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Full paper

Impact of taurine depletion on glucose control and insulin secretion in mice

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ABSTRACT

Taurine, an endogenous sulfur-containing amino acid, is found in millimolar concentrations in mammalian tissue, and its tissue content is altered by diet, disease and aging. The effectiveness of taurine administration against obesity and its related diseases, including type 2 diabetes, has been well documented. However, the impact of taurine depletion on glucose metabolism and fat deposition has not been elucidated. In this study, we investigated the effect of taurine depletion (in the taurine transporter (TauT) knockout mouse model) on blood glucose control and high fat diet-induced obesity. TauT-knockout (TauTKO) mice exhibited lower body weight and abdominal fat mass when maintained on normal chow than wild-type (WT) mice. Blood glucose disposal after an intraperitoneal glucose injection was faster in TauTKO mice than in WT mice despite lower serum insulin levels. Islet beta-cells (insulin positive area) were also decreased in TauTKO mice compared to WT mice. Meanwhile, overnutrition by high fat (60% fat)-diet could lead to obesity in TauTKO mice despite lower body weight under normal chow diet condition, indicating nutrition in normal diet is not enough for TauTKO mice to maintain body weight comparable to WT mice. In conclusion, taurine depletion causes enhanced glucose disposal despite lowering insulin levels and lower body weight, implying deterioration in tissue energy metabolism.

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1. Introduction

Taurine (2-aminoethanesulfonic acid) is widely distributed in nature and in mammals is present in millimolar concentrations in most tissues. Taurine is clinically approved in Japan for the treatment of patients with both chronic heart failure and hepatic disorders (1,2). Moreover, evidence from human clinical and animal studies suggests a beneficial effect of taurine against a variety of other diseases, including diabetes and obesity (3,4). Human taurine content is derived from its biosynthesis in liver, fat, brain etc. and from dietary intake of meat. Seafood is especially rich in taurine (5–7). Tissue taurine content is influenced by diet, as well as by disease and aging (8–11). Dietary taurine insufficiency causes a decrease in plasma taurine levels, which leads to various disorders, such as retinal degeneration, dilated cardiomyopathy and the reduction in reproductive performance in cats which have a low synthetic capacity for taurine (12–14). Importantly, urinary taurine excretion, a marker of taurine intake from the diet, is inversely correlated with mortality rate caused by ischemic heart disease in humans (15,16), indicating the nutritional importance of taurine to prevent lifestyle-related diseases. Moreover, it has been demonstrated that taurine supplementation attenuates obesity, diabetes and hypercholesterolemia in diet-induced and inherent obesity experimental models (17–20).

The taurine transporter (TauT), which transports taurine from the extracellular space into cells to help maintain a high intracellular taurine content, is widely expressed in various tissues. The taurine transporter knockout (TauTKO) mouse exhibits extensive taurine depletion in several tissues (21,22). Especially noteworthy is the 98% decrease in taurine content in heart and skeletal muscle of the TauTKO mice, compared to about 1–2% in WT mice. By comparison, taurine levels in other tissues of the TauTKO mouse, such as brain, kidney and liver, falls to 10–30% of those found in WT mice, indicating a very low capacity of taurine biosynthesis in the heart

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and skeletal muscle. TauTKO mice exhibit lower body weight than WT mice although the amount of food intake is identical (21–23). TauTKO mice also exhibit decreased skeletal muscle weight and cell size, indicating that muscle atrophy contributes to body weight loss. Endurance running time of TauTKO mice is lower than that of the control mice. Moreover, blood glucose is cleared faster during treadmill running in TauTKO mice than in WT mice (23), which may contribute to a reduction in exercise capacity. Taurine depletion alters the respiratory quotient during exercise (21,24), implying that taurine depletion affects the balance in energy metabolism. Taurine has been recently implicated in the regulation of mitochondrial function through various actions, such as modulation of mitochondrial transfer RNA, buffer action and calcium movement (25–27), supporting the idea that taurine might play an important role in energy production. Additionally, several lines of evidence reveal a crucial role of taurine in β cell function. It has been reported that taurine treatment attenuates cell injury induced by several stresses in the islets (28–30). Moreover, long-term taurine supplementation of mice fed a normal diet of taurine reduces plasma glucose during a glucose tolerance test concomitant with an increase in islet size of the pancreas. Therefore, it is logical to assume that taurine depletion may affect the regulation of blood glucose.

In this study, we investigated the effect of taurine depletion using TauTKO mice on blood glucose control, insulin secretion and high fat diet-induced obesity.

2. Materials and methods

2.1. Animal care

The experimental procedures were approved by the Institutional Animal Care and Use Committee of Hyogo University of Health Sciences. TauTKO and littermate mice (C57BL/6 background) were housed in a SPF environment, fed standard chow (MF, Oriental Yeast, Tokyo), had access to water ad libitum and maintained on a 12-h light/dark cycle. Male WT and TauTKO mice were studied.

2.2. High fat diet

In the high fat diet group, mice were fed 60% fat-contained diet (Oriental Yeast) beginning at 3 months of age. Body weight was monitored each week. Sixteen weeks after HFD, mice were subjected intraperitoneal glucose tolerance test. All mice were sacrificed 20–22 weeks after initiation of the high fat diet and tissues were quickly frozen in liquid nitrogen and stored at −80 °C.

2.3. Glucose and insulin tolerance tests

For the intraperitoneal glucose tolerance test, after an overnight fast (16–17 h), mice were injected i.p. a glucose solution (1 g/10 mL water) at 1 mg/g body weight. In the insulin tolerance test, normally fed mice were fasted for 3 h, and then administered i.p. insulin (0.2 U/g body wt) (Nacalai Tesque, Kyoto, Kyoto). Blood glucose levels before and 15, 30, 60, 90 and 120 min after injection were measured in tail vein blood using Precision Xceed with Blood Glucose Test Strips (Abbott Japan, Tokyo). Serum insulin levels before and 15 and 60 min after glucose injection was determined by using an insulin kit (Morinaga Institute of Biological Science, Yokohama, Kanagawa) according to manufacturer's protocol.

2.4. Measurement of tissue taurine content by HPLC

Tissues were homogenized in 100 mM HEPES (pH 7.5). Four volume of 5% sulfosalicylic acid was added to the tissue lysate. After centrifugation, the supernatant was filtered and neutralized with 1 M $NaHCO_3$. Then, samples were subjected to HPLC to determine taurine concentration, using a previous method with slight modification (31). In brief, supernatant was derivatized with an OPA reagent (3 mg of *o*-phthalaldehyde with 50 μL of 95% ethanol, 10 μl of 2-mercaptoethanol in 5 mL of 100 mM borate buffer (pH 10.4)), and then applied to HPLC (D-2000, Hitachi High Technologies, Tokyo) equipped with a reverse phase column (Cosmosil 5C18-MS-II, 150 mm, Nacalai Tesque).

2.5. Westernblot

For preparation of the membrane fraction of skeletal muscle and liver, tissues were minced and homogenized in isotonic buffer (100 mM Sucrose, 100 mM Tris, 45 mM KCl, 10 mM EDTA, pH 7.4), and then were centrifuged to remove debris, nuclei and the mitochondrial fraction. Supernatant was obtained after centrifugation at 200,000× *g* for 1 h (MLA-50, Beckman Coulter, Miami, FL, USA), with the pellet defined as the membrane fraction. The membrane pellet was dissolved in RIPA buffer.

After protein determination using the bicinconic acid assay method (Pierce BCA assay kit, Life Technologies, Grand Island, NY, USA), protein samples were subjected to western blots as previously described (32). Anti-glucose transporter (Glut) −1, −2, −4 (Millipore, Billerica, MA, USA; 1:500) antibodies were used as 1st antibodies.

2.6. Histological analysis

Sections from frozen tissues were cut by cryostat (Carl Zeiss, Jena, Germany). Sections we stained by hematoxylin & eosin methods. For detection of insulin positive cells, pancreatic sections were immunostained by using anti-insulin antibody (ab80, Abcam, Cambridge, UK; 1:100) and Alexa Fluor 488-conjugated second antibody (Life Technologies; 1:400) with Can Get Signal Immunostain according to manufacturer's protocol (Toyobo, Osaka, Osaka). Images were acquired with microscopes (BZ-9000, Keyence, Osaka, Osaka) equipped with imaging software (BZ-II, Keyence).

2.7. Statistics

Each value was expressed as the mean ± standard error (SE). Statistical analysis was performed using Statcel 2nd edition (OMS Publishing Inc). Analysis of variance (ANOVA) was used to analyze blood glucose and body weight changes. Student's t-test or Tukey–Kramer test was used to determine statistical significance between groups. Differences were considered statistically significant when the calculated p value was less than 0.05.

3. Results

3.1. Lean phenotype in TauTKO mice

When mice were fed normal chow, the body weight of TauTKO mice was lower than that of the WT mice at both 3 months and 12 months of age (Fig. 1A) (genotype, $F = 27.66$, $p < 0.001$; time, $F = 55.15$, $p < 0.001$; interaction, $F = 3.64$, $p > 0.05$ by repeated measures two-way ANOVA, $p < 0.01$ between 3-month-old WT and TauTKO, $p < 0.01$ between 12-month-old WT and TauTKO by Tukey–Kramer test) (22). While WT mice contained visceral adipose tissue at 1 year of age, visceral fat deposition was less obvious in TauTKO mice, as the weight of visceral fat was significantly less in TauTKO mice at 1 year of age than in their corresponding WT cohorts ($p < 0.01$ by Student's t-test) (Fig. 1B and C). Dietary intake was not different between WT and TauTKO mice. These data

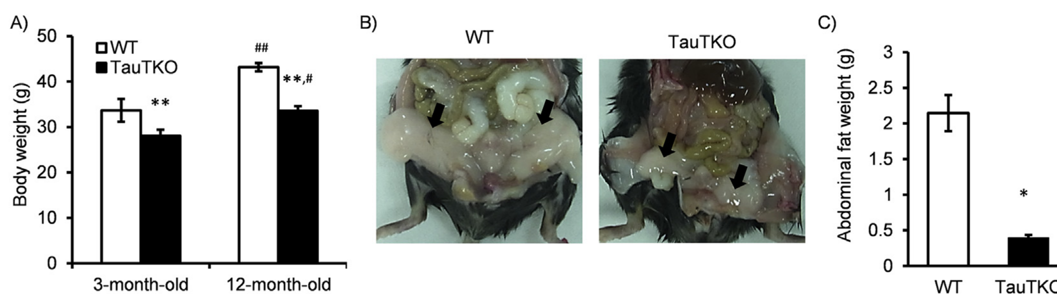

Fig. 1. Less fat deposition in TauTKO mice fed a normal diet. A) Body weight of 3- and 12-month-old WT and TauTKO mice were measured. (n = 6–12). B) Representative ventral images of 12-month-old WT and TauTKO mice. C) Weight of abdominal fat deposits of WT and TauTKO mice. n = 13–16. *; $p < 0.05$ vs WT, ##; $p < 0.01$ vs 3-month-old.

indicate that TauTKO mice are resistant to aging-dependent obesity when maintained on normal chow.

3.2. Alteration of glucose tolerance in TauTKO mice

To test for alteration in glucose metabolism, a glucose tolerance test was performed in young mice. After an i.p. glucose injection, the reduction in glucose levels was faster in TauTKO mice than in WT mice (genotype, F = 11.26, $p < 0.01$; time, F = 68.51, $p < 0.001$; interaction, F = 1.41, $p > 0.05$ by repeated measures two-way ANOVA) (Fig. 2A). By contrast, blood glucose changes after glucose injection was not different between WT (TauT+/+) and heterozygous (TauT+/−) mice (genotype, F = 0.20, $p > 0.05$; time, F = 96.21, $p < 0.001$; interaction, F = 1.04, $p > 0.05$ by repeated measures two-way ANOVA) (Fig. 2B). Surprisingly, serum insulin levels before and 15-min and 60-min after glucose injection were lower in TauTKO mice than WT mice (genotype, F = 19.64, $p < 0.01$; time, F = 20.21, $p < 0.001$; interaction, F = 2.70, $p > 0.05$ by repeated measures two-way ANOVA) (Fig. 2C). Next, insulin sensitivity of TauTKO mouse was tested (Fig. 2D). After an i.p. injection of insulin, TauTKO mouse showed lower blood glucose levels than did WT mouse, but insulin sensitivity (changes in glucose level after insulin injection) was not statistically different between TauTKO and WT mice (genotype, F = 0.78, $p > 0.05$; time, F = 39.71, $p < 0.001$; interaction, F = 0.98, $p > 0.05$ by repeated measures two-way ANOVA).

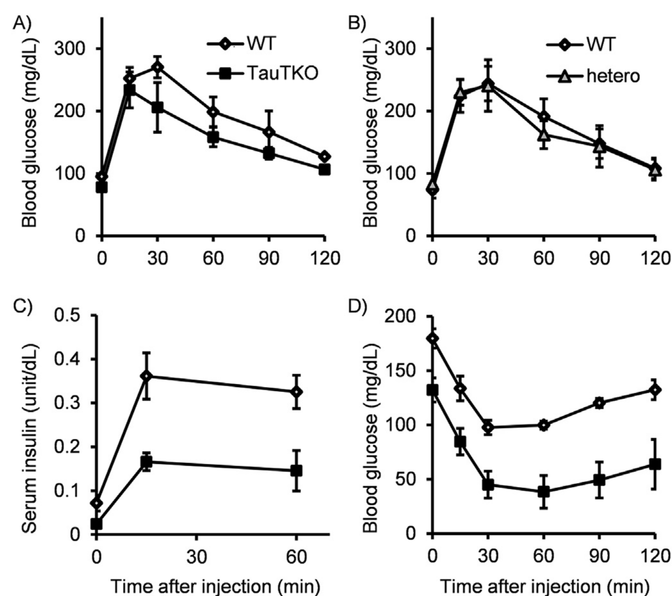

Fig. 2. Glucose and insulin tolerance test in normal diet-fed TauTKO mice. A,B) Blood glucose during glucose tolerance test in 3-month-old WT and TauTKO (A) and in 3-month-old WT and hetero (taut+/−) mice (B). C) Serum insulin levels during glucose tolerance test in 3-month-old WT and TauTKO mice. D) Blood glucose level during insulin resistance test. n = 5–6.

3.3. Expression of glucose transporters in TauTKO tissues

To determine the expression level of glucose transporters, hepatic and muscular protein levels of GLUT1, 2 and 4 in membrane fraction were evaluated (Fig. 3). In muscle and liver, no difference in the levels of the 3 GLUT transporters was observed between TauTKO mice and WT mice.

3.4. Decrease in islet β-cells in TauTKO mice

Next, the morphology of the pancreas in TauTKO mice was examined to further analyze how serum insulin was lower in TauTKO. Pancreatic taurine content of the TauTKO mice was less than 10% of that of the WT (Table 1). Immunohistochemical analysis revealed that the area of insulin positive-islets was less in the TauTKO pancreas than in the pancreas of their WT cohorts (Fig. 4A and B), which may be associated with lower serum insulin levels. These data indicate that taurine depletion interferes with cell growth and/or stress resistance in islet, which in turn contributes to lower insulin levels.

3.5. High fat diet-induced obesity in TauTKO mice

To determine the influence of a high fat diet on body weight of taurine depleted mice, WT and TauTKO mice were fed a diet containing 60% fat (HFD). Sixteen weeks after starting the HFD, the body weight of the TauTKO mouse had increased to a level comparable to that of the WT mice (Fig. 5A). Comparison body weight of 6-month-old WT and TauT mice fed normal diet (ND) or HFD for 16 weeks revealed that body weight between WT and TauTKO mice after HFD is not statistically different, although body weight between ND-fed WT and TauTKO mice at same age is significantly different (genotype, F = 82.99, $p < 0.001$; diet, F = 13.28, $p < 0.01$; interaction, F < 0.001, $p > 0.05$ by repeated measures two-way ANOVA, $p < 0.01$ between 6-month-old ND WT and ND TauTKO, $p > 0.05$ between HFD WT and HFD TauTKO by Tukey–Kramer test) (Fig. 5B). The amount of food consumed by the animals was not different between the two genotypes (average (g/10 g body weight/day); 1.28 (WT) vs 1.43 (TauTKO) at 0 week and 0.55 (WT) vs 0.63 (TauTKO) at 16 week after starting HFD, n = 6 (WT) and 5 (TauTKO)). Growth of abdominal fat in TauTKO mice was dramatically enhanced by the end of the HFD period (Fig. 5C), although TauTKO mice which were fed a normal diet had smaller amounts of abdominal fat than its WT cohorts.

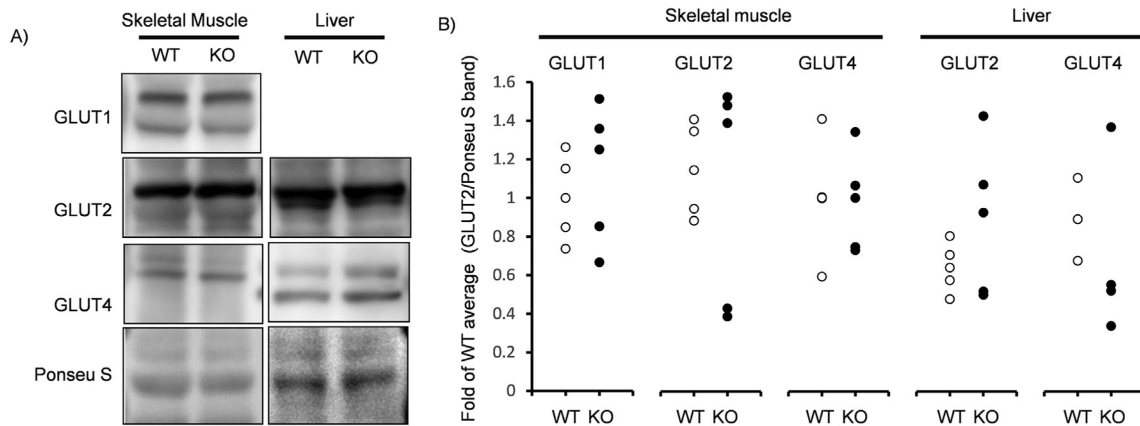

Fig. 3. Glucose transporters in muscle and liver of TauTKO mice. A) Representative western blots for GLUT1, 2 and 4 protein from muscle and liver membrane. Representative images were shown. B) Plot-based graph for GLUT level is shown. Relative GLUTs content were quantified and normalized by a band from ponso S stain. n = 4–6.

Table 1
Taurine content in tissues of WT and TauTKO mice.

	NFD (3-month-old)		HFD 22 wk (8-month-old)	
	WT	TauTKO	WT	TauTKO
Pancreas	2.99 ± 0.12	0.24 ± 0.067*	–	–
Fat	–	–	1.45 ± 0.20	0.32 ± 0.033*

μmol/g tissue weight.
–; not detected.
Data are mean ± SE, n = 3–6.
*$p < 0.05$ vs WT.

4. Discussion

In the present study, we identified unexpected phenotype of TauTKO mice; TauTKO mice displayed lower fasting blood glucose and were more tolerant against glucose injection, although serum insulin level was not higher, rather lower, than WT mice. Next, we investigated the influence of HFD on the TauTKO phenotype. In the case of HFD, body weight gain after HFD was faster in TauTKO mice than WT mice, and body weight in TauTKO mice was comparable to WT mice at the end of experiment.

Mechanism for enhancement of glucose disposal in TauTKO mice has not been clarified, so far. We also observed serum insulin level both before and after glucose injection was much lower in TauTKO mouse. However, insulin sensitivity is not different between TauTKO and WT mice, although we expected that TauTKO mouse is susceptible to insulin to dispose blood glucose. On the other hand, it has previously reported that skeletal muscle lactate content was higher in TauTKO mice than WT mice (23), which suggest that anaerobic glycolytic pathway may be accelerated in TauTKO muscle. Therefore, it is assumable that acceleration of glycolysis in skeletal muscle enhances glucose disposal from blood. Importantly, we have previously found that both nuclear peroxisome proliferator-activated receptor α (PPARα) amount and its target transcription are reduced in TauTKO muscle (23). PPARα is responsible for the transcriptional activation of fatty acid oxidation-related genes (33). Importantly, it has been reported that transgenic mouse overexpressing PPARα in muscle was impaired glucose disposal concomitant with an increase in fatty acid oxidation rates (34,35), suggesting that muscle PPARα level can determine peripheral glucose disposal capacity. These observations indicate that the reduction in PPARα deteriorates glucose and fatty acid utilization in TauTKO muscle, thereby glucose disposal is enhanced as compensatory mechanism.

It has been reported that a high fat diet causes a decrease in blood and adipose taurine content, which is assumed to relate to the development of obesity (17). Therefore, it is logical that the TauTKO mice are susceptible to the development of obesity when placed on a HFD. TauTKO mice are lean and contain few visceral fat deposits when fed a normal diet. However, they reach a body weight comparable to that of the WT mice when fed a HFD. Thus, TauTKO mice appear to have less lipid to store in adipose tissue when fed a normal chow diet, but they store large amounts of lipid when fed a HFD. We have previously reported that TauTKO mice exhibit a low body weight at a young age (at least up to 4 weeks of

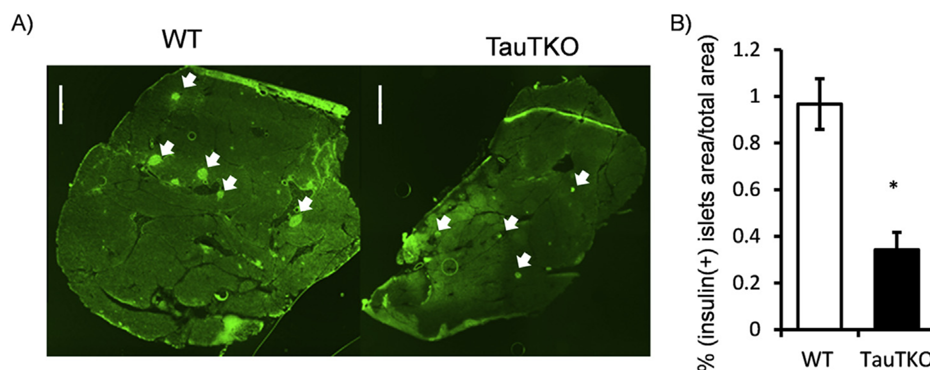

Fig. 4. Pancreas islet in TauTKO mice. A) Representative fluoromicroscopic images of pancreatic sections stained by anti-insulin antibody. Arrows indicate insulin positive islets in pancreas. Scale bars indicate 200 μm. B) Insulin positive area relative to total area was calculated from 4 to 5 pancreas sections for each mouse. n = 3. *; $p < 0.05$ vs WT.

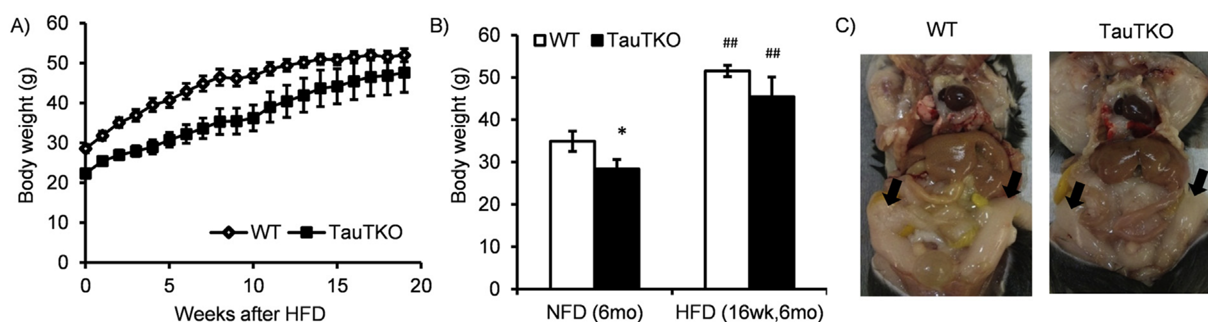

Fig. 5. Body weight and adipose growth of TauTKO mice fed a high fat diet. A) Body weight was monitored weekly from 0 to 20 weeks after initiating the high fat diet in 3-month-old mice. n = 6(WT), 5 (TauTKO). B) Body weight of 6-month-old WT and TauT mice fed either a normal diet or a high fat diet (HFD) for 16 weeks. n = 5–10. *; $p < 0.05$ vs WT, ##; $p < 0.01$ vs normal diet group. (C) Representative ventral images of WT and TauTKO mice fed a high fat diet.

age), diminished tissue weights and a decrease in skeletal muscle and heart cell size, indicating a deficit in growth as a result of taurine depletion (21). A growth defect can result from excessive consumption of substrates that produce energy, since some findings from TauTKO mice indicate a stimulation in metabolic pathways, including enhanced blood glucose disposal. Moreover, we and others have previously reported that lactate accumulates in TauTKO skeletal muscle, indicating the activation of glycolytic pathway in skeletal muscle (23). These data suggest that TauTKO mice alter energy production, which may result in part from the activation of glucose transport and glycolysis. Several papers have demonstrated that an energy imbalance (production/expenditure) causes a decrease in body weight. For example, the lack of Kir-6.2 (sarcolemmal ATP-sensitive Ca^{2+} channel) or a muscle specific loss of Kir-6.2 function results in a decrease in body weight and a reduction in fat depots accompanied with an induction in energy expenditure, all without a change in food intake (36). Additionally, these mice are resistant to HFD-induced obesity. Furthermore, mice lacking SLC25A5 (mitochondrial ATP/Pi transporter) exhibit reduced mitochondrial respiration and less body weight (37). These reports indicate that an increase in fuel metabolism and/or a decrease in energy production prevent body growth and fat deposition. Therefore, it is likely that disorders of energy production and/or expenditure may contribute to the low growth of TauTKO mice.

Plasma insulin levels both before and after glucose injection are lower in TauTKO mice than in WT mice, although TauTKO mice are more tolerant to glucose. We also found that TauTKO contain fewer β cells in the pancreas than do those of the WT mice. These data indicate that taurine is necessary for β-cell function. Therefore, to maintain the islet taurine content by taurine intake may be a good strategy for prevention of diabetes due to islet β cell disorders. Previously, it has been reported that taurine administration for 4 weeks enhances both the growth of the β islets of the pancreas and the degree of insulin secretion (38). Furthermore, taurine protects the β cells from death or a functional defect induced by several stresses, such as hyperglycemia, hyperlipidemia and streptozotocin (28–30). Moreover, taurine treatment delays the onset of diabetes in NOD mice which genetically develop autoimmune diabetes caused by the infiltration of the pancreatic islets by mononuclear leukocytes (39). Meanwhile, HFD-induced islet hypertrophy was also attenuated by taurine supplementation (40). Several mechanisms are expected to underlie the protective role of taurine on β-cell dysfunction. i) Taurine suppresses high glucose-induced reactive oxygen species produced in β-cells (28). ii) Modulation of mitochondrial calcium by taurine may be protective. Taurine treatment improves glucose-stimulated insulin secretion in β-cells overexpressing uncoupling protein-2, an effect associated with an improvement in mitochondrial Ca^{2+} handling (25). iii) Taurine treatment prevents the accumulation of ubiquitinated protein induced by high glucose in β-cells, suggesting that taurine may contribute to the stabilization of protein folding (41). Lack of these beneficial roles of taurine in islet by taurine deficiency may be detrimental to β cell function and survival.

In conclusion, taurine deficiency affects multiple mechanisms of glucose metabolism. The present study suggests that taurine plays an important role in the maintenance of normal substrate metabolism and energy production. The present study also raises the possibility that treatment of diabetic patients with taurine may be useful by protecting pancreatic β-cell function.

Conflict of interest

None declared.

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