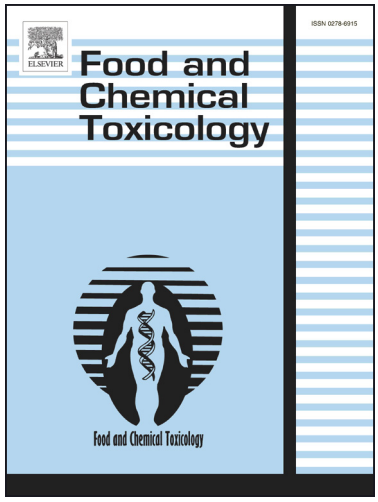

Taurine Ameliorates Neuropathy via Regulating NF-κB and Nrf2/HO-1 Signaling Cascades in Diabetic Rats

Can Ali Agca, Mehmet Tuzcu, Armagan Hayirli, Kazim Sahin

PII: S0278-6915(14)00257-9
DOI: http://dx.doi.org/10.1016/j.fct.2014.05.023
Reference: FCT 7983

To appear in: *Food and Chemical Toxicology*

Received Date: 31 December 2013
Accepted Date: 27 May 2014

Please cite this article as: Agca, C.A., Tuzcu, M., Hayirli, A., Sahin, K., Taurine Ameliorates Neuropathy via Regulating NF-κB and Nrf2/HO-1 Signaling Cascades in Diabetic Rats, *Food and Chemical Toxicology* (2014), doi: http://dx.doi.org/10.1016/j.fct.2014.05.023

Taurine Ameliorates Neuropathy via Regulating NF-κB and Nrf2/HO-1 Signaling Cascades in Diabetic Rats

Can Ali Agca[a], Mehmet Tuzcu[b], Armagan Hayirli[c], Kazim Sahin[d*]

[a]*Department of Molecular Biology and Genetics, Faculty of Science, Bingol University, Bingol, Turkey*

[b]*Department of Biology, Faculty of Science, Firat University, Elazig, Turkey*

[d]*Department of Animal Nutrition, Faculty of Veterinary, Ataturk University, Erzurum, Turkey*

[c]*Department of Animal Nutrition, Faculty of Veterinary Medicine, Firat University, Elazig, Turkey*

Running Title: Taurine in Neuropathy

*Corresponding author: Kazim Sahin, DVM, Ph.D.

Professor of Animal Nutrition,

Faculty of Veterinary Medicine,

Firat University, 23119 Elazig, Turkey

Phone: +90 424 237 0000 Ext: 3938

Fax: +90 424 238 8173

Email: nsahinkm@yahoo.com

Abstract

Diabetic neuropathy is one of common complications of diabetes mellitus. Hyperglycemiainduced oxidative stress involves in the development of diabetic neuropathy, which could be reversed by supplementation of taurine, an endogenous antioxidant. This experiment was conducted to evaluate alterations in the expressions of transcription factors [nuclear factor kappa B (NF-κB), nuclear factor-E2-related factor-2 (Nrf2), and hemeoxygenase 1 (HO-1)] and glucose transporters and glucose metabolism in the brain of diabetic rats. In a 2x2 factorially arranged groups, taurine (2%) or water was administered per orally to healthy and streptozotocin (STZ)-induced diabetic rats (n=10 per group) for 8 weeks. Diabetes was associated with weight loss, hyperglycemia, and oxidative stress as reflected by increased serum malondialdehyde (MDA) concentrations. Diabetic rat brains had increased the NF-κB expression and decreased the Nrf2, HO-1, GLUT1,3 expressions as compared to

healthy rat brains. Supplemental taurine did not alter body weight and blood glucose concentration, but partially reduced serum MDA concentration in the diabetic rats. Taurine also partially alleviated neuroinflammation as reflected by suppressed the NF-κB expression and enhanced the Nrf2, HO-1, GLUT1,3 expressions in the diabetic rats. In conclusion, taurine reduces the severity of oxidative stress through activating antioxidative defense signaling pathway in diabetic rat brain.

Keywords: Diabetic neuropathy; oxidative stress; taurine; NF-κB; Nrf2; HO-1

Abbreviations:

ARE, antioxidant response element; Body weight, BW; GLUT1, glucose transporter protein 1; GLUT3, glucose transporter protein 3; HO-1, heme oxygenase 1; IR, insulin receptor; Keap1, Kelch-like ECH-associated protein; MDA, malondialdehyde; NF-κB, nuclear factor kappa B; Nrf2, nuclear factor-E2-related factor-2; ROS, reactive oxygen species; STZ, streptozotocin.

1. Introduction

Diabetes mellitus is a chronic metabolic disorder leading to serious complications, such as neuropathy, retinopathy, and autonomic dysfunctions. Neuropathy is one of the most common complications and its prevalence is more than 50% among diabetic patients (Sima and Sugimoto, 1999). Diabetes is associated with an increased oxidative stress due to excessive production of reactive oxygen species (ROS) and/or defects in antioxidant defense system, which lead to nerve hypoxia/ischemia, impaired nerve growth factor support (Van Dam, 2002; McCrimmon et al., 2012), and neuroinflammation (Vincent et al., 2008) as well as neuronal damage in the central and peripheral nervous systems (Little et al., 2007).

Nuclear factor-kappa B (NF-κB), a transcription factor, has complex roles in neuron survival and functions as well as cell cycle changes when cellular stress is provoked, ROS is produced and DNA damage is occurred (Massa et al., 2006; Mosley et al., 2006). It involves in the pathogenesis of several inflammatory diseases including diabetic neuropathy (Cameron and Cotter, 2008). The activation of NF-κB is extremely important for both oxidative stress and inflammatory signaling pathway in diabetic rat brain.

Nuclear factor erythroid 2-related factor 2 (Nrf2), another transcription factor, is considered the primary cellular defence against cytotoxicity caused by oxidative stress, through regulating induction of phase II detoxifying (glutathione S-transferases) or antioxidant enzymes (heme oxygenase-1, HO-1) (Jaiswal, 2004; Itoh et al., 2004). Nrf2 retains in the cytoplasm with Kelch-like ECH-associated protein (Keap1) under normal conditions and is separated from Keap1, and then is Nrf2 is translocated into the nucleus where it binds to antioxidant response element (ARE) to augment a number of antioxidative genes when severe oxidative stress occurs (Itoh et al., 1999; Li and Kong, 2009). Namely, Nrf2 is evaluated as the hub of defense against oxidative stress in the pathophysiology of diabetic neuropathy (Negi et al., 2011a).

Because glucose is a predominant fuel, its homeostasis is crucial to cerebral tissues. Insulin in the central nervous system is highly critical in terms of whole body metabolism and nutrient availability as well as uptake (Porte et al., 2005; Anitha et al., 2012). Insulin-stimulated glucose metabolism occurs in the brain-insulin receptors (IR). Glucose transporters (GLUTs) play essential functions in the delivery of glucose. GLUT1-3 are neuron-specific glucose transporter and responsible for neuronal glucose homeostasis (Duelli and Kuschinsky, 2001). Intracellular vesicles storing GLUTs are translocated to the plasma membrane and facilitate glucose uptake during insulin stimulation. Under diabetic conditions, reduced

expression of GLUTs results in the disruption of insulin signaling and glucose uptake and utilization. Overall, these alterations favor hyperglycemia (Nizamutdinova et al., 2009).

Several studies suggest that some micronutrient including taurine can prevent or reverse the hyperglycemia-induced cerebral and neuronal dysfunctions (Obrosova et al., 2001; Terada et al., 2011; Ito et al., 2012). Taurine, a free sulfonic acid, is synthesized from the metabolism of methionine and cysteine mainly in the liver and brain (Jacobsen and Smith, 1968; Tappaz et al., 1992). Meat, seafood, and milk are rich in taurine (Huxtable, 1992). Taurine is abundantly found in a variety of organs of most mammals, including brain, heart, and kidney, but it is essential nutrient in cats (Hansen, 2001). It acts as a neuromodulator, a neuroprotector, an antioxidant, and an anti-inflammatory agent (Hagar, 2004; Banerjee et al., 2008; Pan et al., 2010; 2011; Sun et al., 2011). It has been reported that insulin dependent and non-insulin dependent diabetic patients had low plasma taurine concentrations (Franconi et al., 2004; 2006; Schaffer et al., 2009). The hippocampus and hypothalamus taurine contents were shown to increase by taurine supplementation (Dawson et al.,1999) because exogenous taurine could pass blood-brain barrier upon ingestion (Huxtable, 1992). Taurine supplementation has been shown to have rewarding effects on reducing the severity of diabetes mellitus and diabetic complications through ameliorating oxidative stress (Obrosova and Stevens, 1999; Obrosova et al., 2001; Franconi et al., 2004; Ito et al., 2012) and enhancing insulin secretion (Chang and Kwon, 2000; Pandya et al., 2010). However, the exact mechanism by which supplemental taurine exerts hypoglycemic action in diabetic subjects has not been fully elucidated. Therefore, this experiment was conducted to evaluate alterations in the transcription factors and GLUTs and glucose metabolism in the cerebrum of diabetic rats.

2. Materials and methods

2.1. Animals, experimental design, and diabetes induction

Forty male Wistar rats (8 weeks old; 180–200 g) were obtained from the Animal Experimental Unit, Firat University. Rats were kept in a room with a temperature of 22±3°C and relative humidity of 55±5%% and subjected to 12 h light:12 h dark cycle. The animals were on a standard diet with tap water available *ad libitum*. All animal procedures were in accordance with the guidelines for care and use of laboratory animals and were approved by the Animal Experimentation Ethics Committee of Firat University (Elazig, Turkey).

After providing compliance with the conditions the rats were randomly divided into 4 groups, each containing 10 animals. The groups were as follows: (i) Control group: Rats administered with water as placebo, (ii) Taurine group: Rats administered with 2% taurine orally (w/v in water), (iii) STZ group: Rats administered with single dose of streptozotocin (STZ) to induce diabetes, and (iv) STZ+Taurine group: Diabetic rats treated with taurine orally (2% w/v in water) starting from day 4 relative to STZ injection. The experiment lasted for 8 weeks.

Diabetes was induced by a single intraperitoneal injection of STZ after overnight fasting [60 mg/kg body weight (BW) in 0.1 M cold citrate buffer (pH 4.5), (Sigma, St. Louis, MO, USA)]. The positive control group was given single dose citrate buffer within water via intraperitoneal injection. Taurine (Carl Roth GmbH, Karlsruhe, Germany) was dissolved in water (2%, w/v) (Yao et al., 2009).

2.2. Laboratory analyses

2.2.1. Blood glucose and serum malondialdehyde (MDA) concentrations

Fasting blood glucose concentration was measured using a portable glucometer (Accu-Check Active, Roche Diagnostics, Mannheim, Germany) on days 2, 28, and 56 relative to the experiment.

Blood samples were centrifuged at 3000 ×*g* for 10 min and sera were separated for analysis of MDA using a fully automatic HPLC (Shimadzu, Kyoto, Japan), consisting of a pump (LC-20AD), a UV–visible detector (SPD-20A), an inertsil ODS-3 C18 column (250 X 4.6 mm, 5 m), a column oven (CTO-10ASVP), an autosampler (SIL-20A), a degasser unit (DGU-20A5), and a computer system with LC solution Software (Shimadzu) (Barim and Karatepe, 2010).

2.2.2. Western blot analysis

Rats were sacrificed by cervical dislocations and brains were promptly removed at the end of the experiment. Prior to protein isolation, the brain sample was homogenized (10% w/v) in an ice-cold 1 ml of hypotonic buffer A containing 10 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES, pH 7.8), 10 mM KCl, 2 mM $MgCl_2$, 1 mM dithiothreitol (DTT), 0.1 mM ethylene diaminetetraacetic acid (EDTA), and 0.1 mM phenylmethylsulfonyl fluoride (PMSF). The homogenates were added with 80 µl of 10% Nonidet P-40 (NP-40) solution and then centrifuged at 14,000 ×*g* for 2 min. The supernatant was collected as a cytosolic fraction for HO-1 and GLUTs 1,3. The precipitated nuclei was washed with 500 µl of buffer A plus 40 µl of 10% NP-40, centrifuged, re-suspended in 200 µl of buffer C [50 mM HEPES (pH 7.8), 50 mM KCl, 300 mM NaCl, 0.1 mM EDTA), 1 mM DTT, 0.1 mM PMSF, and 20% glycerol], and re-centrifuged for 5 min at 14,800 ×*g*. The supernatant containing nuclear protein was collected for determination of NF-κB and Nrf2. Concentration of the protein was determined according to the procedure described by Lowry using a commercial protein assay kit (Sigma).

For SDS-PAGE buffer containing 2% β-mercaptoethanol was added to the supernatant. Equal amounts of protein (50 µg) were electrophorezed and subsequently transferred to nitrocellulose membranes (Schleicher and Schuell Inc., Keene, NH, USA).

Nitrocellulose blots were washed twice in phosphate-buffered saline (PBS) and blocked with 1% bovine serum albumin in PBS for 5 min at room temperature for 1 h prior to application of the primary antibody (Abcam, Cambridge, UK). Primary antibody was diluted (1:1000, 1:1000, 1:1000, 1μg/ml, 1:8000 for NF-κB, Nrf2, HO-1, and GLUT1, and GLUT3, respectively) in the same buffer containing 0.05% Tween-20. The nitrocellulose membrane was incubated overnight at 4ºC with protein antibody. The blots were washed and incubated with horseradish peroxidase-conjugated goat anti-mouse IgG (Abcam). Protein loading was controlled using a monoclonal mouse antibody against β-actin antibody (Abcam). Blots were performed at least three times to confirm data reproducibility. Bands were analyzed densitometrically using an image analysis system (Image J; National Institute of Health, Bethesda, USA).

2.2.3. Data analysis

Data were analyzed by a one-way ANOVA using the GLM Procedure (SPSS version 13.0, Chicago, IL, USA). The Tukey's post-hoc test option was employed to elucidate group mean differences. Difference was considered significant at $P<0.05$.

3. Results

3.1. Effects of taurine on BW and blood parameters in diabetic rats

Body weight and blood parameters are shown in the Table 1. Taurine administration did not alter final BW. Diabetes caused 29.2% regression in final BW as compared to the control group ($P<0.05$). However, taurine administration did not recover BW loss in the diabetic rats.

Taurine administration did not affect blood glucose concentration. Diabetic rats had a 5.28-fold higher blood glucose concentration than the control rats ($P<0.0001$). Despite taurine administration blood glucose concentration of the diabetic rats remained unchanged.

Serum MDA concentrations of rats in the control and taurine groups were similiar. Diabetes was associated with a 2.37-fold elevation in serum MDA concentration (P<0.0001). Taurine administration partially alleviated oxidative stress, as reflected by 33.59% reduction serum MDA concentration as compared to the unsupplemented diabetic rats (P<0.05).

3.2. Effects of taurine on NF-κB and Nrf2/HO-1 expressions in diabetic rats

Taurine administration did not affect the NF-κB expression in the healthy rats. Diabetes caused a 65.52%-increase in the NF-κB expression (Fig. 1A; P<0.0001). Taurine administration partially suppressed elevation in the NF-κB expression in the diabetic rats (Fig. 1A; 25.07% decrease; P<0.05).

Taurine administration affected expressions of neither Nrf2 (Fig. 1B) nor HO-1 (Fig. 1C) in healthy rats. Diabetic status, however, was associated with 50.39 and 61.96% suppressions in the Nrf2 (Fig. 1B) and HO-1 (Fig. 1C) expressions, respectively (P<0.0001 for both). While taurine administration partially alleviated suppression in the Nrf2 expression (Fig. 1B; 36.27% increase; P<0.05) in the diabetic rats, it was not affective to ameliorate suppression in the HO-1 expression (Fig. 1C).

3.3. Effects of taurine on GLUT1 and GLUT3 expressions in diabetic rats

The GLUT1 (Fig. 1D) and GLUT3 (Fig. 1E) expressions in the healthy rats did not change in response to taurine administration. Diabetes was associated with 35.19 and 46.65% suppressions in their expressions, respectively (Fig. 1D and E; P<0.0001 for both). Taurine administration to the diabetic rats partially alleviated suppressions in the expressions of both GLUT1 (Fig. 1D; 22.59%) and GLUT3 (Fig. 1E; 22.78%) in the diabetic rats (P<0.05 for both).

4. Discussion

The BW loss, hyperglycemia, and oxidative stress (Table 1) ascertained establishment of diabetes induction. The weight loss in diabetes results from increased muscle wasting (Ravi et al., 2004). The destruction of pancreatic β cells by STZ administration can lead to hyperglycemia (Yamamoto et al., 1981) and ROS generation (Shanmugam et al., 2011) as reflected by elevated serum MDA concentration. Despite occurrence of a partial alleviation in oxidative stress, weight loss and hyperglycemia were not normalized by taurine treatment in the diabetic rats (Table 1).

The etiology of diabetic neuropathy is multifactorial, which includes oxidative stress resulting from hyperglycemia (Vincent et al., 2004; Edwards et al., 2008). The role of oxidative stress in the pathogenesis of diabetic complications is linked to either enhanced ROS production or suppressed ROS-scavenging capacity. In agreement with our data (Table 1), Obrosova et al. (2001) reported that taurine supplementation reduced an increase in serum MDA concentration in the diabetic rats. Das et al. (2012) also reported that STZ-induced diabetes decreased BW and caused hyperglycemia and hypoinsulinemia, elevated the cardiac damage markers and led to alterations in plasma lipid profile. The diabetic rats had a decreased activity of antioxidant enzymes and increased activity of oxidant enzymes (*i.e.*, xanthine oxidase) as well as increased level of lipid peroxidation, protein carbonylation, ROS generation, proinflammatory cytokines' release (Das et al., 2012). Taurine treatment normalized hypoglycemia and alleviated diabetes-evoked oxidative stress (Das et al., 2012). In another experiment, it was shown that taurine supplementation to diabetic rats reduced plasma MDA and nitric oxide concentrations and increased plasma glutathione level as compared to untreated diabetic rats (Pandya et al., 2010). Water consumption is increased in diabetic subjects due to polydipsia. The suggested taurine level in diabetes studies is 1-2%

(Das et al., 2012; Yao et al., 2009). In this study, however, water consumption was not measured. Thus, actual taurine intake remained uncertain for suggestion.

Nrf2 is key regulator of the antioxidative defense pathway (Motohashi and Yamamoto, 2004) and it is activated in STZ-induced diabetes and diabetic neuropathy (Negi et al., 2011a; 2011b). The induction of HO-1 is an adaptive cellular defense response against oxidative stress and protection of cells in pathophysiological states including diabetes (Song et al., 2007). Similar to our data (Fig 1B; Fig. 1C; Table 1), Kumar et al. (2012) also showed decrease in the expressions of Nrf2 and HO-1 as serum MDA increased in experimentally induced diabetic neuropathy. Taurine supplementation partially recovered the expression of HO-1, cytoprotective anti-oxidant enzyme (Fig. 1C), through activating the Nrf2 expression (Fig. 1C).

Normally, Nrf2 is present in the cytosol. Stressing conditions make it be translocated into the nucleus. In hyperglycemia, ROS production stimulates the signal transduction pathway to activate the expressions of the transcription factor NF-κB that helps control the expression of numerous genes involving in inflammation (*i.e*., cytokines, chemokines, growth factors, immune receptors, cellular ligands, and adhesion molecules) (Kuhad and Chopra, 2009). Nuclear factor-kappa B plays a critical role in pathophysiology of diabetic neuropathy and accompanying inflammation and oxidative stress (Cameron and Cotter, 2008; Kumar and Sharma, 2010; Baker et al., 2011; Kumar et al., 2011). These conditions activate the NF-κB expression as a body response (Song et al., 2009; Baker et al., 2011) as in the present experiment (Fig. 1A). Studies coping with taurine supplementation also showed inhibition of NF-κB protein abundance in lung (Giri et al., 2000; Gurujeyalakshmi et al., 2000) and cardiac (Das et al., 20012) tissues, which were associated with suppression of nitric oxide, release of proinflammatory cytokines, and activity of myeloperoxidase.

GLUT1 and GLUT3 are important for the transport of glucose in brain tissue. Glucose transport in the blood-brain barrier is mediated by GLUT1 which is particularly expressed in endothelial cells of blood brain barrier (Virgintino et al., 1997; Vannucci et al., 1998). GLUT-3, a neuron-specific glucose transporter, is solely responsible for the delivery of glucose into neurons (Duelli and Kuschinsky, 2001). A number of studies coping with diabetes show that mRNA abundance of GLUT1 and GLUT3 protein decreases (Reagan et al., 1999; Kainulainen et al., 2003; Zhang et al., 2009). In STZ-induced diabetic animals, glucose utilization by cerebral tissues (Duelli et al., 1994) and glycolytic enzymes' activities (Plaschke and Hoyer, 1993) decrease. Moreover, IR, IGF-1, and GLUT mRNA expressions are suppressed in diabetic rats, which are accompanied by low insulin production (Anitha et al., 2012; Reagan et al., 1999). Duelli et al. (2000) reported that hyperglycemia was associated with reduced GLUT1 expression and unaltered GLUT3 expression in rat brain. Taurine may function directly on IRs and GLUTs to facilitate glucose uptake by the cardiac tissues (Maturo and Kulakowski, 1988; Das et al., 2012). Taurine activates hepatic PI3 Kinase, Akt, hexokinase and augments the translocation of GLUT2 to hepatic membrane in diabetic rats (Rashid et al., 2013). Das et al. (2012) reported that taurine supplementation to diabetic conditions increased phosphorylation at tyrosine residue of IR and IR substrate 1 as well as GLUT4 expressions for uptake by the cardiac tissues. In the present study, diabetic rats had lower GLUT1,3 expressions in the brain than healthy rats (Fig. 1D, Fig. 1E), which were partially enhanced by taurine administration (~23%)..

In conclusion, diabetic status is accompanied by weight loss, hyperglycemia, and oxidative stress as well as enhanced the NF-κB expression and suppressed the Nrf2, HO-1, GLUT1, and GLUT3 expressions. Taurine partially suppressed the NF-κB expression and enhanced Nrf2, HO-1, GLUT1, and GLUT3 expressions. Taurine appears to reduce the severity of oxidative stress through activating antioxidative defense signaling pathway in

diabetic rat brain. In order to determine the need, further studies coping with supplemental taurine in diabetic condition should monitor water intake if it is provided via water.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgements

This work was supported by Firat University (FUBAP–FF.11.23) and partially by the Turkish Academy of Sciences (TUBA).

References

Anitha, M., Abraham, P.M., Paulose, C.S., 2012. Striatal dopamine receptors modulate the expression of insulin receptor, IGF-1 and GLUT-3 in diabetic rats: effect of pyridoxine treatment. European Journal of Pharmacology 696, 54-61.

Baker, R.G., Hayden, M.S., Ghosh, S., 2011. NF-kappaB, inflammation, and metabolic disease. Cell Metabolism 13, 11-22.

Banerjee, R., Vitvitsky, V., Garg, S.K., 2008. The undertow of sulfur metabolism on glutamatergic neurotransmission. Trends in Biochemical Sciences 33, 413-419.

Barim, O., Karatepe, M., 2010. The effects of pollution on the vitamins A, E, C, betacarotene contents and oxidative stress of the freshwater crayfish, Astacus leptodactylus. Ecotoxicology and Environmental Safety 73, 138-142.

Cameron, N.E., Cotter, M.A., 2008. Pro-inflammatory mechanisms in diabetic neuropathy: focus on the nuclear factor kappa B pathway. Current Drug Delivery 9, 60-67.

Chang, K.J., Kwon, W., 2000. Immunohistochemical localization of insulin in pancreatic beta-cells of taurine-supplemented or taurine-depleted diabetic rats. Advances in Experimental Medicine and Biology 483, 579-587.

Das, J., Vasan, V., Sil, P.C., 2012. Taurine exerts hypoglycemic effect in alloxan-induced diabetic rats, improves insulin-mediated glucose transport signaling pathway in heart and ameliorates cardiac oxidative stress and apoptosis. Toxicology and Applied Pharmacology 258, 296-308.

Dawson, R. Jr., Liu, S., Eppler, B., Patterson, T., 1999. Effects of dietary taurine supplementation or deprivation in aged male Fischer 344 rats. Mechanisms of ageing and development 107, 73-91.

Duelli, R., Kuschinsky, W., 2001. Brain glucose transporters: relationship to local energy demand. News in Physiological Sciences 16, 71-76.

Duelli, R., Maurer, M.H., Staudt, R., Heiland, S., Duembgen, L., Kuschinsky, W., 2000. Increased cerebral glucose utilization and decreased glucose transporter Glutl during chronic hyperglycemia in rat brain. Brain Research 858, 338-347.

Duelli**,** R., Schrock, H., Kuschinsky, W., Hoyer, S., 1994. Intracerebroventricular injection of streptozotocin induces discrete local changes in cerebral glucoseutilization in rats. International Journal of Developmental Neuroscience 12, 737-743.

Edwards, J.L., Vincent, A.M., Cheng, H.T., Feldman, E.L., 2008. Diabetic neuropathy: mechanisms to management. Pharmacology & Therapeutics 120, 1-34.

Franconi, F., Di Leo, M.A., Bennardini, F., Ghirlanda, G., 2004. Is taurine beneficial in reducing risk factors for diabetes mellitus? Neurochemical Research 29, 143-150.

Franconi, F., Loizzo, A., Ghirlanda, G., Seghieri, G., 2006. Taurine supplementation and diabetes mellitus. Current Opinion in Clinical Nutrition and Metabolic Care 9, 32-36.

Giri, S.N., Gurujeyalakshmi, G., Wang, Y., 2000. Suppression of bleomycin-induced increased production of nitric oxide and NF-kB activation by treatment with taurine and niacin. Advances in Experimental Medicine and Biology 483, 545-561.

Gurujeyalakshmi, G., Wang, Y., Giri, S.N., 2000. Taurine and niacin block lung injury and fibrosis by down-regulating bleomycin-induced activation of transcription nuclear factor-kappaB in mice. The Journal of Pharmacology and Experimental Therapeutics 293, 82-90.

Hagar, H.H., 2004. The protective effect of taurine against cyclosporine A-induced oxidative stress and hepatotoxicity in rats. Toxicology Letters 151, 335-343.

Hansen, S.H., 2001. The role of taurine in diabetes and the development of diabetic complications. Diabetes/Metabolism Research and Reviews 17, 330-346.

Huxtable, R.J., 1992. Physiological actions of taurine. Physiological Reviews 72, 101-163.

Ito, T., Schaffer, S.W., Azuma, J., 2012. The potential usefulness of taurine on diabetes mellitus and its complications. Amino Acids 42, 1529-1539.

Itoh, K., Tong, K.I., Yamamoto, M., 2004. Molecular mechanism activating Nrf2-Keap1 pathway in regulation of adaptive response to electrophiles. Free Radical Biology & Medicine 36, 1208-1213.

Itoh, K., Wakabayashi, N., Katoh, Y., Ishii, T., Igarashi, K., Engel, J.D.,Yamamoto, M., 1999. Keap1 represses nuclear activation of antioxidant responsive elements by Nrf2 through binding to the amino-terminal Neh2 domain. Genes & Development 13, 76-86.

Jacobsen, J.G., Smith, L.H., 1968. Biochemistry and physiology of taurine and taurine derivatives. American Physiological Society 48, 429-511.

Jaiswal, A.K., 2004. Nrf2 signaling in coordinated activation of antioxidant gene expression. Free Radical Biology & Medicine 36, 1199-1207.

Kainulainen, H., Schumann, A., Vilja, P., Joost, H.G., 1993. In-vivo glucose uptake and glucose transporter proteins GLUT1 and GLUT3 in brain tissue from streptozotocin-diabetic rats. Acta Physiologica Scandinavica 149, 221-225.

Kuhad, A., Chopra, K., 2009. Attenuation of diabetic nephropathy by tocotrienol: involvement of NFkB signaling pathway. Life Sciences 84, 296-301.

Kumar, A., Negi, G., Sharma, S.S., 2011. JSH-23 targets nuclear factor kappa B (NF-kappaB) and reverses various deficits in experimental diabetic neuropathy: effect on neuroinflammation and antioxidant defence. Diabetes, Obesity & Metabolism 13, 750-758.

Kumar, A., Negi, G., Sharma, S.S., 2012. Suppression of NF-κB and NF-κB regulated oxidative stress and neuroinflammation by BAY 11-7082 (IκB phosphorylation inhibitor) in experimental diabetic neuropathy. Biochimie 94, 1158-1165.

Kumar, A., Sharma, S.S., 2010. NF-kappaB inhibitory action of resveratrol: a probable mechanism of neuroprotection in experimental diabetic neuropathy. Biochemical and Biophysical Research Communications 394, 360-365.

Li, W., Kong, A.N., 2009. Molecular mechanisms of Nrf2-mediated antioxidant response. Molecular Carcinogenesis 48, 91-104.

Little, A.A., Edwards, J.L., Feldman, E.L., 2007. Diabetic neuropathies. Practical Neurology 7, 82-92.

Massa, P.T., Aleyasin, H., Park, D.S., Mao, X., Barger, S.W., 2006. NFkappaB in neurons? The uncertainty principle in neurobiology. Journal of Neurochemistry 97, 607-618.

Maturo, J., Kulakowski, E.C., 1988. Taurine binding to the purified insulin receptor. Biochemical Pharmacology 37, 3755-3760.

McCrimmon, R.J., Ryan, C.M., Frier, B.M., 2012. Diabetes and cognitive dysfunction. Lancet 16, 2291-2299.

Mosley, R.L., Benner, E.J., Kadiu, I., Thomas, M., Boska, M.D., Hasan, K., Laurie, C., Gendelman, H.E., 2006. Neuroinflammation, oxidative stress and the pathogenesis of Parkinson's disease. Clinical Neuroscience Research 6, 261-281.

Motohashi, H., Yamamoto, M., 2004. Nrf2–Keap1 defines a physiologically important stress response mechanism. Trends in Molecular Medicine 10, 549-557.

Negi, G., Kumar, A., Joshi, R.P., Sharma, S.S., 2011a. Oxidative stress and Nrf2 in the pathophysiology of diabetic neuropathy: old perspective with a new angle. Biochemical and Biophysical Research Communications 408, 1-5.

Negi, G., Kumar, A., Sharma, S.S., 2011b. Melatonin modulates neuroinflammation and oxidative stress in experimental diabetic neuropathy: effects on NF-kappaB and Nrf2 cascades. Journal of Pineal Research 50, 124-131.

Nizamutdinova, I.T., Jin, Y.C., Chung, J.I., Shin, S.C., Lee, S.J., Seo, H.G., Lee, J.H., Chang, K.C., Kim, H.J., 2009. The anti-diabetic effect of anthocyanins in streptozotocin-induced diabetic rats through glucose transporter 4 regulation and prevention of insulin resistance and pancreatic apoptosis. Molecular Nutrition and Food Research 53, 1419-1429.

Obrosova, I.G., Fathallah, L., Stevens, M.J., 2001. Taurine counteracts oxidative stress and nerve growth factor deficit in early experimental diabetic neuropathy. Experimental Neurology 172, 211-219.

Obrosova, I.G., Stevens, M.J., 1999. Effect of dietary taurine supplementation on GSH and NAD(P)-redox status, lipid peroxidation, and energy metabolism in diabetic precataractous lens. Investigative Ophthalmology & Visual Science 40, 680-688.

Pan, C., Giraldo, G.S., Prentice, H., Wu, J.Y., 2010. Taurine protection of PC12 cells against endoplasmic reticulum stress induced by oxidative stress. Journal of Biomedical Science 1, S17.

Pan, C., Prentice, H., Price, A.L., Wu, J.Y., 2011. Beneficial effect of taurine on hypoxia- and glutamate-induced endoplasmic reticulum stress pathways in primary neuronal culture. Amino Acid 43, 1141-1146.

Pandya, K.G., Patel, M.R., Lau-Cam, C.A., 2010. Comparative study of the binding characteristics to and inhibitory potencies towards PARP and in vivo antidiabetogenic potencies of taurine, 3-aminobenzamide and nicotinamide. Journal of Biomedical Science 24, S16.

Plaschke, K., Hoyer, S., 1993. Action of the diabetogenic drug streptozotocin on glycolytic and glycogenolytic metabolism in adult rat brain cortex and hippocampus. International Journal of Developmental Neuroscience 11, 477-483.

Porte, D. Jr., Baskin, D.G., Schwartz, M.W., 2005. Insulin signaling in the central nervous system: a critical role in metabolic homeostasis and disease from *C. elegans* to humans. Diabetes 54, 1264-1276.

Rashid, K., Das, J., Sil, P.C., 2013. Taurine ameliorate alloxan induced oxidative stress and intrinsic apoptotic pathway in the hepatic tissue of diabetic rats. Food and Chemical Toxicology 51, 317-329.

Ravi, K., Ramachandran, B., Subramanian, S., 2004. Effect of Eugenia Jambolana seed kernel on antioxidant defense system in streptozotocin-induced diabetes in rats. Life Sciences 75, 2717-2731.

Reagan, L.P., Magarinos, A.M., Lucas, L.R., Van Bueren, A., McCall, A.L., McEwen, B.S., 1999. Regulation of GLUT-3 glucose transporter in the hippocampus of diabetic rats subjected to stress. The American Journal of Physiology 276, 879-886.

Schaffer, S.W., Azuma, J., Mozaffari, M., 2009. Role of antioxidant activity of taurine in diabetes. Canadian Journal of Physiology and Pharmacology 87, 91-99.

Shanmugam, K. R., Mallikarjuna, K., Nishanth, K., Kuo, C. H., Reddy, K. S., 2011. Protective effect of dietary ginger on antioxidant enzymes and oxidative damage in experimental diabetic rat tissues. Food Chemistry 124, 1436-1442.

Sima, A.A., Sugimoto, K., 1999. Experimental diabetic neuropathy: an update. Diabetologia 42, 773-788.

Song, F., Qi, X., Chen, W., Jia, W., Yao, P., Nussler, A.K., Sun, X., Liu, L., 2007. Effect of Momordica grosvenori on oxidative stress pathways in renal mitochondria of normal and alloxan-induced diabetic mice. Involvement of heme oxygenase-1. European Journal of Nutrition 46, 61-69.

Song, M.Y., Kim, E.K., Moon, W.S., Park, J.W., Kim, H.J., So, H.S., Park, R., Kwon, K.B., Park, B.H., 2009. Sulforaphane protects against cytokine- and streptozotocin-induced

beta-cell damage by suppressing the NF-kappaB pathway. Toxicology and Applied Pharmacology 235, 57-67.

Sun, M., Gui Y., Zhao, Y., Xu, C., 2011. Protective functions of taurine against experimental stroke through depressing mitochondriamediated cell death in rats. Amino Acids 40, 1419-1429.

Tappaz, M., Almarghini, K., Legay, F., Remy, A., 1992. Taurine biosynthesis enzyme cysteine sulfinate decarboxylase CSD from brain: the long and tricky trail to identification. Neurochemical Research. 17, 849-59.

Terada, T., Hara, K., Haranishi, Y., Sata, T., 2011. Antinociceptive effect of intrathecal administration of taurine in rat models of neuropathic pain. Canadian Journal of Anaesthesia 58, 630-637.

Van Dam, P.S., 2002. Oxidative stress and diabetic neuropathy: pathophysiological mechanisms and treatment perspectives. Diabetes Metabolism Research and Reviews 18, 176-184.

Vannucci, S.J., Clark, R.R., Koehler-Stec, E., Li, K., Smith, C.B., Davies, P., Maher, F., Simpson, I.A., 1998. Glucose transporter expression in brain: relationship to cerebral glucose utilization. Developmental Neuroscience 20, 369-379.

Vincent, A.M., Edwards, J.L., Sadidi, M., Feldman, E.L., 2008. The antioxidant response as a drug target in diabetic neuropathy. Current Drug Targets 9, 94-100.

Vincent, A.M., Russell, J.W., Low, P., Feldman, E.L., 2004. Oxidative stress in the pathogenesis of diabetic neuropathy. Endocrine Reviews 25, 612-628.

Virgintino, D., Robertson, D., Monaghan, P., Errede, M., Bertossi, M., Ambrosi, G., Roncali, L., 1997. Glucose transporter glut1 in human brain microvessels revealed by ultrastructural immunocytochemistry. Journal of Submicroscopic Cytology and Pathology 29, 365-370.

Yamamoto, H., Uchigata, Y., Okamoto, H., 1981. Streptozotocin and alloxan induce DNA strand breaks and poly(ADP-ribose) synthetase in pancreatic islets. Nature 294, 284-286.

Yao, H.T., Lin, P., Chang, Y.W., Chen, C.T., Chiang, M.T., Chang, L., Kuo, Y.C., Tsai, H.T., Yeh, T.K., 2009. Effect of taurine supplementation on cytochrome P450 2E1 and oxidative stress in the liver and kidneys of rats with streptozotocin-induced diabetes. Food Chemical Toxicology 47, 1703-1709.

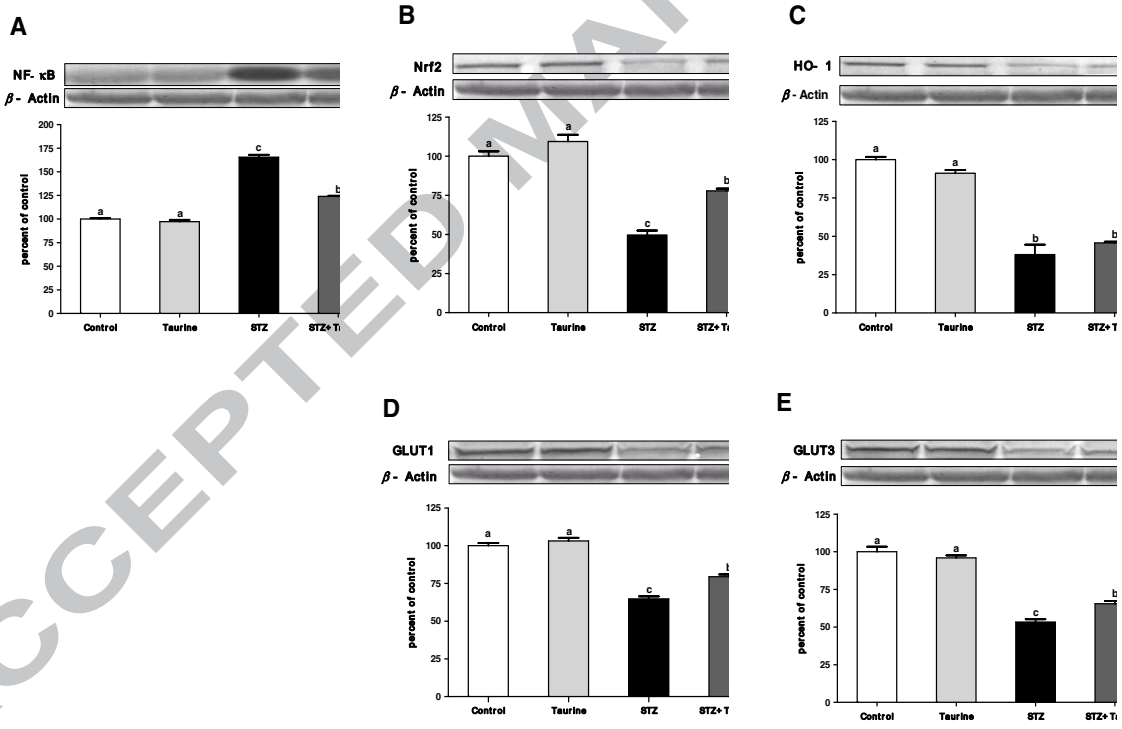

Fig. 1. Effects of taurine administration (2%, w/v, p.o. for 8 weeks) on (**A**) nuclear factor-kappa B (NF-κB), (**B**) nuclear factor-E2-related factor-2 (Nrf2), (**C**) heme oxygenase 1(HO-1), (**D**) glucose transporter protein 1 (GLUT1) and (**E**) glucose transporter protein 3 (GLUT3) expressions in the brain of streptozotocin (STZ)-induced diabetic rats. Results are expressed as percent of the control. Blots were repeated at least 4 times and a representative blot is shown. Actin was included to ensure equal protein loading. Bars without a common superscript differ among the experimental groups [control (water), taurine (2%, w/v, p.o), streptozotocin (60 mg/kg body weight, i.v.) to induce diabetes, and tarurine administration to diabetic rats)] (Turkey's post-hoc test, $P<0.05$).

Table 1. Effect of taurine administration on final body weight and blood glucose and serum malondialdehit (MDA) concentrations in rats with streptozotocin (STZ)-induced diabetes.

	Groups[1]			
Variable	Control	Taurine	STZ	STZ+Taurine
Body weight, g	275.0±0.33[a]	270.9±0.16[a]	194.6±0.39[b]	207.2±0.41[b]
Blood glucose, mg/dl	92.5±2.9[c]	97.0±2.62[c]	488.6±23.88[a]	453.5±16.37[a]
Serum MDA, µmol/L	0.331±0.031[c]	0.337±0.035[c]	0.783±0.089[a]	0.520±0.041[b]

[1]Control = rats received water (p.o.); Taurine = rats received 2% taurine (w/v, p.o.); STZ = rats received single administration of streptozotocin (i.v.); STZ+Taurine = diabetic rats received 2% taurine (w/v, p.o.). Means within the same row without a common superscript differ ($P < 0.05$).

Highlights

- Diabetes may promote neuropathy.
- Taurine supplementation (2%) via drinking water activates antioxidaditive defense system.
- Taruine reduces serum MDA concentration, suppresses the NF-κB expression, and enhances the Nrf2, HO-1, GLUT1,3 expressions.