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ORIGINAL ARTICLE

# Antidepressant effect of taurine in diabetic rats

**Greice Caletti · Danielly B. Olguins · Elis F. Pedrollo · Helena M. T. Barros · Rosane Gomez**

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**Abstract** Clinical and preclinical studies have shown that diabetic individuals present more depressive behaviors than non-diabetic individuals. Taurine, one of the most abundant free amino acids in the central nervous system, modulates a variety of biological functions and acts as an agonist at $GABA_A$ receptors. Our objective was to assess the antidepressant effect of taurine in diabetic rats. Additionally, we studied the effect of taurine on weight gain, water and food intake, and blood glucose levels in diabetic and non-diabetic rats. Male Wistar rats were divided into control (CTR) and streptozotocin-induced diabetic (STZ) groups and were administered daily 0, 25, 50 or 100 mg/kg of taurine ($n = 10$ per subgroup) intraperitoneally. After 28 days of treatment, the animals were exposed to the forced swimming test, and their behaviors were recorded. Weight gain, water and food intake, and blood glucose levels were measured weekly. Our results showed that STZ rats had a higher immobility duration than CTR rats, and taurine decreased this depressive-like behavior in STZ rats at doses of 25 and 100 mg/kg. Both of these doses of taurine also decreased water intake and improved weight gain in STZ rats. All doses of taurine decreased the water intake in CTR rats. Taurine, at a dose of 100 mg/kg, decreased food intake and blood glucose levels in STZ rats. Because taurine is a GABA agonist and both amino acids are lower in the plasma of diabetic and depressive individuals, we hypothesize that taurine may represent a new adjuvant drug for the treatment of depression in diabetic individuals.

**Keywords** Water intake · Food intake · GABA agonist · Depression · Glycemia

G. Caletti · D. B. Olguins · H. M. T. Barros · R. Gomez
Programa de Pós Graduação em Ciências da Saúde, Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre, Brazil

E. F. Pedrollo · H. M. T. Barros
Departamento de Ciências da Saúde, Disciplina de Farmacologia, Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre, Brazil

R. Gomez (✉)
Departamento de Farmacologia, Instituto de Ciências Básicas da Saúde, Universidade Federal do Rio Grande do Sul (UFRGS), Rua Sarmento Leite, 500/202, Porto Alegre, RS 90050-170, Brazil
e-mail: rosane.gomez@ufrgs.br

## Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by (1) autoimmune destruction of $\beta$-cells in the pancreas and lack of insulin (type 1 DM) or (2) insulin resistance from insulin insufficiency (type 2 DM) (Daneman 2006; Bonner-Weir 2000; Del Prato and Marchetti 2004). For both type 1 and type 2 DM, the goal of treatment is to maintain the blood glucose levels as close to normal as possible to delay long-term macrovascular, microvascular, and neurological complications, which are major causes of morbidity and mortality in these patients (Wolffenbuttel and van Haeften 1995).

The psychosocial impact associated with the hardship imposed by the diabetes diagnosis and/or the effect of chronic hyperglycemia in the central nervous system may contribute to depression in people with diabetes (Gavard et al. 1993; Lustman and Clouse 2005). In fact, diabetic patients have a nearly 30% higher risk for depression than the general population, and depression is associated with worse diabetes outcomes (Lustman et al. 2000;

Champaneri et al. 2010). Preclinical studies have also shown that diabetic rats and mice have more depressive-like behaviors than non-diabetic individuals in the forced swimming test (FST), an animal model of depression (Anjaneyulu et al. 2003; Gomez and Barros 2000).

Although the therapeutic effects of classical antidepressants have been explained on the basis of their action on serotonergic or noradrenergic neurotransmission, the idea that other neurotransmitter systems are also involved in this effect has gained support, mainly because these "old" drugs improve mood in a little more than half of depressed patients after a few weeks of chronic use (Sen and Sanacora 2008). Clinical and preclinical data suggest that the gamma-aminobutyric acid (GABA) neurotransmitter plays a role in the pathophysiology of depression and in the mechanisms of action of antidepressants (Luscher et al. 2011; Brambilla et al. 2003; Sanacora and Saricicek 2007; Gomez and Barros 2000; Gomez et al. 2003). In fact, GABA agonists have been prescribed as an adjuvant for the treatment of depression in humans (Morishita 2009; Smith et al. 2002, 2010), and they have been demonstrated to reverse depressive-like behaviors shown by diabetic rats in the FST (Gomez and Barros 2000).

Taurine, a 2-aminoethanesulfonic acid, is one of the most abundant free amino acids in the central nervous system and in peripheral tissues (Albrecht and Schousboe 2005; Jia et al. 2008; Wu and Prentice 2010). The physiological and therapeutic properties of this amino acid have been explored and have revealed that taurine modulates a variety of biological functions, including osmoregulation (Bustamante et al. 2001), antioxidant (Birdsall 1998; Oja and Saransaari 2007), anti-obesity (Tsuboyama-Kasaoka et al. 2006; Zhang et al. 2004) and hypoglycemic processes (Ribeiro et al. 2009; Cherif et al. 1998). Moreover, taurine is unevenly distributed in the central nervous system and acts as an agonist at inhibitory $GABA_A$ and glycine receptors, fulfilling almost all of the criteria necessary to be accepted as a neurotransmitter (Wu and Prentice 2010; Albrecht and Schousboe 2005; Jia et al. 2008). More recent studies have also shown that taurine supplementation modulates glucose homeostasis and regulates insulin release from pancreatic beta cells, improving the glycemic profile in insulin-dependent, non-insulin-dependent, and insulin-resistant diabetic individuals (Hansen 2001; Schaffer et al. 2009; Carneiro et al. 2009; L'Amoreaux et al. 2010a). Interestingly, plasma taurine levels are lower in insulin-dependent diabetes mellitus patients (Franconi et al. 1995) and in streptozotocin-induced diabetic animals (Franconi et al. 1996; Trachtman et al. 1995). Coincidently, taurine is greatly diminished in the plasma and the cerebrospinal fluid of depressive patients (Perry et al. 1975).

Because taurine has a neuromodulatory effect on the GABA system and is lower in the plasma of diabetic and depressive individuals, we hypothesize that taurine may represent a new adjuvant drug for the treatment of depression in diabetic individuals. Thus, the main objective of this study was to assess the antidepressant effect of taurine in diabetic rats. As a secondary objective, we studied the effect of taurine on weight gain, food and water intake, and blood glucose levels in diabetic and non-diabetic rats.

## Materials and methods

### Animals

Male Wistar adult rats (250–300 g), born and reared in the animal facility of Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Brazil, were housed in polypropylene cages (40 × 33 × 17 cm), four per cage, under standard environmental conditions, such as a room temperature of 22 ± 2°C and a 12 h light–dark cycle (7:00 a.m.–7:00 p.m.). All rats had free access to food and water. Diabetes was induced in half of the rats ($n = 40$) by a single dose of streptozotocin, 60 mg/kg administered intraperitoneally (i.p.) (Gomez and Barros 2000). Diabetes was confirmed 48 h later by a glucometer (Glucotrend, Boehringer Institute, Mannheim, Germany), and animals that had blood glucose levels lower than 200 mg/dL were discarded. Diabetic rats were then randomly selected to receive daily doses of 25, 50 or 100 mg/kg of taurine or saline ($n = 10$ per group) i.p. for 30 days. Non-diabetic control rats ($n = 40$) received vehicle on the day of diabetes induction and were subsequently allocated to receive saline or the same doses of taurine as the STZ rats, following the same protocol as before. Our experimental protocol was carried out in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals and in accordance with the Brazilian Law for the Scientific Use of Animals after its approval by the Ethical Committee for Animal Experimentation at UFCSPA (558/09). All efforts were made to minimize animal suffering and to use only the number of animals necessary to produce reliable scientific data.

### Drugs

Taurine (Biofarma, São Paulo, Brazil) was dissolved in a saline solution at doses of 25, 50 and 100 mg/kg/mL. These doses of taurine were selected on the basis of a previous study from another group (Chen et al. 2004). Streptozotocin (STZ), 60 mg/kg/mL, was prepared in phosphate buffer, pH 4.5, immediately before its administration.

### Forced swimming test

On the 30th day after diabetes induction and the 28th day after taurine treatment, animals were exposed to the forced swimming test (FST), following a slightly modified Porsolt's protocol (Porsolt et al. 1977; Nin et al. 2008). Briefly, the animals were individually introduced to an inescapable pool (22 × 22 × 35 cm) filled with 27 cm of cool water (25°C). Two swim sessions were conducted: an initial 15-min training section followed 24 h later by a 5-min test section. After each swimming session, the animals were gently towel dried and returned to their cages. Taurine or vehicle solution was administered three times: 24, 5 and 1 h before the test section. Behaviors in the test section were recorded for subsequent ethological analysis by a trained researcher who was blind to the different treatments (BASIC software, Kevin Willioma, KD Ware Computer, Boston, MA). Immobility was defined as the sum of the freezing and floating behaviors. Freezing was considered to be the total cessation of all movements except for breathing, and floating was defined as the movement of the back paws necessary to keep their noses out of the water. Mobility was defined as the sum of the climbing and swimming behaviors. Climbing was scored when the rats performed active up and down movements with both forepaws close to the aquarium walls, vigorously trying to escape. Swimming was measured when the rats made movements at the center of the aquarium in an attempt to escape. Diving and head shaking were also considered to be active mobile behaviors (Nin et al. 2008). The antidepressant effect of the drugs was inferred when they decreased immobility duration behaviors. All behavioral experiments were performed between 1:00 and 3:00 p.m.

### Open field test

To rule out pharmacological effects on general motor activity that might account for the behavioral patterns in the FST, rats were previously exposed to the open field test. On the 25th day after diabetes induction and 55 min after taurine or saline administration, animals were individually placed in a circular white arena (diameter 80 cm) surrounded by a 35-cm high wall, which was divided into 25 concentric squares by black lines painted on the floor. The test was performed in a quiet room for 5 min. The rat was placed in the center of the arena, and the number of squares crossed with all four paws, the number of rearing responses, the number of grooming responses and the number of fecal boli were recorded by a video camera and later analyzed by an observer blind to subject condition (Walsh and Cummins 1976). The floor was hygienized between each rat to remove any trace of odor.

### Food and water intake, body weight and glycemic control

Food and water intake were recorded every other day, and the body weight and blood glucose levels were measure weekly during all of the experiments. The blood glucose levels were measured by a glucometer (Boehringer Mannheim, Germany) by taking a blood drop from a superficial puncture in the distal end of the rat's tail, immediately before taurine administration. On the 21st day, the non-fasting glycemia was measured; a second measure was taken 1 h after taurine administration to evaluate the acute effect of taurine on blood glucose levels. We also measured the blood glucose levels 15 min before the FST.

### Statistical analysis

Statistical analyses were performed using a two-way analysis of variance (2-way ANOVA) for two factors: the different doses of taurine and the diabetes condition. When appropriate, the ANOVA was followed by the Bonferroni post hoc test. The Pearson correlation was applied to investigate correlations between immobility duration and blood glucose levels before the FST. All results were expressed as the mean ± the standard error of the mean (SEM). In all tests, the level of statistical significance was $P < 0.05$.

## Results

### Antidepressant effect of taurine

Our results showed that diabetic rats presented depressive-like behaviors during the FST, and taurine ($P < 0.001$) at doses of 25 and 100 mg/kg reversed these behaviors ($P = 0.001$; Fig. 1). Indeed, these doses of taurine significantly decreased the time spent freezing (Fig. 1a) and increased the time spent climbing (Fig. 1c), without affecting floating (Fig. 1b) or swimming behaviors (Fig. 1d). These results demonstrate the antidepressant effect of this amino acid. Diabetic rats had a lower frequency of head shakes than non-diabetic rats (CTR0: 23.6 ± 3.8 × STZ0: 9.7 ± 3.4 times, $P = 0.018$), and all doses of taurine significantly increased this behavior in diabetic rats (STZ25: 18.5 ± 3.2; STZ50: 18.1 ± 4.0; STZ100: 13.9 ± 3.1 head shakes, $P = 0.021$). Rats did not dive during the FST. Additionally, we could discard a possible false-positive antidepressant effect of taurine on the FST because, as observed by others (El Idrissi et al. 2009; Murakami and Furuse 2010), diabetic and non-diabetic rats did not change their general motor activity in the open field test after chronic taurine treatment (Table 1).

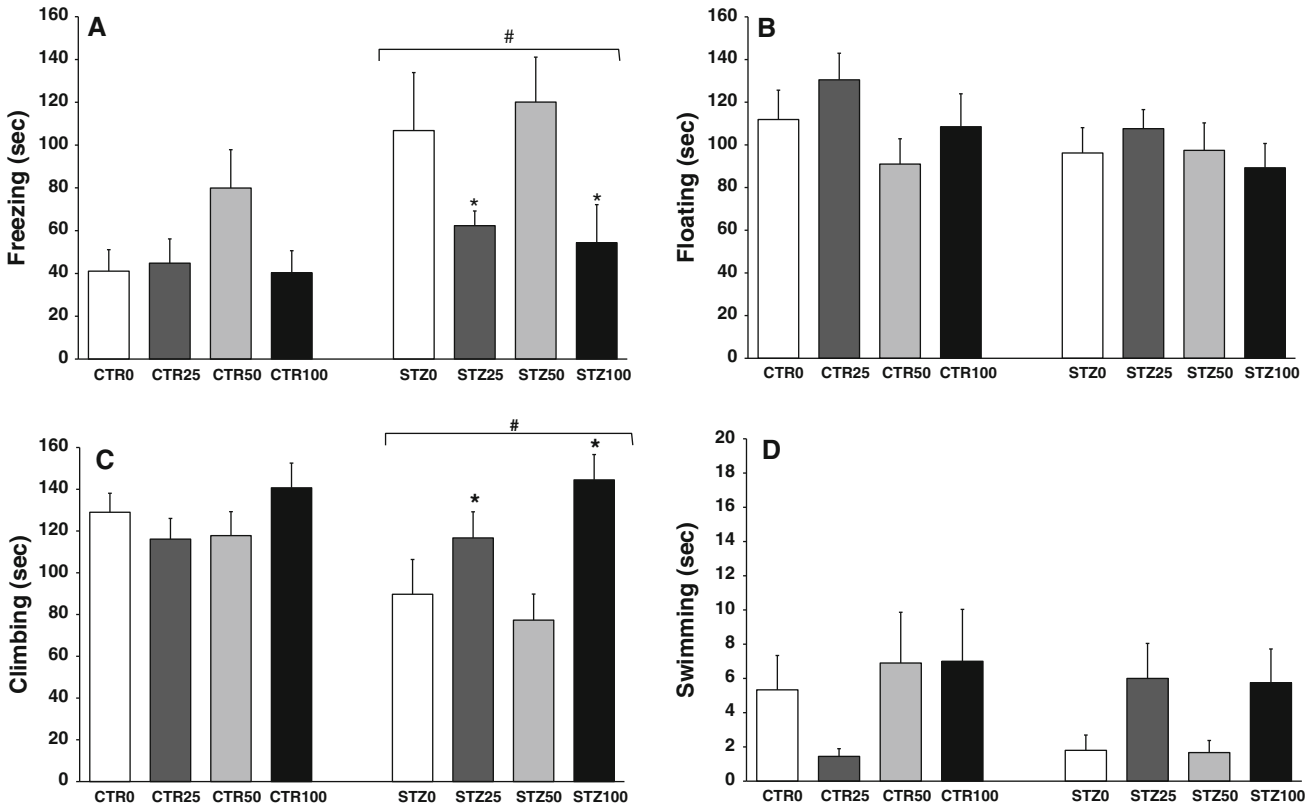


**Fig. 1** Time spent on immobility behaviors—freezing (**a**) and floating (**b**)—or mobility behaviors—climbing (**c**) and swimming (**d**)—in diabetic (STZ) and non-diabetic (CTR) rats after chronic taurine treatment at doses of 0, 25, 50 or 100 mg/kg during FST (300 s). Data express mean ± SEM; $n = 10$ rats/group, two-way ANOVA + Bonferroni test; #different from the CTR rats, $P < 0.001$; *different from STZ0 and STZ50, $P = 0.001$

**Table 1** Chronic taurine treatment at doses of 0, 25, 50 or 100 mg/kg did not affect frequency or duration of general motor activity in diabetic (STZ) and non-diabetic (CTR) rats during the open field test (300 s)

| Group | Frequency | | | | Time (s) | |
|---|---|---|---|---|---|---|
| Behavior | Squares crossed | Rearing | Grooming | Fecal boli | Rearing | Grooming |
| CTR0 | 120.7 ± 71.8 | 36.8 ± 16.9 | 1.5 ± 0.7 | 1.5 ± 2.1 | 47.6 ± 35.2 | 12.0 ± 11.9 |
| CTR25 | 132.7 ± 38.3 | 39.3 ± 19.2 | 1.1 ± 0.7 | 1.7 ± 1.2 | 60.2 ± 26.7 | 7.1 ± 5.5 |
| CTR50 | 128.8 ± 44.3 | 35.7 ± 12.2 | 1.2 ± 0.9 | 2.0 ± 1.8 | 50.4 ± 17.9 | 10.6 ± 14.1 |
| CTR100 | 125.9 ± 22.1 | 36.1 ± 9.7 | 1.3 ± 1.3 | 2.0 ± 2.3 | 55.7 ± 21.8 | 8.6 ± 9.2 |
| STZ0 | 110.9 ± 24.4 | 23.3 ± 10.2 | 1.2 ± 1.4 | 1.1 ± 1.3 | 34.5 ± 16.3 | 8.0 ± 17.6 |
| STZ25 | 101.4 ± 23.8 | 29.5 ± 11.8 | 1.7 ± 1.9 | 1.1 ± 1.6 | 48.1 ± 28.1 | 9.9 ± 15.5 |
| STZ50 | 100.1 ± 26.2 | 22.8 ± 7.4 | 0.6 ± 0.9 | 2.4 ± 1.8 | 31.8 ± 11.3 | 4.8 ± 7.4 |
| STZ100 | 121.0 ± 31.9 | 30.1 ± 9.5 | 0.8 ± 0.7 | 0.9 ± 0.9 | 42.0 ± 13.9 | 5.5 ± 6.7 |

Data express mean ± SEM; $n = 10$ rats/group, two-way ANOVA, $P > 0.05$

## Blood glucose parameters

Blood glucose levels were measured immediately after diabetes induction and then once a week thereafter to determine the temporal effect of taurine on glucose levels of non-fasting diabetic and non-diabetic rats. As shown in Fig. 2, diabetic rats had higher blood glucose levels during the 4 weeks of the experiment ($P < 0.001$). However, after the second week, a 100 mg/dL dose of taurine significantly decreased the blood glucose levels in diabetic rats ($P < 0.001$). The average decrease was 72.6 mg/dL, which represents about an 18% decrease from the basal blood glucose levels measured in the first week.

In the third week, we also tested the acute effect of taurine on blood glucose levels in non-fasting diabetic and non-diabetic rats. Analyses were performed immediately

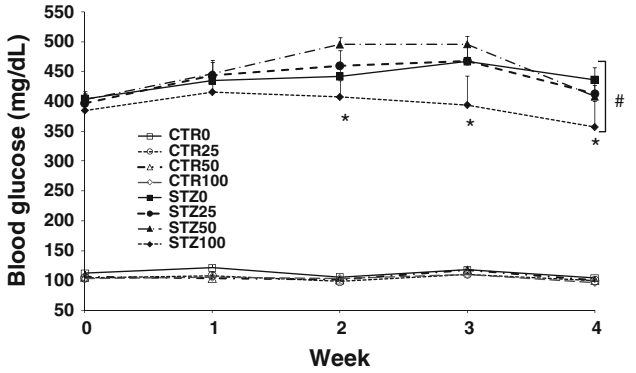


**Fig. 2** Weekly changes in blood glucose levels in diabetic (STZ) and non-diabetic (CTR) rats treated daily with taurine at doses of 0, 25, 50 or 100 mg/kg. Data express mean ± SEM; $n = 10$ rats/group, two-way ANOVA + Bonferroni test; #different from the CTR rats, $P < 0.001$; *different from STZ0, STZ25, and STZ50 after the second week of treatment

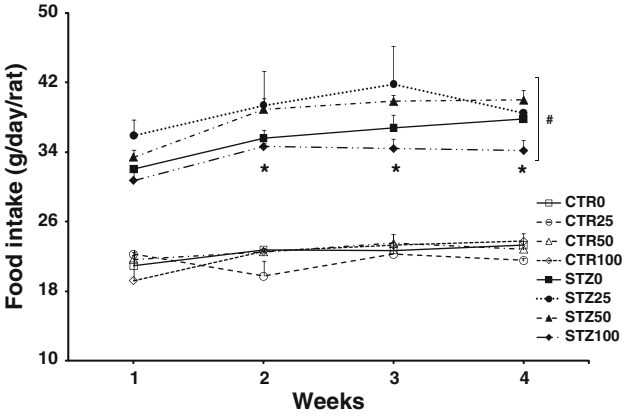


**Fig. 3** Weekly changes in food intake in diabetic (STZ) and non-diabetic (CTR) rats treated daily with taurine at doses of 0, 25, 50 or 100 mg/kg. Data express mean ± SEM; $n = 10$ rats/group, two-way ANOVA + Bonferroni test; #different from the CTR rats ($P < 0.001$); *different from STZ0, STZ25, and STZ50 ($P = 0.002$) after the second week of treatment

before and 1 h after taurine administration; there were no changes in blood glucose levels in diabetic and non-diabetic rats, demonstrating that the hypoglycemic effect of taurine requires chronic treatment.

To evaluate the effect of blood glucose levels on behaviors during the FST, we also measured the blood glucose levels 15 min before the rats were introduced to the FST. Pearson's test detected a direct correlation between blood glucose levels and immobility behaviors ($r = 0.35$; $P = 0.021$), showing increased immobility with elevated glycemia.

## Food and water intake and weight gain

Food intake was higher in diabetic than in non-diabetic rats ($P < 0.001$), and 100 mg/kg dose of taurine decreased food intake significantly in diabetic rats after the second week of treatment ($P = 0.002$; Fig. 3). Water intake was also higher in diabetic than in non-diabetic rats ($P < 0.001$). However, all doses of taurine decreased water intake in non-diabetic rats (Fig. 4a) in accordance with the duration of the treatment ($P < 0.001$). The highest dose of taurine decreased water intake in non-diabetic rats beginning at the first week of treatment, while the lower dose decreased water intake after the second week. The middle dose decreased water intake only after the third week. In diabetic rats (Fig. 4b), the 100 mg/kg dose also decreased water intake beginning at the first week, and the 25 mg/kg dose decreased water intake after the second week ($P < 0.001$). However, in this group, the 50 mg/kg dose did not affect water intake.

As expected, diabetic rats had a lower weight gain during the 4 weeks of the experiment ($P < 0.001$).

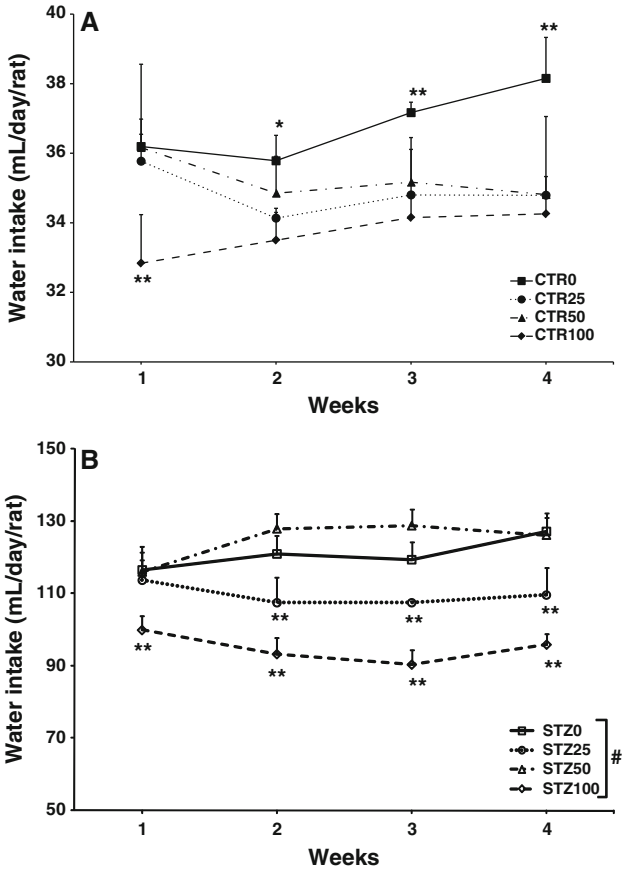


**Fig. 4** Weekly changes in water intake in **a** non-diabetic (CTR) and **b** diabetic (STZ) rats treated daily with taurine at doses of 0, 25, 50 or 100 mg/kg. Data express mean ± SEM; $n = 10$ rats/group, two-way ANOVA + Bonferroni test; **different from other doses; *different from CTR25 and CTR100; #different from the CTR rats ($P < 0.001$)

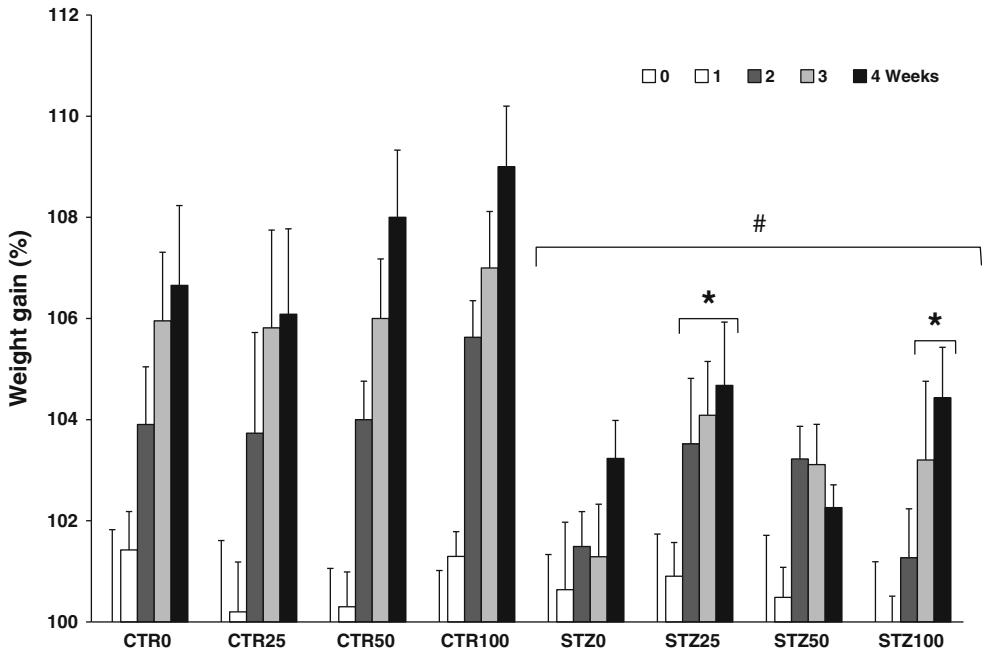


**Fig. 5** Rate of weekly weight gain of diabetic (STZ) and non-diabetic (CTR) rats treated daily with taurine at doses of 0, 25, 50 or 100 mg/kg. Data express mean ± SEM; $n = 10$ rats/group, two-way ANOVA + Bonferroni test; #different from the CTR rats ($P < 0.001$); *different from STZ0 and STZ50 ($P = 0.013$) after the second week of treatment

However, weight loss was significantly lower in diabetic rats treated with 25 and 100 mg/kg doses of taurine than those treated with 0 and 50 mg/kg doses after the second week of treatment (Fig. 5).

## Discussion

Because taurine has a variety of biological functions, its therapeutic properties were explored. Here, we showed that taurine has an antidepressant effect in diabetic rats, as shown by the decrease in immobility behaviors in the FST. This antidepressant effect was dependent of the dose and only observed in diabetic rats.

The antidepressant effect of taurine has been explored in non-diabetic mice; however, the results from these studies are controversial. Mice fed a diet rich in taurine for 30 days had fewer depressive-like behaviors in the FST (Murakami and Furuse 2010). However, similar to our study, Whirley and Einat (2008) did not find any antidepressant effect of taurine after three consecutive days of intraperitoneal administration (100 and 400 mg/kg taurine) in non-diabetic mice. Our results are not comparable to those studies that fed rats a taurine diet, because the authors did not present the daily food intake per rat, although our rats were treated for almost the same length of time. Interestingly, we showed that taurine has an antidepressant effect at doses of 25 and 100 mg/kg specifically in diabetic rats. Sanberg and Ossenkopp (1977) also showed that non-diabetic rats acutely treated with taurine at doses of 50 mg/kg were significantly less active in the open field test than those treated only with saline and those treated with taurine at doses of 100 mg/kg. The bell-shaped curve response observed by taurine here is not unusual for drugs (Ichihara et al. 1988; Moriguchi et al. 2009). The mechanisms underlying this bell-shaped dose response curve are not clear; however, we may suggest that small and larger doses of taurine interact differently on post-, or extra-synaptic $GABA_A$ receptors, or modulate other neurotransmitter systems. Although the behaviors in the FST have shown both reliability and validity for detecting the antidepressant effect of drugs, the model does not mimic some neurochemical changes that occur in the brain of a depressive individual. Rodents are acutely exposed to the test, whereas depression is a long-term disease. Because chronic hyperglycemia is associated with neurophysiological and structural changes in the brain and a higher risk of depression in diabetic individuals (Biessels et al. 2002; Lustman et al. 2000; Champaneri et al. 2010), we hypothesize that chronic hyperglycemia in our diabetic rats mimics some neurochemical aspects of depression. Thus, diabetic rats are more sensitive to the antidepressant effect of drugs than non-diabetic rats in the FST. In fact, previous results from our group have shown that diabetic rats have lower brain GABA levels and more depressive-like behaviors than non-diabetic rats in the FST (Gomez and Barros 2000; Gomez et al. 2003). We also showed that clonazepam, a $GABA_A$ agonist, reversed these depressive-like behaviors at doses

of 0.25 and 0.5 mg/kg only in diabetic rats (Gomez et al. 2003; Gomez and Barros 2000). Coincidently, diabetic and depressive patients have lower levels of taurine in the plasma and the cerebrospinal fluid than the general population (Perry et al. 1975; Franconi et al. 1995, 1996; Albrecht and Schousboe 2005; Jia et al. 2008). Changes in the GABA system may explain the taurine antidepressant effect. It is well established that taurine is structurally related to GABA and acts as an agonist for $GABA_A$ receptors (Medina and DeRobertis 1984; Levinskaya et al. 2006; El Idrissi et al. 2003, 2009; L'Amoreaux et al. 2010b). Chronic supplementation of taurine in the drinking water increases the levels of GABA, as well as its synthesizing enzyme, glutamate decarboxylase (GAD), in the mice brain (Levinskaya et al. 2006; El Idrissi and Trenkner 2004). Also, $GABA_A$ receptors are downregulated after chronic administration of taurine in the mice hippocampus (El Idrissi and Trenkner 2004). Moreover, taurine-induced chloride influx is inhibited by the $GABA_A$ receptor antagonist, bicuculline (El Idrissi and Trenkner 2004), and taurine administration reduces the severity of kainic acid-induced seizures in mice (El Idrissi et al. 2003). Here, taurine also increased head-shake behavior in diabetic rats, a specific behavior increased by $GABA_A$ agonist administration in rodents (Vargas et al. 1996; de Boer et al. 1980). Moreover, we do not discard that, indirectly, through GABA neurotransmission, taurine modulates other neurotransmitter systems such as serotonin or noradrenaline that are known to be involved on the effect of classical antidepressants. Thus, we may explain the antidepressant effect of taurine in diabetic rats on the basis of its deficiency in these individuals and its action as an agonist at $GABA_A$ receptors.

Because of the effect of taurine on the GABA system, one could anticipate a decrease in active behaviors in animals tested in the open field. Like others, we did not find changes in the behaviors after chronic administration of different doses of taurine in this test (Table 1). Indeed, acute taurine treatment decreased active behaviors in the open field test at doses of 43 or 50 mg/kg (El Idrissi et al. 2009; Sanberg and Ossenkopp 1977). However, when taurine was administered in the drinking water (0.05%), during 4 weeks, mice do not show changes in any parameter analyzed in this test (El Idrissi et al. 2009). Those authors hypothesize that chronic taurine administration downregulates the $GABA_A$ receptor expression and function, suggesting that the duration of the treatment is important to show different behavioral effects (El Idrissi et al. 2009; L'Amoreaux et al. 2010b; Levinskaya et al. 2006).

The antidepressant effect of taurine shown here cannot be attributed to the decrease in blood glucose levels, because diabetic rats maintained higher blood glucose levels than non-diabetic rats throughout the experiment (Fig. 2). Although the 100 mg/kg dose of taurine significantly decreased the blood glucose levels after the second week of treatment in diabetic rats, blood glucose levels did not drop below 200 mg/dL, which is our limit to consider reversion of diabetes in these rats. Furthermore, the 25 mg/kg antidepressant dose of taurine did not affect blood glucose levels, demonstrating the antidepressant effect of this amino acid. The hypoglycemic effect of taurine in non-insulin-dependent rats is thought to be related to increased sensitivity to insulin at the cell membrane level or to increased insulin release from $\beta$-cells (Bustamante et al. 2001). The hypoglycemic effect of taurine in insulin-dependent diabetic individuals has not been completely elucidated, although studies have suggested that it is not mediated by enhanced insulin release (Kulakowski and Maturo 1984). We may infer that because $GABA_A$ receptor is expressed on pancreatic $\alpha$-cells where glucagon is synthesized and released (Gilon et al. 1991), and because taurine binds to the $GABA_A$ receptor causing the hyperpolarization of $\alpha$-cells and inhibiting release of glucagon (Bustamante et al. 2001; Gavrovskaya et al. 2008; L'Amoreaux et al. 2010a), the hypoglycemic effect presented by taurine here is mediated by the decrease in glucagon secretion. Thus, it is possible that, similar to amylin analogs such as pramlintide (Singh-Franco et al. 2007), taurine decreases blood glucose levels by suppressing glucagon secretion.

We also measured some nutritional parameters, such as food and water intake and weight gain. As expected, diabetic rats ate more than non-diabetic rats during the experiment. In spite of their higher food intake, the diabetic rats lost weight. However, taurine significantly decreased food intake and prevented weight loss for the diabetic rats at a 100 mg/kg dose after the second week of treatment. Further studies will clarify if these effects are related to $\beta$-cell function or another mechanism involved in glucose homeostasis in diabetic rats. Although studies have shown an anti-obesity effect of taurine, we did not detect changes in food intake and weight gain in our non-diabetic rats (Tsuboyama-Kasaoka et al. 2006). In fact, those studies were performed in obese rats, showing that taurine prevents fat deposition and ameliorates the plasma lipid profile (Tsuboyama-Kasaoka et al. 2006). For humans, taurine intake is not correlated to body weight and has some beneficial effects on the serum lipid profile (Sung and Chang 2009; Zhang et al. 2004). Thus, it appears that the beneficial effect of taurine in obese individuals is related to the improvement of the plasma lipid profile rather than food intake or weight loss.

Additionally, as shown in previous studies, we demonstrated that taurine decreases water intake in diabetic and non-diabetic rats. The highest dose of taurine (100 mg/kg)

decreased water intake in both diabetic and non-diabetic rats beginning at the first week of administration. Other doses showed this hypodipsic effect only after subsequent weeks of taurine administration. In diabetic rats, however, this effect was only seen at the 25 mg/kg dose. This is the first study to show this effect in diabetic rats. In non-diabetic rats, intraperitoneal injections of taurine, at doses that do not affect motor activity, have been shown to decrease water intake (Hruska et al. 1975). Because taurine is a $GABA_A$ agonist and increases plasma and brain GABA levels (Murakami and Furuse 2010; Franconi et al. 1995), we infer that the hypodipsic effect seen in our non-diabetic rats is related to the interaction of taurine with the GABA system. In fact, $GABA_A$ agonists produce a dose-related inhibition of water consumption that is abolished by pretreatment with $GABA_A$ receptor antagonists in rats (Houston et al. 2002).

In conclusion, taurine, at doses of 25 and 100 mg/kg, produces an antidepressant effect in diabetic rats exposed to FST after 28 days of treatment. Additionally, these two doses decreased the water intake and prevented weight loss in the same group of animals. The 100 mg/kg dose of taurine also decreased food intake and blood glucose levels in diabetic rats. Because taurine is a GABA agonist and both amino acids are lower in the plasma of diabetic and depressive individuals, we hypothesize that taurine may represent a new alternative drug for the treatment of depression in diabetic individuals. Moreover, because taurine modulates a variety of biological functions, including membrane stabilization, osmoregulation, antioxidation, cell proliferation and immune responses (Oja and Saransaari 2007), it could be used as an adjuvant to delay central and peripheral complications associated with chronic hyperglycemia in these individuals. Additional studies are necessary to clarify the mechanisms involved in the antidepressant and metabolic effects of taurine.

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

## References

Albrecht J, Schousboe A (2005) Taurine interaction with neurotransmitter receptors in the CNS: an update. Neurochem Res 30: 1615–1621

Anjaneyulu M, Chopra K, Kaur I (2003) Antidepressant activity of quercetin, a bioflavonoid, in streptozotocin-induced diabetic mice. J Med Food 6:391–395

Biessels GJ, van der Heide LP, Kamal A, Bleys RL, Gispen WH (2002) Aging and diabetes: implications for brain function. Eur J Pharmacol 441:1–14

Birdsall TC (1998) Therapeutic applications of taurine. Altern Med Rev 3:128–136

Bonner-Weir S (2000) Life and death of the pancreatic beta cells. Trends Endocrinol Metab 11:375–378

Brambilla P, Perez J, Barale F, Schettini G, Soares JC (2003) GABAergic dysfunction in mood disorders. Mol Psychiatry 8:721–737

Bustamante J, Lobo MV, Alonso FJ, Mukala NT, Gine E, Solis JM, Tamarit-Rodriguez J, Martin del Rio R (2001) An osmotic-sensitive taurine pool is localized in rat pancreatic islet cells containing glucagon and somatostatin. Am J Physiol Endocrinol Metab 281:E1275–E1285

Carneiro EM, Latorraca MQ, Araujo E, Beltrá M, Oliveras MJ, Navarro M, Berná G, Bedoya FJ, Velloso LA, Soria B, Martín F (2009) Taurine supplementation modulates glucose homeostasis and islet function. J Nutr Biochem 20:503–511

Champaneri S, Wand GS, Malhotra SS, Casagrande SS, Golden SH (2010) Biological basis of depression in adults with diabetes. Curr Diab Rep 10:396–405

Chen SW, Kong WX, Zhang YJ, Li YL, Mi XJ, Mu XS (2004) Possible anxiolytic effects of taurine in the mouse elevated plus-maze. Life Sci 75:1503–1511

Cherif H, Reusen B, Ahn MT, Hoet JJ, Remacle C (1998) Effects of taurine on the insulin secretion of rat fetal islets from dams fed a low protein diet. J Endocrinol 159:341–348

Daneman D (2006) Type 1 diabetes. Lancet 367:847–858

de Boer T, Bartels K, Metselaar HJ, Bruinvels J (1980) Di-n-propylacetate-induced abstinence behaviour as a possible correlate of increased GABA-ergic activity in the rat. Psychopharmacology 71:257–267

Del Prato S, Marchetti P (2004) Beta- and alpha-cell dysfunction in type 2 diabetes. Horm Metab Res 36:775–781

El Idrissi A, Trenkner E (2004) Taurine as a modulator of excitatory and inhibitory neurotransmission. Neurochem Res 29:189–197

El Idrissi A, Messing J, Scalia J, Trenkner E (2003) Prevention of epileptic seizures by taurine. Adv Exp Med Biol 526:515–525

El Idrissi A, Boukarrou L, Heany W, Malliaros G, Sangdee C, Neuwirth L (2009) Effects of taurine on anxiety-like and locomotor behavior of mice. Adv Exp Med Biol 643:207–215

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, Miceli M, Fazzini A, Seghieri G, Caputo S, DiLeo MA, Lepore D, Ghirlanda G (1996) Taurine and diabetes. Humans and experimental models. Adv Exp Med Biol 403:579–582

Gavard JA, Lustman PJ, Clouse RE (1993) Prevalence of depression in adults with diabetes. Diabetes Care 16:1167–1178

Gavrovskaya LK, Ryzhova OV, Safonova AF, Matveev AK, Sapronov NS (2008) Protective effect of taurine on rats with experimental insulin-dependent diabetes mellitus. Bull Exp Biol Med 146:226–228

Gilon P, Bertrand G, Loubatieres-Mariani MM, Remacle C, Henquin JC (1991) The influence of gamma-aminobutyric acid on hormone release by the mouse and rat endocrine pancreas. Endocrinology 129:2521–2529

Gomez R, Barros HM (2000) Ethopharmacology of the antidepressant effect of clonazepam in diabetic rats. Pharmacol Biochem Behav 66:329–335

Gomez R, Vargas CR, Wajner M, Barros HM (2003) Lower in vivo brain extracellular GABA concentration in diabetic rats during forced swimming. Brain Res 968:281–284

Hansen SH (2001) The role of taurine in diabetes and the development of diabetes complications. Diabetes Metab Res Rev 17:330–346

Houston AJ, Wong JC, Ebenezer IS (2002) Effects of subcutaneous administration of the gamma-aminobutyric acid(A) receptor agonist muscimol on water intake in water-deprived rats. Physiol Behav 77:445–450

Hruska RE, Thut PD, Huxtable RJ, Bressler R (1975) Suppression of conditioned drinking by taurine and related compounds. Pharmacol Biochem Behav 3:593–599

Ichihara K, Nabeshima T, Kameyama T (1988) Opposite effects induced by low and high doses of apomorphine on single-trial passive avoidance learning in mice. Pharmacol Biochem Behav 30:107–113

Jia F, Yue M, Chandra D, Keramidas A, Goldstein PA, Homanics GE, Harrison NL (2008) Taurine is a potent activator of extrasynaptic Gaba A receptors in the thalamus. J Neurosci 28:106–115

Kulakowski EC, Maturo J (1984) Hypoglycemic properties of taurine: not mediated by enhanced insulin release. Biochem Pharmacol 33:2835–2838

L'Amoreaux WJ, Cuttitta C, Santora A, Blaize JF, Tachjadi J, El Idrissi A (2010a) Taurine regulates insulin release from pancreatic beta cell lines. J Biomed Sci 17:S11

L'Amoreaux WJ, Marsillo A, El Idrissi A (2010b) Pharmacological characterization of GABAA receptors in taurine-fed mice. J Biomed Sci 17(S1):S14

Levinskaya N, Trenkner E, El Idrissi A (2006) Increased GAD-positive neurons in the cortex of taurine-fed mice. Adv Exp Med Biol 583:411–417

Luscher B, Shen Q, Sahir N (2011) The GABAergic deficit hypothesis of major depressive disorder. Mol Psychiatry 16: 383–406

Lustman PJ, Clouse RE (2005) Depression in diabetic patients: the relationship between mood and glycemic control. J Diabetes Complicat 19:113–122

Lustman PJ, Anderson RJ, Freedland KE, de Groot M, Carney RM, Clouse RE (2000) Depression and poor glycemic control: a meta-analytic review of the literature. Diabetes Care 23:934–942

Medina JH, DeRobertis E (1984) Taurine modulation of the benzodiazepine gamma–aminobutyric acid receptor complex in brain membranes. J Neurochem 42:1212–1217

Moriguchi S, Shioda N, Han F, Yeh JZ, Narahashi T, Fukunaga K (2009) Galantamine enhancement of long-term potentiation is mediated by calcium/calmodulin-dependent protein kinase II and protein kinase C activation. Hippocampus 19:844–854

Morishita S (2009) Clonazepam as a therapeutic adjunct to improve the management of depression: a brief review. Hum Psychopharmacol 24:191–198

Murakami T, Furuse M (2010) The impact of taurine- and beta-alanine-supplemented diets on behavioral and neurochemical parameters in mice: antidepressant versus anxiolytic-like effects. Amino Acids 39:427–434

Nin MS, Salles FB, Azeredo LA, Frazon AP, Gomez R, Barros HM (2008) Antidepressant effect and changes of GABAA receptor gamma2 subunit mRNA after hippocampal administration of allopregnanolone in rats. J Psychopharmacol 22:477–485

Oja SS, Saransaari P (2007) Pharmacology of taurine. Proc West Pharmacol Soc 50:8–15

Perry TL, Bratty PJ, Hansen S, Kennedy J, Urquhart N, Dolman CL (1975) Hereditary mental depression and Parkinsonism with taurine deficiency. Arch Neurol 32:108–113

Porsolt RD, Bertin A, Jalfre M (1977) Behavioral despair in mice: a primary screening test for antidepressants. Arch Int Pharmacodyn Ther 229:327–336

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 25:370–379

Sanacora G, Saricicek A (2007) GABAergic contributions to the pathophysiology of depression and the mechanism of antidepressant action. CNS Neurol Disord Drug Targets 6:127–140

Sanberg PR, Ossenkopp KP (1977) Dose–response effects of taurine on some open-field behaviors in the rat. Psychopharmacology (Berlin) 53(2):207–209

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

Sen S, Sanacora G (2008) Major depression: emerging therapeutics. Mt Sinai J Med 75:204–225

Singh-Franco D, Robles G, Gazze D (2007) Pramlintide acetate injection for the treatment of type 1 and type 2 diabetes mellitus. Clin Ther 29:535–562

Smith WT, Londborg PD, Glaudin V, Painter JR (2002) Is extended clonazepam cotherapy of fluoxetine effective for outpatients with major depression? J Affect Disord 70:251–259

Smith LA, Cornelius VR, Azorin JM, Perugi G, Vieta E, Young AH, Bowden CL (2010) Valproate for the treatment of acute bipolar depression: systematic review and meta-analysis. J Affect Disord 122:1–9

Sung MJ, Chang KJ (2009) Dietary taurine and nutrients intake and anthropometric and body composition data by abdominal obesity in Korean male college students. Adv Exp Med Biol 643:429–435

Trachtman H, Futterweit S, Maesaka J, Ma C, Valderrama E, Fuchs A, Tarectecan AA, Rao PS, Sturman JA, Boles TH et al (1995) Taurine ameliorates chronic streptozocin-induced diabetic nephropathy in rats. Am J Physiol 269:429–438

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 147:3276–3284

Vargas C, Tannhauser M, Tannhauser SL, Barros HM (1996) Lithium and valproate combined administration: acute behavioural effects and drug plasma levels. Pharmacol Toxicol 79:87–91

Walsh RN, Cummins RA (1976) The Open-Field Test: a critical review. Psychol Bull 83:482–504

Whirley BK, Einat H (2008) Taurine trials in animal models offer no support for anxiolytic, antidepressant or stimulant effects. Isr J Psychiatry Relat Sci 45:11–18

Wolffenbuttel BH, van Haeften TW (1995) Prevention of complications in non-insulin-dependent diabetes mellitus (NIDDM). Drugs 50:263–288

Wu JY, Prentice H (2010) Role of taurine in the central nervous system. J Biomed Sci 17:S1

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 26:267–271