important effect on insulin sensitivity in obese individuals (BRUCE; HAWLEY, 2004). A TAU-rich diet has been investigated with the purpose to improve the quality of life of obese individuals. The TAU (2-aminoethanesulfonic acid) is an amino acid common in human diet, present at high concentrations in cells and plasma of mammals. It is also involved in several important physiological functions like the maintenance of structural integrity of the membrane, calcium regulation, modulation of phosphorylation of proteins, osmoregulation and neurotransmission (HUXTABLE, 1992). Studies have shown that a TAU-rich diet improves blood pressure, liver alterations, and decreases the plasma concentration of cholesterol (NANDHINI et al., 2005). The plasma concentration of TAU also appears to be important in the functioning of pancreatic β -cells and in the action of insulin, since there is low plasma concentration of TAU in pre-diabetic and diabetic conditions (TSUBOYAMA-KASAOKA et al., 2006). Other studies have reported that TAU improves glucose homeostasis and insulin sensitivity in lean rodents (LOIZZO et al., 2007; CARNEIRO et al., 2009; RIBEIRO et al., 2009). The TAU supplementation seems to have important role on preventing fat accumulation in genetically obese mice or induced by a fat-rich diet (TSUBOYAMA-KASAOKA et al., 2006). Nevertheless, studies on the effects of TAU on MSG-obese animals have not yet been performed. In this way, this study evaluated the effects of TAU supplementation and practice of PE, associated or not, on obesity and glucose homeostasis of MSG-obese mice.

Material and methods

Animals and induced obesity

Pregnant female *Swiss* mice were obtained from the Central Animal House of the State University of West Paraná and kept in the sectorial animal house of the Laboratory of Physiology under controlled conditions of light (12h; 12 min. L/D cycle) and temperature ($23 \pm 2^\circ\text{C}$) and received food and water *ad libitum*. All experimental procedures were approved the Ethics Committee on Animal Experimentation and Practical Classes (CEEAAP) of the State University of West Paraná, according to protocol n. 23/09. To induce obesity, the neonate male *Swiss* mice received in the cervical region subcutaneous injections of MSG (4 g kg^{-1} body weight day^{-1}) or hyperosmotic saline (1.25 g kg^{-1} body weight day^{-1}) during the first five days of life, composing the MSG group and control (CTL), respectively.

Supplementation with TAU and physical training

The supplementation with TAU and the PE began at 30 days of life of the animals. From these procedures, the animals were distributed into five experimental groups: 1) sedentary control (CTL); sedentary MSG; 3) MSG TAU sedentary (MSG TAU); 4) MSG exercised (MSG PE); and 5) MSG exercised TAU (MSG PE TAU). The TAU was given in drinking water, at doses of 5%, throughout experimental period (up to 90 days of life). The PE was performed for 15 continuous min per day, three days a week, with an overload of 2.5% of body weight attached to the tail (SCOMPARIN et al., 2006). A maximum of eight animals at a time swam in an aquarium ($39 \times 38 \times 28 \text{ cm}$), with controlled water temperature at $31 \pm 2^\circ\text{C}$. The animals swam up to 90 days of life. For this study, it was used from six to 11 animals per group.

Food and water intake, weight gain and Lee index

Food intake was obtained weekly, and water consumption was evaluated three times a week. These parameters were calculated through ration or liquid that was given, subtracted the leftovers, divided by the number of mice in the box. The animals were weighed individually once a week to obtain body weight. The weight gain was calculated by subtracting the weight of each week from the initial weight. When sacrificed (90 days of life), the fat accumulation was evaluated by the Lee index [cube root of body weight (g) / nose-anal length (cm) $\times 1000$] and by the weight of retroperitoneal fat.

Glucose tolerance test (GTT) insulin tolerance test (ITT)

At 85 days of life and after 12 h of fasting, the animals were subjected to GTT. Initially, the animals were weighted and a blood drop was taken from the tail to obtain fasting glucose (time 0), using a glucometer. Then, glucose was administered orally (2 g glucose kg⁻¹ body weight) and glycemia was observed in times 15, 30, 60, 120 and 180 min for GTT. In turn, for ITT (two days after GTT), the animals fasted for 8h and received an intraperitoneal injection of insulin at a dose of 1.5 U kg⁻¹. Blood samples were collected before injection and in times 9, 12, 15 and 18 min after administration of insulin. The glucose decay rate (K_{ITT}) was estimated by using the equation $0.693/t_{1/2}$.

Biochemical analyses

At sacrifice, total blood was collected, centrifuged and the plasma was removed for evaluation of total cholesterol (COL) and triglycerides (TG), which were determined by means of commercial kits, following manufacturers' instructions (Boehringer Mannheim®, Germany; Merck®, Germany, respectively).

Statistical analysis

The results were expressed as mean value \pm standard error. To evaluate the effects of MSG obesity, it was used the Student's *t*-test. For statistical comparison of the effects of TAU supplementation and PE, associated or not, an Analysis of Variance (ANOVA) was applied. When *F* was significant, the differences in the mean values were evaluated with a *p* value corrected by Newman-Keuls. The significance level adopted was *p* < 0.05.

Results and discussion

The Lee index and the weight of retroperitoneal fat were 15% and 49%, respectively; with higher values in MSG treated mice in relation to CTL animals, but the NAL was smaller (Table 1). Also, the supplementation with TAU and the PE, associated or not, had no influence on Lee index and weight of retroperitoneal fat of the MSG obese animals.

Table 1. Effect of neonatal MSG treatment, of supplementation of TAU and PE on the Lee index, naso-anal length (NAL) and weight of retroperitoneal fat in male Swiss mice.

	CTL	MSG	MSG TAU	MSG PE	MSG PE TAU
Lee Index (g ^{1/3} /cm.1000)	343 \pm 4	393 \pm 7*	377 \pm 4	387 \pm 9	378 \pm 5
NAL (cm)	11 \pm 0.2*	9.5 \pm 0.2*	9.7 \pm 0.2*	8.7 \pm 0.1 ^{abd}	9.6 \pm 0.1 ^c
Retroperitoneal fat (% body weight)	0.61 \pm 0.05	0.91 \pm 0.07*	0.82 \pm 0.08	0.75 \pm 0.04	0.92 \pm 0.09

Values are expressed as mean \pm standard error. **p* < 0.05 CTL \times MSG. Letters refer to the statistical differences (*p* < 0.05) between groups: a) MSG; b) MSG TAU; c) MSG PE; d) MSG PE TAU. N = 6-11.

The plasma concentration of glucose and total COL was similar between CTL and MSG-obese mice (Figure 1A and C). These parameters were not changed in MSG obese animals, supplemented with TAU or subjected to PE, associated or not (Figure 1B and D). The concentration of TG was 74% higher in MSG group compared to CTL (Figure 1E), and interestingly, the supplementation with TAU and the PE, alone or associated, promoted a reduction of about 38% in triglyceridemia of MSG-obese animals (Figure 1F).

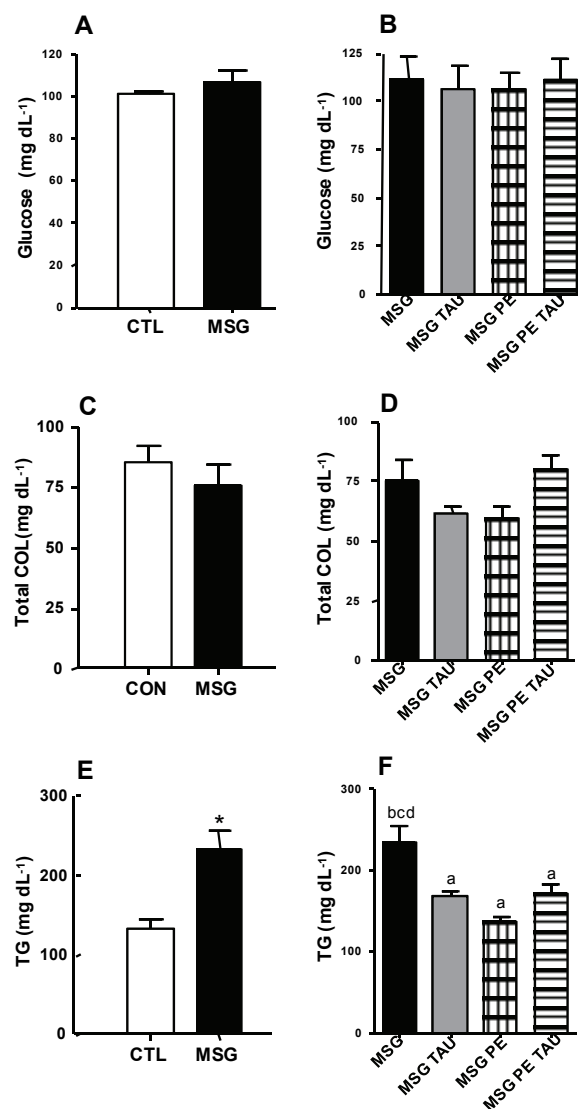


Figure 1. Effect of neonatal MSG treatment on plasma concentration of glucose (A); COL (C) and TG (E). **p* < 0.05. Effect of TAU and PE, isolated or associated, on glycemia (B); total cholesterol (D) and triglycerides (F) in MSG-obese mice. Letters refer to the statistical differences (*p* < 0.05) between the groups: a) MSG; b) MSG TAU; c) MSG PE; d) MSG PE TAU. N = 6-11.

The Figure 2A shows that the area under the glucose curve during the GTT was 56% higher in

MSG-obese mice in relation to CTL. However, the glucose curve of animals subjected to PE alone or associated with TAU supplementation was significantly lower in relation to MSG sedentary animals not supplemented (Figure 2B).

The K_{ITT} of MSG-obese animals was 52% lower in relation to control animals (Figure 2C). Nevertheless, the K_{ITT} of MSG-animals submitted to PE and supplementation with TAU, singly, was around 79% higher in relation to MSG, and the association between TAU and PE increased 2.4 times the K_{ITT} of MSG-obese animals (Figure 2D).

The present study corroborates literature data, which shows that the neonatal MSG treatment leads to obesity in *Swiss* mice, as shown by the increase of Lee index and weight of retroperitoneal fat; in addition to the reduction of NAL of the animals (BALBO et al., 2000; SCOMPARIN et al., 2006; ANDREAZZI et al., 2009). The neonatal MSG treatment causes destruction of the hypothalamic arcuate nucleus, responsible for regulating the release of growth hormone, reducing its secretion that leads to reduced lipolysis and growth of the animal (MAITER et al., 1991). Fasting hyperinsulinemia is a common feature of obesity, both in humans and animals (BRAY; YORK, 1998; BALBO et al., 2007). Macho et al. (2000) report that the lipogenesis is increased in adipocytes of MSG animals. It is well known that the insulin is lipogenic and Balbo et al. (2007) demonstrated the importance of hyperinsulinemia for the fat accumulation in MSG mice. Despite the insulin resistance in MSG-animals, Prada et al. (2005) argue that the resistance is tissue-specific to muscle, liver and hypothalamus, while the adipose tissue remains sensitive to insulin.

Numerous strategies are used to find treatments against obesity or techniques to prevent it. The swimming had started at 21 days of life, and reduced the fat accumulation in MSG-obese animals (SCOMPARIN et al., 2006). TAU supplementation prevents the fat accumulation in rodents genetically obese or submitted to fat-rich diet (TSUBOYAMA-KASAOKA et al., 2006). However, under the proposed protocol in the present study, the PE and TAU diet, associated or isolated, have no influence on Lee index and weight of retroperitoneal fat of MSG-obese mice.

In unpublished results, the food and water intake was similar among all evaluated groups. According to literature, MSG-obese animals are normophagic (BALBO et al., 2000). Studies also demonstrate that the food intake of MSG-obese rats, subjected to swimming and sedentary, is similar (GOBATTO et al., 2002).

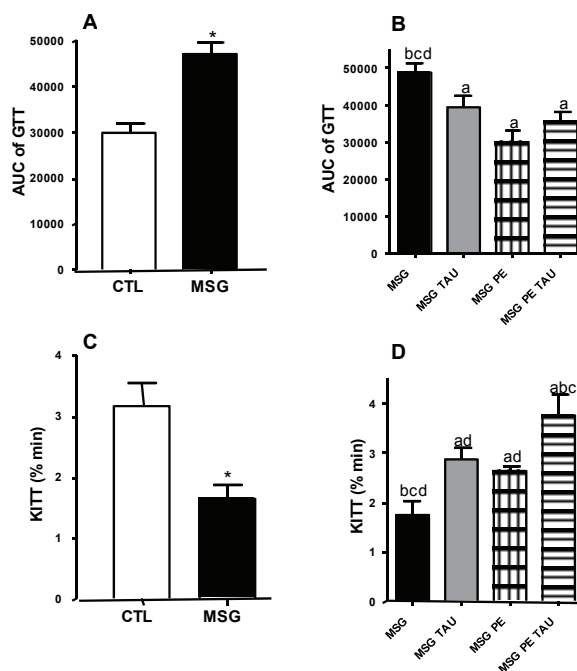


Figure 2. Effect of neonatal MSG treatment on the area under the glucose curve during the GTT (A) and on the K_{ITT} (C) * $p < 0.05$; and effect of supplementation with TAU and PE, associated or not, on the area under the glucose curve during the GTT (B) and on the K_{ITT} (D) in MSG-obese mice. Bars represent the mean \pm standard error. Letters refer to the statistical differences ($p < 0.05$) between the groups: a) MSG; b) MSG TAU; c) MSG PE; d) MSG PE TAU. N = 6-8.

The supplementation with TAU does not influence water and food intake in lean *Swiss* mice (RIBEIRO et al., 2009).

TAU did not alter weight gain of MSG-mice. However, the swimming reduced significantly this parameter, compared to MSG-sedentary animals (results not shown). The effect of swimming on the reduction of body weight of MSG-obese rats was observed by several authors (MELLO et al., 2001; GOBATTO et al., 2002; SOUZA et al., 2003). The same was observed in *db/db* obese mice (OH et al., 2006). In relation to the effects of TAU on body weight, the literature is still very contradictory. *OETF* (Otsuka Long-Evans Tokushima Fatty) rats, spontaneously type 2 diabetic and supplemented with TAU with a dose of 5% have had no significant reduction in body weight (NAKAYA et al., 2000). A similar result was found in rats fed high-fat diet and supplemented with several TAU concentrations (YOKOGOSHI et al., 1999). However, the supplementation with TAU, at dose of 5% and 3 g day⁻¹, promoted a reduction in body weight in genetically obese *KK* mice (FUJIHARA et al., 1970) and obese humans (ZHANG et al., 2004), respectively.

According to our results, the plasma concentration of glucose and total COL was similar between control and MSG-obese mice.

These parameters was not altered in MSG-obese mice, supplemented with TAU or subjected to PE, associated or not. However, the TG level was higher in MSG group, compared to CTL, and the supplementation with TAU and the PE, isolated or associated, have promoted a reduction in triglyceridemia. Gobatto et al. (2002) stated that glucose and cholesterol of MSG-obese rats, subjected to swimming, were equal to those of MSG-sedentary animals, but the practice of physical exercise reduced the concentration of TG. *OLETF* rats are hypertriglyceridemic in relation to non-diabetic animals (type 2 diabetes), and the supplementation with TAU significantly reduced the TG level (NAKAYA et al., 2000). This effect of TAU was also observed in obese individuals (ZHANG et al., 2004).

The neonatal MSG treatment had no effect on fasting glucose, but the normoglycemia is kept as a function of the hyperinsulinemia observed in these animals, which gradually develops to insulin resistance (NAGATA et al., 2006; BALBO et al., 2007). In the present study, the area under glucose curve during the GTT was higher in MSG-obese mice, in comparison to CTL group, suggesting glucose intolerance in these animals. The K_{ITT} of MSG-obese animals was lower than lean animals, indicating insulin resistance in this obesity model, corroborating the literature (MACHO et al., 2000; BALBO et al., 2007; ANDREAZZI et al., 2009). Aerobic activity can improve glucose tolerance and reduce insulin resistance in MSG-obese rats (MELLO et al., 2001). In the present study, the glycemia during the GTT of animals supplemented with TAU and subjected to PE, isolated or associated, was significantly lower in relation to the MSG sedentary animals not supplemented pointing out that the proposed strategy improves glucose tolerance. Recent studies have evidenced that supplementation with TAU improves glucose tolerance and insulin sensitivity in lean mice (LOIZZO et al., 2007; CARNEIRO et al., 2009; RIBEIRO et al., 2009).

It was observed that the supplementation with TAU increased the K_{ITT} of MSG-obese animals in relation to those not supplemented, unusually evidencing that this treatment is effective to decrease insulin resistance in obesity induced by neonatal MSG treatment. The same was observed in animals subjected to PE. Nonetheless, the association between TAU and PE led to a significantly greater reduction, compared to both strategies isolated, in the insulin resistance of these animals.

Conclusion

The world is waiting for a strategy or treatment able to control the growing epidemic of obesity besides the undesirable effects that accompany this syndrome. With regard to the multifactorial etiology of this disease, the study on several models of experimental obesity is of paramount importance. The present study allowed concluding that the supplementation with TAU and the practice of PE, associated or isolated, have no influence on the accumulation of fat in MSG-obese animals. But both TAU supplementation and aerobic PE, in the form of swimming, associated or not, are efficient to reduce plasma concentration of triglycerides and insulin resistance in MSG-obese Swiss mice, and the association of TAU with PE significantly decreased the insulin resistance, compared with both strategies singly.

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