# Chapter 14
# Taurine Supplementation Restores Insulin Secretion and Reduces ER Stress Markers in Protein-Malnourished Mice

**Thiago Martins Batista, Priscilla Muniz Ribeiro da Silva, Andressa Godoy Amaral, Rosane Aparecida Ribeiro, Antonio Carlos Boschero, and Everardo Magalhães Carneiro**

**Abstract** Endoplasmic reticulum (ER) stress is a cellular response to increased intra-reticular protein accumulation or poor ER function. Chronic activation of this pathway may lead to beta cell death and metabolic syndrome (MS). Poor nutrition during perinatal period, especially protein malnutrition, is associated with increased risk for MS in later life. Here, we analyzed the effects of taurine (TAU) supplementation upon insulin secretion and ER stress marker expression in pancreatic islets and in the liver from mice fed a low-protein diet. Malnourished mice had lower body weight and plasma insulin. Their islets secreted less insulin in response to stimulatory concentrations of glucose. TAU supplementation increased insulin secretion in both normal protein and malnourished mice. Western blot analysis revealed lower expression of the ER stress markers CHOP and ATF4 and increased phosphorylation of the survival protein Akt in pancreatic islets of TAU-supplemented mice. The phosphorylation of the mitogenic protein extracellular signal-regulated kinase (ERK1/2) was increased after acute incubation with TAU. Finally, the ER stress markers p-PERK and BIP were increased in the liver of malnourished mice and TAU supplementation normalized these parameters.

T.M. Batista (✉) • P.M.R. da Silva • A.C. Boschero • E.M. Carneiro
Departamento de Biologia Funcional e Estrutural, Instituto de Biologia,
Universidade Estadual de Campinas, SP, Brazil
e-mail: thiagombatista@yahoo.com.br

A.G. Amaral
Divisão de Nefrologia e Medicina Molecular,
Universidade de São Paulo, São Paulo, SP, Brazil

R.A. Ribeiro
Núcleo em Ecologia e Desenvolvimento Sócio-Ambiental de Macaé (NUPEM),
Universidade Federal do Rio de Janeiro (UFRJ), Macaé, RJ, Brazil

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In conclusion, malnutrition leads to impaired islet function which is restored with TAU supplementation possibly by increasing survival signals and lowering ER stress proteins. Lower ER stress markers in the liver may also contribute to the improvement of insulin action on peripheral organs.

## Abbreviations

| | |
|---|---|
| ATF4 | Activating transcription factor 4 |
| BIP | Binding immunoglobulin protein |
| CHOP | *C/EBP* homologous protein |
| ER | Endoplasmic reticulum |
| ERK1/2 | Extracellular signal-regulated kinase |
| IRE-1 | Inositol-requiring enzyme-1 |
| PERK | PKR-like ER kinase |
| SERCA | Sarco(endo)plasmic reticulum $Ca^{2+}$-ATPase |
| TAU | Taurine |

## 14.1 Introduction

The ER is a highly specialized organelle where newly synthesized proteins are folded into their tridimensional structure which is crucial for their biological activity (Hotamisligil 2010). ER stress is a cellular response activated by the intra-reticular accumulation of misfolded proteins due to increased protein synthesis or poor ER function. Adequate protein folding is dependent on ER $Ca^{2+}$ stores that are maintained by the sarco(endo)plasmic reticulum $Ca^{2+}$-ATPase (SERCA) pump that actively transports $Ca^{2+}$ from the cytoplasm to the ER lumen (Eizirik et al. 2008). In fact, ER $Ca^{2+}$ depletion using SERCA pump inhibitors such as thapsigargin leads to impaired protein folding capacity and activation of ER stress response initiated by the ER membrane-residing proteins PKR-like ER kinase (PERK), inositol-requiring enzyme-1 (IRE1), and activating transcription factor-6 (ATF6) (Lytton et al. 1991; Lin et al. 2008). In addition, ER stress immediately inhibits protein synthesis that occurs through the PERK/eIF2/ATF4 branch of this pathway. Persistence of the stressing conditions increases the expression of the transcription factor C/EBP homologous protein (CHOP) leading to cell death via apoptosis (Hotamisligil 2010).

Poor nutrition during gestation and early life can predispose to the development of metabolic disturbances in adulthood such as hypertension, obesity, and type 2 diabetes mellitus (Remacle et al. 2007). Previous studies showed that low-birth-weight children had increased risk for becoming insulin resistant in adulthood (Hales and Barker 1992; Jaquet et al. 2000). Increased ER stress was already reported in protein malnutrition (Sparre et al. 2003; Vo and Hardy 2012) as well as

type 2 diabetes (Ozcan et al. 2004; Cnop et al. 2012) and may be the molecular link between these conditions.

Taurine (TAU) is a sulfur-containing amino acid know to exert positive effects upon beta cell function and glucose homeostasis (Nakaya et al. 2000; Tsuboyama-Kasaoka et al. 2006; Carneiro et al. 2009; Ribeiro et al. 2009; Ribeiro et al. 2012). Plasma TAU levels are reduced in plasma of protein-restricted dams and their fetuses (Cherif et al. 1998). It was previously reported by our group that TAU supplementation to malnourished rats normalized insulin secretion and glucose tolerance and increased protein expression of SERCA3 in pancreatic islets (Batista et al. 2012), suggesting improved islet ER function. Here we assessed the effects of TAU supplementation upon insulin secretion and ER stress markers in pancreatic islets and in the liver from malnourished mice.

## 14.2 Methods

### *14.2.1 Animals and Groups*

All experiments were approved by the ethics committee at UNICAMP. The studies were carried out on 21-day-old male Swiss mice obtained from the breeding colony at UNICAMP and maintained at 22 ± 1°C, on a 12-h light–dark cycle, with free access to food and water. The mice were distributed into four groups: mice that received a diet containing 17% of protein without (NP) or with 2.5% of TAU in their drinking water (NPT), or mice submitted to an isocaloric diet containing 6% of protein (low-protein diet) without (LP) or with TAU supplementation (LPT). During experimental period, body weight was monitored weekly. Diet composition was previously reported (Filiputti et al. 2008).

### *14.2.2 Plasma Insulin*

At the end of the diet and supplementation period, anesthetized fed mice were decapitated and their blood was collected and centrifuged at 10,000 rpm for 5 min at 4°C. Plasma was collected and stored at −20°C. Plasma insulin was measured by radioimmunoassay (RIA; as previously reported by Ribeiro et al. 2010).

### *14.2.3 Islet Isolation and Static Insulin Secretion*

Islets were isolated by collagenase digestion of the pancreas. For static incubations, five islets from each group were first incubated for 30 min at 37°C in Krebs–bicarbonate (KBR) buffer with the following composition: NaCl 115 mmol/L, KCl 5 mmol/L, CaCl2 2.56 mmol/L, MgCl2 1 mmol/L, NaHCO3 10 mmol/L, and

HEPES 15 mmol/L, supplemented with 5.6 mmol/L glucose and 3 g of BSA/L, and equilibrated with a mixture of 95% $O_2$/5% $CO_2$ to give pH 7.4. This medium was then replaced with fresh buffer and the islets were incubated for 1 h with 2.8, 11.1, 16.7, or 22.2 mmol/L glucose. At the end of the incubation, the supernatant was collected and insulin of the medium was measured by RIA.

### *14.2.4 Western Blot*

Liver fragments and pancreatic islets were homogenized in extraction buffer containing 100 mmol/L Tris pH 7.5, 10 mmol/L sodium pyrophosphate, 100 mmol/L sodium fluoride, 10 mmol/L EDTA, 10 mmol/L sodium vanadate, 2 mmol/L PMSF, and 1% Triton X-100. The extracts were then centrifuged at 12,000 rpm at 4°C for 40 min to remove insoluble material. The protein concentration in the supernatants was assayed using the Bradford dye method (Bradford 1976). Next, samples were treated with a Laemmli sample buffer containing dithiothreitol. After heating at 95°C for 5 min, the proteins were separated by electrophoresis (30–70 μg protein/lane, 10% gels). Following electrophoresis, proteins were transferred to nitrocellulose membranes. The membranes were treated overnight with a blocking buffer (5% nonfat dried milk, 10 mmol/L Tris, 150 mmol/L NaCl, and 0.02% Tween 20) and were subsequently incubated with specific antibodies against p-Akt, Akt, p-ERK, ERK, ATF4, CHOP, α-tubulin (Santa Cruz Biotechnology Inc., Santa Cruz, CA, USA), and p-PERK, BIP (Cell Signaling Inc. Danvers, MA, USA). Detection was performed after 2-h incubation with a horseradish peroxidase-conjugated secondary antibody (1:10,000, Invitrogen, São Paulo, SP, BRA). The band intensities were quantified by optical densitometry using the free software, Image J Tool (http://ddsdx.uthscsa.edu/dig/itdesc.html).

### *14.2.5 Statistical Analysis*

Results are presented as means ± SEM for the number of determinations (n) indicated. The statistical analyses were carried out using two-way analysis of variance (ANOVA) followed by the Newman–Keuls post hoc test ($P \leq 0.05$) and performed using GraphPad Prism version 4.00 for Windows (GraphPad Software, San Diego, CA, USA).

## 14.3 Results

### *14.3.1 Growth Analysis*

Body weight (BW) was recorded weekly as illustrated in Fig. 14.1a. Total BW, calculated by the area under curve (AUC), was reduced in LP compared with NP mice ($P < 0.001$; Fig. 14.1b). TAU supplementation had no effect on BW of either group.

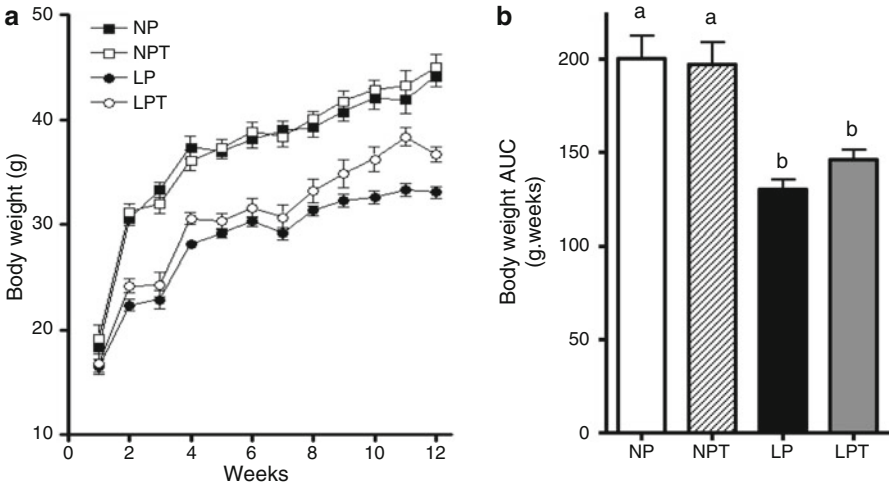


**Fig. 14.1** (**a**) Body weight and (**b**) area under growth curve (AUC) of NP, NPT, LP, and LPT mice. Values are mean ± SEM ($n = 8$); different letters over bars indicate statistical difference; $P < 0.05$ (two-way ANOVA, Newman–Keuls post hoc test)

### *14.3.2 Plasma Insulin and Insulin Secretion*

Fed plasma insulin levels were reduced in LP mice compared with NP ($P < 0.05$, Fig. 14.2a). TAU supplementation had no effect on this parameter.

Insulin release by isolated islets from LP mice was reduced at all stimulatory glucose concentrations (11.1–22.2 mmol/L) when compared to NP group (Fig. 14.2b, $P < 0.05$). TAU supplementation increased insulin secretion in NPT islets in the presence of 16.7 and 22.2 mmol/L glucose ($P < 0.03$) and at all glucose concentrations LPT islets showed a similar insulin secretion to that observed of NP islets (Fig. 14.2b).

### *14.3.3 ER Stress Marker Protein Expression*

Isolated islets from LP mice showed a similar expression of ER stress markers compared with NP (Fig. 14.3). TAU supplementation significantly reduced CHOP protein expression in both NPT and LPT islets compared with NP ($P < 0.05$ and $P < 0.01$, respectively, Fig. 14.3a) and lowered islet ATF4 protein content only in NPT group ($P < 0.05$, Fig. 14.3b). PERK phosphorylation (p-PERK) and BIP expression were not altered between groups (Fig. 14.3c, d). The phosphorylated form of the pro-survival protein Akt (p-Akt) was increased in NPT compared with NP islets ($P < 0.05$; Fig. 14.3e). Also, NP pancreatic islets incubated with 3 mmol/L TAU presented higher ERK1/2 phosphorylation (p-ERK1/2) after 90 s ($P < 0.001$) and

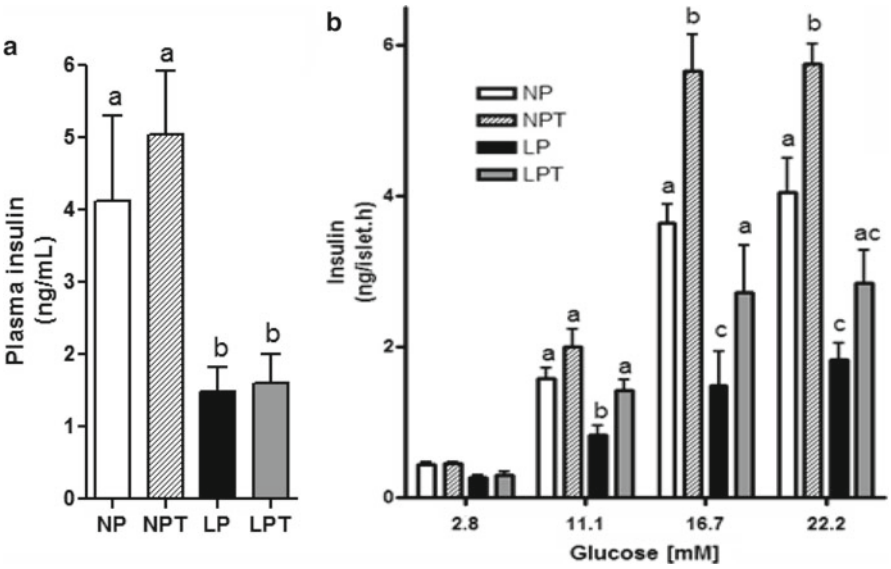


**Fig. 14.2** (**a**) Fed plasma insulin ($n = 5$–16) and (**b**) glucose-induced insulin secretion in isolated pancreatic islets ($n = 8$) from NP, NPT, LP, and LPT mice. Values are mean ± SEM; different letters over bars indicate statistical difference; $P < 0.05$ (two-way ANOVA, Newman–Keuls post hoc test)

15 min ($P < 0.05$) and returned to normal levels after 1 h (Fig. 14.3f). Akt phosphorylation was not altered by acute incubation with TAU (Fig. 14.3g).

Despite no modification in islet protein ER stress maker profile in LP islets, p-PERK and BIP protein expression in the liver of LP mice was higher than in NP mice ($P < 0.05$; Fig. 14.4a, b). Increased liver ER stress marker expression in LPT mice was prevented by TAU supplementation.

## 14.4 Discussion

Here, we describe that mice fed on a low-protein diet have lower BW and plasma insulin and isolated islets from these mice secrete less insulin in response to glucose (Figs. 14.1 and 14.2). These findings are in accordance with previous studies from our group (Amaral et al. 2010; Filiputti et al. 2010; da Silva et al. 2012) and others (Chen et al. 2009; Theys et al. 2009).

In this study, TAU supplementation enhanced glucose-stimulated insulin secretion (GSIS) in isolated islets from control and malnourished mice (Fig. 14.2b). TAU supplementation was already reported to enhance beta cell responsiveness to nutrients and other stimuli (Carneiro et al. 2009; Ribeiro et al. 2009). These effects of TAU were mainly due to the improvement upon beta cell

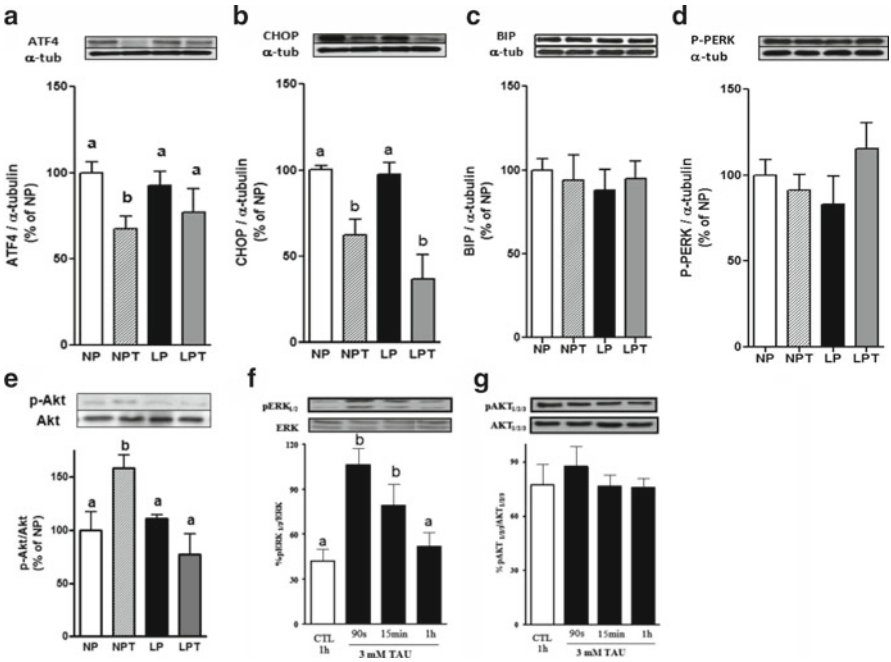


**Fig. 14.3** Protein expression of (**a**) CHOP, (**b**) ATF4, (**c**) BIP, (**d**) p-PERK, and (**e**) p-Akt and α-tubulin (internal control) in islets from NP, NPT, LP, and LPT mice ($n = 4–7$). Groups of fresh isolated islets from NP mice were incubated with 3 mmol/L TAU for evaluation of (**f**) p-$ERK_{1/2}$/$ERK_{1/2}$ and (**g**) pAkt/Akt ratio. Values are mean ± SEM ($n = 5$); different letters *over bars* indicate statistical difference; $P < 0.05$ (two-way ANOVA, Newman–Keuls post hoc test)

$Ca^{2+}$ handling, since enhanced $Ca^{2+}$ uptake and the β2 subunit of the voltage-sensitive $Ca^{2+}$ channel protein expression were observed in islets from TAU-treated mice (Ribeiro et al. 2009). Another finding is that TAU supplementation enhanced intracellular $Ca^{2+}$ mobilization using the cholinergic agonist, carbachol (Ribeiro et al. 2010), suggesting an increased compartmentalization of the cation into the ER that may be maintained by SERCA3, since isolated islets from malnourished and control TAU-supplemented rats presented higher expression of this protein (Batista et al. 2012).

Considering these actions of TAU upon intra-reticular $Ca^{2+}$ stores and that maternal protein-restriction leads to increased ER stress marker expression in the offspring (Sparre et al. 2003; Vo and Hardy 2012), we decided to evaluate the expression of these proteins in pancreatic islets and in the liver from malnourished mice supplemented with TAU. Western blot analysis revealed that malnutrition did not alter the expression of ER stress markers in pancreatic islets but PERK phosphorylation and BIP expression were increased in the liver from malnourished mice (Figs. 14.3 and 14.4). It was reported that young malnourished rats display increased glucose tolerance and insulin sensitivity (Reis et al. 1997; da Silva et al. 2012), but at 15

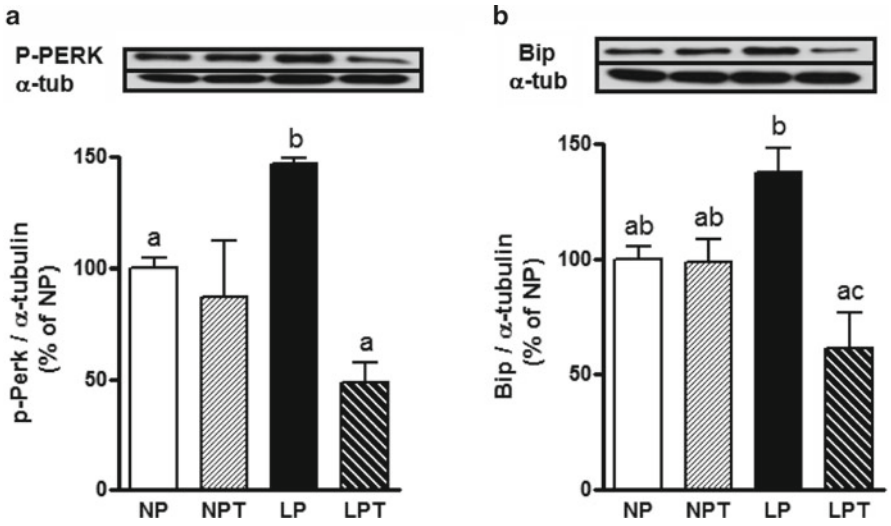


**Fig. 14.4** Protein expression of (**a**) p-PERK and (**b**) BIP in liver of NP, NPT, LP, and LPT mice. Values are mean ± SEM ($n = 5$); different letters over bars indicate statistical difference; $P < 0.05$ (two-way ANOVA, Newman–Keuls post hoc test)

months of age insulin signaling in adipocytes was impaired (Ozanne et al. 2001) and at 17 months, these rats become diabetic (Petry et al. 2001). Since ER stress impairs insulin signaling and is associated to the pathogenesis of obesity and type 2 diabetes (Ozcan et al. 2004; Zhou et al. 2011), we believe that this pathway may link the transition from increased sensitivity to insulin resistance that occurs throughout the life span in malnourished rodents.

Finally, we observed that TAU supplementation normalized ER stress markers in the liver from malnourished mice and lowered their expression in pancreatic islets from both supplemented groups (Figs. 14.3 and 14.4). TAU was reported to reduce ER stress induced by several agents in different tissues and cell types. In primary neuron cultures, TAU treatment reduces hypoxia and glutamate-induced ER stress (Pan et al. 2012). TAU protects H4IIE liver cells from palmitate-induced cell death and caspase-3 activation and prevents hepatic steatosis in high sucrose-fed rats through suppression of the PERK/eIF2/ATF4 branch of the ER stress pathway (Gentile et al. 2011). The proper mechanisms by which TAU reduces ER stress are still not clear. Here we show for the first time that TAU supplementation increases p-Akt in pancreatic islets and acute incubation with this amino acid increased islet p-ERK1/2 content (Fig. 14.3e, f). These findings could be explained by a direct interaction of TAU with the insulin receptor leading to its activation (Maturo & Kulakowski 1988; Carneiro et al. 2009). Transgenic mice overexpressing Akt in the heart showed prevention of contractile dysfunction provoked by tunicamycin, a chemical that induces ER stress (Zhang et al. 2011). Thus, TAU-induced increase in Akt activation (Fig. 14.3e) could contribute to decreased ER stress protein expression in pancreatic islets.

## 14.5 Conclusion

In conclusion, our data indicate that ER stress is present in the liver from protein-malnourished mice and this could be a risk factor for the development of insulin resistance and type 2 diabetes in later life. TAU supplementation increases insulin secretion capacity and reduces ER stress proteins in pancreatic islets and in the liver possibly through increased Akt and ERK 1/2 activation.

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