

Taurine Ameliorates High Glucose Induced Apoptosis in HT-22 Cells



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Abstract Diabetes causes memory loss. Hippocampus is responsible for memory and increased apoptosis was found in diabetes patients. Taurine improved memory in diabetes condition. However, mechanism is unclear. In current study, hippocampal cell line HT-22 cells were subjected to analysis as five groups i.e. Control, High glucose (HG) at concentration of 150 mM, HG + 10 mM (T1), 20 mM (T2) and 40 mM (T3) taurine solution. TUNEL assay showed that HG increased the number of apoptotic cell significantly while taurine reduced apoptosis. Taurine increased phosphorylation of Akt in HT-22 cell treated with HG, and increased phosphorylation of Bad (p-Bad) was seen suggesting involvement of Akt/Bad signaling pathway. Expression of Bcl-2 was reduced in HG group but taurine improved this. Bax expression showed opposite trend. This indicated that taurine may reduce apoptosis by controlling balance of Bcl-2 and Bax. When the activation of Akt was blocked by using of perifosine, the effect of taurine disappears either partially or altogether. Thus, it was clear

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that taurine reduces apoptosis via Akt/Bad pathway in HT-22 cells exposed to HG which further improves downstream balance of Bcl-2 and Bax. This mechanism may be involved in apoptosis of hippocampus cells in diabetic condition.

Keywords High glucose · Apoptosis · HT-22 cell · Taurine · Anti-apoptosis

Abbreviations

DM	Diabetes mellitus
MTT	4,5-Dimethyl-thiazol-2-yl)-2,5-diphenyl-tetrazolium bromide
HG	High glucose
TUNEL	In situ TdT-mediated dUTP nick end labeling

1 Introduction

Diabetes mellitus (DM), a chronic metabolic disorder is the most severe and prevail cause of morbidity and mortality in modern civilization (Chinenye et al. 2012). This disorder is the consequence of long time durability of high glucose (HG) level in blood and metabolic defects of pivotal biomolecules such as carbohydrates, proteins and lipids (Baynes 1991). There are two types of diabetes i.e. type I, associated with impairment in insulin secretion and type II is resulted by resistance of insulin (Chuhwak and Pam 2007). There are various influences caused by chronic hyperglycemia on the body and central nervous system (CNS). Several chronic effects on the brain have been expounded, such as decreased synaptic plasticity (Reagan 2012; Revsin et al. 2009) neurotoxicity, neuroinflammation, decreased cell proliferation, increased neuronal apoptosis (Hawkins and Davies 2001; Verdile et al. 2015; Zhang et al. 2008). Indeed, some evidence showed that diabetes causes cognitive deficits (McCrimmon et al. 2012). In this regard, some adults with diabetes performed learning and memory impairment (Tonoli et al. 2014) and mainly cognitive, memory and learning deficits (Ojo and Brooke 2015; Reagan 2012; Revsin et al. 2009; Stranahan et al. 2008; Vieira et al. 2015).

The hippocampus, located between the thalamus and the medial temporal lobe of the brain, is responsible for such functions as orientation and memory, but many aspects of molecular and cellular mechanisms regarding its physiological function and changes in pathological conditions remain to be elucidated. For example, the dementia and Alzheimer's disease (AD), has been shown that there were severe pathological changes in the hippocampus, leading to progressive memory loss and other cognitive decline (Eustache et al. 2001). On the other hand, some paper showed that apoptosis occurs in hippocampal cells in diabetes which is associated with memory impairment (Li et al. 2002). So, we had an idea that if apoptosis in hippocampus of diabetic condition is controlled then we can effectively alleviate memory deficits in the diabetic conditions.

Taurine, a semi-essential amino acid, has several important functions, especially on the mammalian CNS acting in various processes such as osmoregulation, neuro-modulation, membrane stabilization and cell proliferation (De Luca et al. 2015). Kim et al. (2012) discussed that taurine ameliorated hyperglycemia and dyslipidemia. Diabetic nerve injury was aggravated by taurine depletion (Stevens et al. 1993). It was found that taurine prevented sensory as well as motor conduction velocity deficits in STZ induced diabetic rats (Pop-Busui et al. 2001). Taurine also addressed apoptosis in hepatic cells (Rashid et al. 2013), in renal tubules (Hizoh and Haller 2002) and cardiac myocytes (Takatani et al. 2004). It is clear from above data that taurine has anti-apoptotic and anti-diabetic properties and also ameliorates diabetes-induced neuropathy. But mechanism of taurine of against diabetes induced apoptosis in hippocampus is yet unclear.

Owing to properties of taurine it was hypothesized that it may prevent apoptosis in the hippocampal cells during diabetes and which may be beneficial against memory impairment in diabetes and can be used as therapeutic strategy against diabetes-induced neuropathy. Hence, this study was designed to check the anti-apoptotic effect of taurine and explore its mechanism in HT-22 cells, hippocampal cell line, exposed to HG.

2 Methods

2.1 HT-22 Cells Cultures

HT-22 cells were purchased from BeNa Culture Collection (Kunshan city, Jiangsu province, China). Cells grown in Dulbecco's Modified Eagle Medium (DMEM) containing 10% Fetal Bovine Serum (FBS), 1% streptomycin (100 mg/ml), penicillin G (100 U/ml), and then incubated at 37 °C with 5% CO₂.

2.2 Experimental Grouping

The cells were divided into five groups, Con group: control group, cells treated with normal culture medium. HG group: cells were cultured by normal medium with 150 mM glucose. Three taurine treatment groups: cells were co-treated of glucose (150 mM) with 10 mM, 20 mM and 40 mM taurine as T1, T2 and T3 groups, respectively. To intervention experiments of pathway inhibitor, cells were treated with Akt inhibitor (Perifosine). Con group: cells were cultured by normal medium. HG group: cells were exposed to 150 mM glucose. HG + T group: cells were cultured with normal medium co-treatment of 150 mM glucose with 40 mM taurine. HG + T + Perifosine group: The 150 mM glucose, 40 mM taurine and 5 μM Perifosine were added into the normal medium to culture the cells.

2.3 *MTT Assay*

Cell viability was measured by using MTT Assay. In brief, HT-22 cells were seeded in 96-well culture plates at the density of 8×10^3 cells/well for 24 h (h). And then treated as Con, HG, T1, T2 and T3 groups for 48 h. After treatment, added 100 μ l (0.5 mg/ml) MTT to each well and incubated for 4 h at 37 °C with 5% CO₂. Then each cell culture medium was replaced with 100 μ l DMSO. The ELISA microplate reader was used to test the value of OD at 570 nm. The viability was presented as the percentage survival rate taking control as 100%.

2.4 *Tunel Assay*

The apoptosis in HT-22 cells was checked by TUNEL assay, the cell nucleus was stained by DAPI. The images were taken by the fluorescence microscope made by Olympus Japan (Model No IX-70). In the results, the apoptosis of cells were stained as green. Count TUNEL-positive cells in 100 cells in 200 \times field of view, calculated the number of apoptotic cell in six random fields, and the apoptotic index (AI) = (the number of apoptotic cell/(6 \times 100) \times 100%).

2.5 *Caspase-3 Activity*

Caspase-3 Colorimetric Assay Kit (Beyotime, China) was used to evaluate caspase-3 activity. All steps are followed the kit instructions. The related outcomes were showed as a ratio to control.

2.6 *Western Blot Analysis*

The HT-22 cells were seeded in 100 mm dishes at the density of 2×10^6 cells/dish for 24 h. And then control group was given DMEM without FBS. HG group was given DMEM with glucose (150 mM), glucose (150 mM) +10 mM taurine as T1, glucose (150 mM) +20 mM taurine as T2 and glucose (150 mM) +40 mM taurine as T3. After 48 h incubation, the cells were collected to homogenize in ice cold RIPA Protein Extraction Reagent (Beyotime, China), mixed with 1% proteinase inhibitor and phosphatase inhibitor. The concentration of lysates was quantified by a BCA Protein Assay Kit (Beyotime, China). The lysates (40 μ g of protein) were separated by electrophoresis in 12% SDS-PAGE transferred to PVDF. The membranes were blocked with 5% skimmed milk in TBS-T. Then incubated the first

antibody like Akt/p-Akt, Bad/p-Bad, Bcl-2, Bax and β -actin at 4 °C overnight. The membranes were rinsed three times with $1 \times$ TBS-T and then incubated for 2 h with HRP-conjugated secondary antibody. The immuno-labeling were detected using the UVP Bio-Spectrum Imaging System.

2.7 Statistical Analysis

All data were analyzed by one-way ANOVA, followed by Bonferroni's post-hoc test using the program Graph Pad Prism 5.0. The results were present by mean \pm SD, and the difference was regarded as statistically significant when $p \leq 0.05$.

3 Results

3.1 Effect of Taurine on Cell Viability of HT-22 Cells Treated with HG

Cell viability was measured by using MTT assay. The result showed that the cell viability in HG group was reduced compared to the Con group. The cell viability was no significant difference between T1 group and HG group, while, it was significantly increased ($p < 0.05$) in T2 and T3 groups than that in HG group. These results indicated that HG could decreased the HT-22 cells viability, but taurine improved the viability of HT-22 cells treated with HG (Fig. 1).

3.2 Effect of Taurine on HT-22 Cell Apoptosis Induced by HG

The apoptotic cells were detected by TUNEL Assay. The TUNEL-positive cells were stained in green color, and the cell nuclei were stained by DAPI (Fig. 2a). Our results showed that the number of apoptotic cell have significantly increased in HG group ($p < 0.05$) as compared to Con group (Fig. 2b). In contrast, amounts of TUNEL-positive cells significantly reduced in T2 group and T3 group than that in HG group ($p < 0.05$). It was revealed that taurine attenuated the apoptosis of HT-22 cells induced by HG.

Caspase-3 activity was measured by caspase-3 assay kit, as shown in Fig. 2c, caspase-3 activity was increased in HG group compared to the Con group, while caspase-3 activity was decreased in T2 and T3 groups compared with HG group. It suggested that taurine could decreased caspase-3 activity in HT-22 cells exposed to HG.

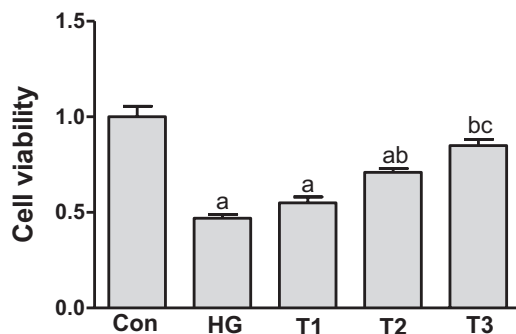


Fig. 1 The effect of taurine on viability of HT-22 cells treated with HG. The results were present by mean \pm SD. Significant statistical difference was indicated by ^a $p < 0.05$ with respect to the Con group, ^b $p < 0.05$ with respect to the HG group, ^c $p < 0.05$ with respect to the T1 group

3.3 Effect of Taurine on Expression of Akt/p-Akt, Bad/p-Bad

The Akt is an important regulator to control apoptosis by activating downstream signaling molecules. Bad, as a downstream mediator of p-Akt, could improve the cell survival when it is activated. In order to ensure the Akt/Bad signaling pathway whether involving in controlling apoptosis in HT-22 cells induced by HG, the level of expression in Akt/p-Akt and Bad/p-Bad in HT-22 cells were measured by western blot (Fig. 3a, b). The results showed that the expression of Akt and Bad has no significant difference among whole groups, however, the expression of p-Akt was significantly increased in T2 and T3 groups compared with the HG group. Similar expression trend was found in p-Bad ($p < 0.05$), except the T1 group, which had no significant difference compared to the HG group. These results indicated that taurine up-regulated the expression of p-Akt and p-Bad in HT-22 cells induced by HG.

To confirm the expression changes of p-Bad being mediated by Akt in HG-induced HT-22 cells treated with taurine, the expression of Bad/p-Bad was measured in HG/taurine-treated HT-22 cells in the presence of perifosine. As shown in Fig. 3c, the expression of p-Bad in HG + T + Perifosine group was significantly decreased, comparing with HG + T group ($p < 0.05$), which implied the up-regulating expression of p-Bad being mediated by Akt/Bad pathway.

3.4 Effect of Taurine on Expression of Bcl-2 and Bax

Bcl-2 family members are the key factor in apoptosis signals especially anti-apoptotic protein Bcl-2 and pro-apoptotic protein Bax. The balance between them directly decides the fate of the cells accepting death message, and the ratio of Bax/Bcl-2 determines the susceptibility of a cell to apoptosis. The changes in expression

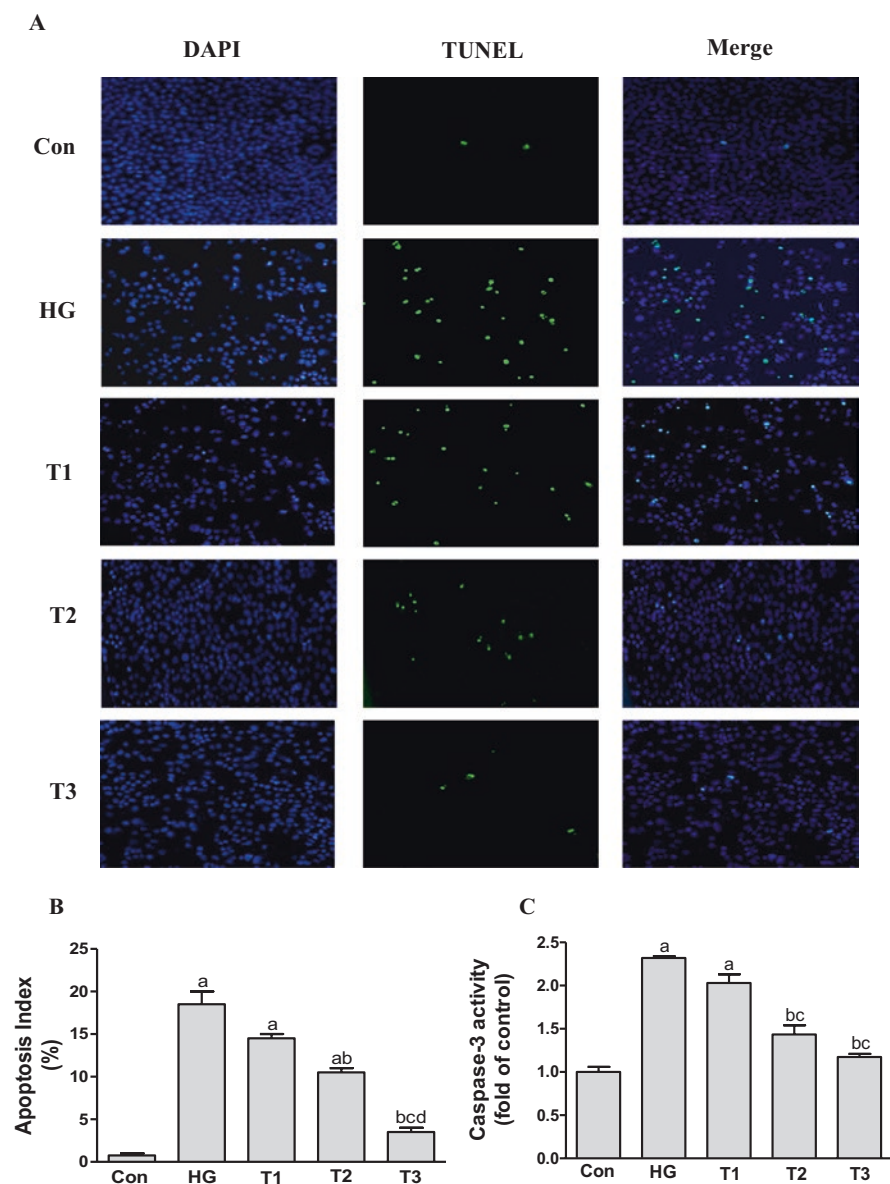


Fig. 2 The effect of taurine on apoptosis of HT-22 cells induced by HG. (a) Representative images of TUNEL stained cells are shown for the Con group, HG group and T1, T2 and T3 groups. (b) Quantify on data of the apoptotic cell. (c) Caspase-3 activity was detected in each group. Data are shown as the mean \pm SD ($n = 3$ per group). Significant statistical difference was indicated by ^a $p < 0.05$ with respect to the Con group, ^b $p < 0.05$ with respect to the HG group, ^c $p < 0.05$ with respect to the T1 group, ^d $p < 0.05$ with respect to the T2 group

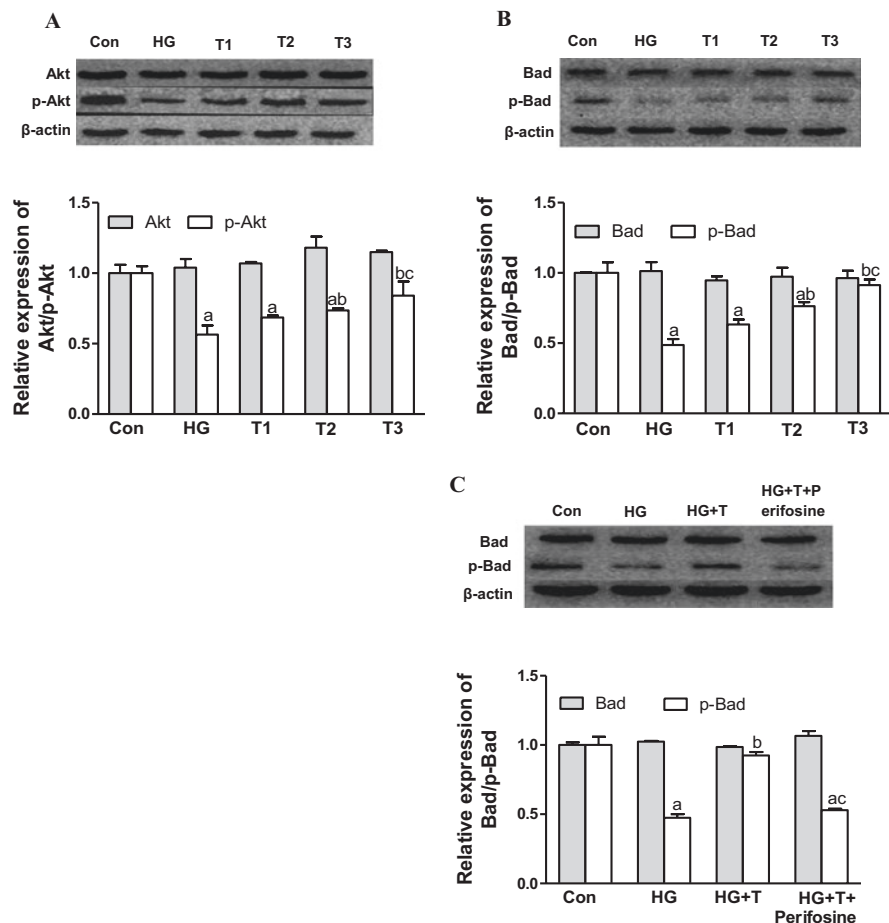


Fig. 3 The effect of taurine on expression of Akt/p-Akt (a), Bad/p-Bad (b). The expression of protein was analyzed by Western blot. The relative proteins were expressed by the ratio of sample to β -actin. Data obtained from three separated analyses are expressed as mean \pm SD ($n = 3$ per group). Significant statistical difference was indicated by ^a $p < 0.05$ with respect to the Con group, ^b $p < 0.05$ with respect to the HG group, ^c $p < 0.05$ with respect to the T1 group. The effect of taurine on expression of Bad/p-Bad of HT-22 cells treated with Perifosine (c). Significant statistical difference was indicated by ^a $p < 0.05$ with respect to the Con group, ^b $p < 0.05$ with respect to the HG group, ^c $p < 0.05$ with respect to the HG + T group

of Bcl-2 and Bax were measured by western blot (Fig. 4a, b). Results showed that the expression of Bcl-2 decreased in HG group but the level of Bcl-2 was increased in T2, T3 groups compared to the HG group ($p < 0.05$). The expression of Bax showed the reverse condition. The ratio of Bax/Bcl-2 was showed in Fig. 3c, the ratio was significantly increased in HG group compared with Con group, the ratio of Bax/Bcl-2 was decreased in T2 and T3 groups compared to the HG group. The level of Bcl-2, Bax and the ratio of Bax/Bcl-2 treated with Perifosine was showed

as Fig. 4d–f. Compared to the Con group, the expression of Bcl-2 was decreased but Bax was increased in HG groups ($p < 0.05$), the expression of Bcl-2 was decreased but Bax was increased in HG/taurine co-treated HT-22 cells in the presence of Perifosine. These results revealed that taurine up-regulated the expression of Bcl-2 and down-regulated the expression of Bax in HG-induced HT-22 cells by Akt/Bad pathway.

3.5 Inhibition of Akt Abolishes the Anti-apoptotic Effects of Taurine

The central role of Akt signaling in the anti-apoptotic effect of taurine prompted us to test whether inhibition of Akt was capable of blocking taurine-enhanced cell survival. The TUNEL assay and caspase-3 activity were tested with or without Perifosine. The results showed that the number of apoptotic cell have significantly increased in HG group ($p < 0.05$) as compared to Con and HG + T groups (Fig. 5a, b), compared with the HG + T group, the number of apoptotic cell has increased in HG + T + Perifosine group. The caspase-3 activity showed the same condition as the apoptosis index (Fig. 5c). It was indicated that the anti-apoptotic effects of taurine on HG-induced HT-22 cells were mediated by Akt/Bad pathway.

4 Discussion

Some evidences indicate that diabetes causes learning and memory deficits (McCrimmon et al. 2012). The hippocampus, which plays a critical role in cognitive function, it had been found that there were structural changes according to some imaging studies in the diabetic patients (Verdile et al. 2015). Moreover, it was shown that apoptosis occurs in hippocampal cells in diabetes which is associated with memory impairment (Li et al. 2002). It prompted us that anti-apoptosis may ameliorate the cognitive impairment caused by diabetes. On the other hand, taurine improved memory in diabetic rats (Rahmeier et al. 2016). So we presumed that taurine may play a role of ameliorating cognitive deficits through controlling apoptosis of hippocampus neuronal cells in diabetic rats. In current study, we tested the cell viability and apoptosis by MTT, TUNEL assay and caspase-3 activity kit. The results showed that administration of HG decreased cell survival rate and increased apoptosis drastically as compared to control same like (Hajjalizadeh et al. 2014), but addition of taurine successfully checked this decline, improved cell survival and decreased apoptosis rate in a dose dependent manner. It was also reported that taurine reduced apoptosis in PC12 exposed to HG in vitro (Maher et al. 2005), being in accordance with our study. These results indicate that taurine protects against HG-induced apoptosis in HT-22 cells.

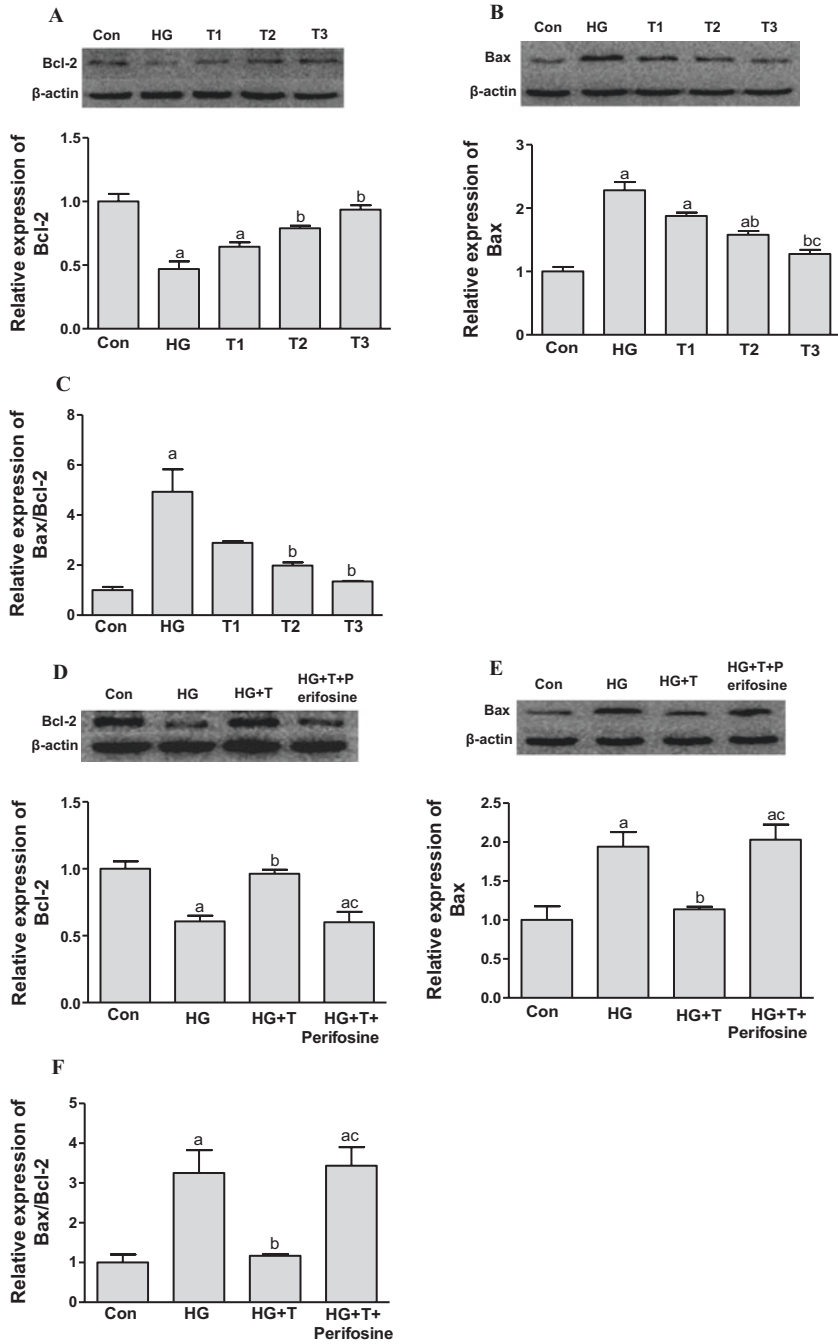


Fig. 4 The effect of taurine on expression of Bcl-2 (a), Bax (b) and ratio of Bax/Bcl-2 (c) of HT-22 cells treated with HG. The relative proteins were expressed by the ratio of sample to β -actin.

Akt is a regulator of cell processes and cell survival (Srivastava et al. 2008) and can regulate cell apoptosis by activating a series of downstream signaling molecules. The studies showed that the phosphorylation of Akt inhibited apoptosis and the inhibition of Akt phosphorylation induced apoptosis (Takatani et al. 2004). To investigate whether the anti-apoptotic effect of taurine is associated with phosphorylation of Akt, the expression levels of Akt and p-Akt were measured by Western blot assay. HG significantly decreased the expression of p-Akt in HT-22. However, taurine recovered this HG induced down-regulation of p-Akt. Takatani et al. reported that treatment of taurine significantly reversed decrease in phosphorylation level of Akt in cardiac myocyte cells taken from ischemic rats (Takatani et al. 2004). Our results indicate that taurine activates Akt in HT-22 cells exposed to HG. Bad is a member of Bcl-2 proteins. It is a downstream mediator of p-Akt and directly interacts with Bcl-2, forms heterodimers and concomitantly generates Bax homodimers, thus inducing cell death (Datta et al. 1997). Akt phosphorylates Bad in vitro and in vivo (Datta et al. 1997). Phosphorylation of Bad (p-Bad) is suspected to improve cell survival (Steenbergen et al. 2003). The present study showed that Bad was not significantly different among the groups. However, Taurine improved p-Bad in HG indicating phosphorylation of Bad. Thus, in our study, the level of p-Akt was improved by taurine which in turn improved phosphorylation of Bad. This indicates that Akt/Bad signaling pathway may be involved in apoptosis in HT-22 cells induced by HG.

Survival and turnover of the different body cells is based on a critical balance between anti-apoptotic and pro-apoptotic regulators. Disease is caused by disturbance of this balance. Bcl-2 family members are the key factor in apoptosis signals especially Bcl-2 and Bax. These are mostly represented members having structure similarity but have opposite function. The balance between them directly decides the fate of the cells accepting death message. In addition, up-regulation of several anti-apoptotic members of the Bcl-2 family proteins, Bcl-2 is such a protein, has been strongly associated with increased resistance to apoptosis (Garchon et al. 1994; Hanke 2000). It was found that taurine improved Bcl-2 expression in diabetic rats (Das and Sil 2012). It was found that Bax expression increased in PC-12 cells treated with HG and mild reduction was seen for Bcl-2 spinal cord of diabetic rats (Kaeidi et al. 2013). Similar results were found in our study, HG down-regulated Bcl-2 and up-regulated Bax in HT-22 cells. However, taurine reduced expression of Bax and increased expression of Bcl-2 according to dose. These findings indicated that taurine reduced apoptosis in HT-22 cells exposed to HG may be by improving Bax and Bcl-2 balance.

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Fig. 4 (continued) Data obtained from three separate analyses are expressed as mean \pm SD (n = 3 per group). Significant statistical difference was indicated by ^a $p < 0.05$ with respect to the Con group, ^b $p < 0.05$ with respect to the HG group, ^c $p < 0.05$ with respect to the T1 group. The effect of taurine on expression of Bcl-2 (**d**), Bax (**e**) and ratio of Bax/Bcl-2 (**f**) of HT-22 cells treated with Perifosine. Significant statistical difference was indicated by ^a $p < 0.05$ with respect to the Con group, ^b $p < 0.05$ with respect to the HG group, ^c $p < 0.05$ with respect to the HG + T group

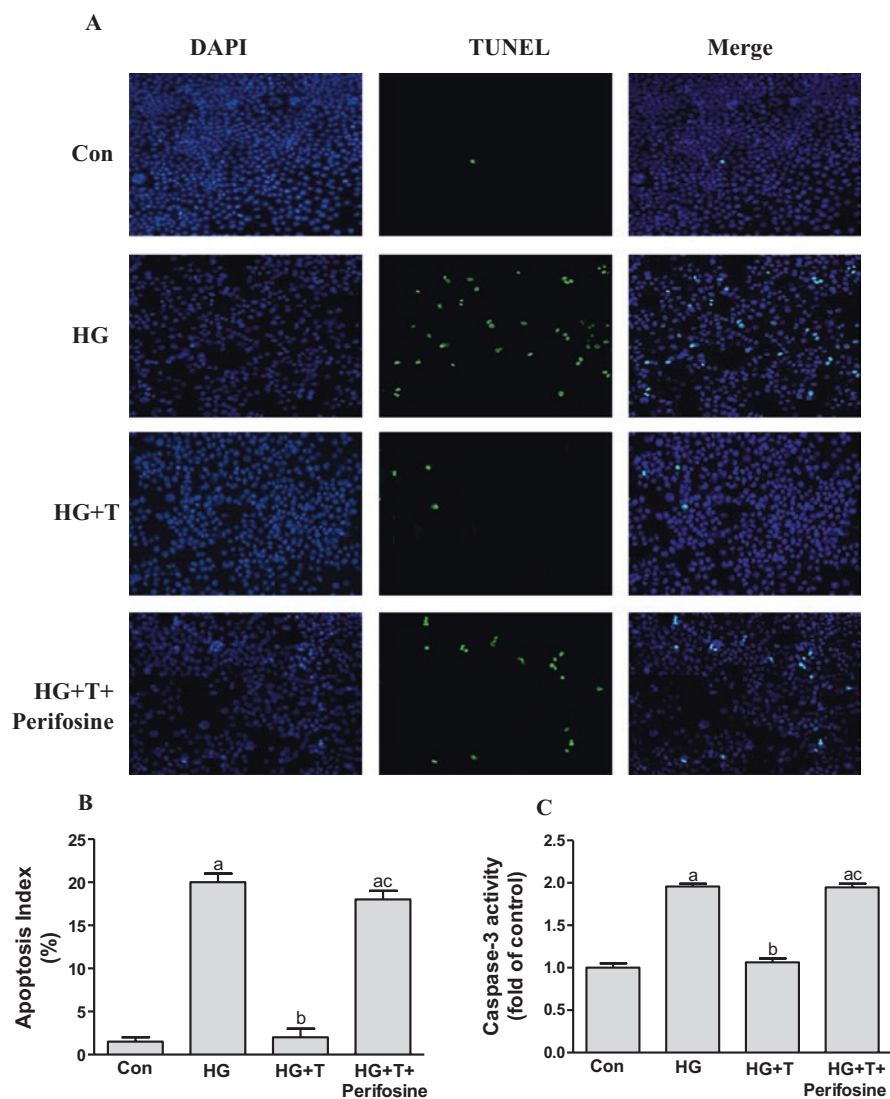


Fig. 5 The effect of taurine on apoptosis in HT-22 cells treated with Perifosine. **(a)** Representative images of TUNEL stained cells are shown for the Con group, HG group and HG + T groups and HG + T + Perifosine. **(b)** Quantify on data of the apoptotic cells. **(c)** Caspase-3 activity. All data obtained from three separate analyses are expressed as mean \pm SD ($n = 3$ per group). Significant statistical difference was indicated by ^a $p < 0.05$ with respect to the Con group, ^b $p < 0.05$ with respect to the HG group, ^c $p < 0.05$ with respect to the HG + T group

In order to confirm this assumption that taurine involved Akt/Bad pathway in its activity, Akt inhibitor (perifosine) was used (Kondapaka et al. 2003). We found that taurine could not perform well in presence of perifosine. Taurine improved p-Bad expression in HT-22 cells under HG condition but in presence of perifosine, it did not give good results. Similarly, taurine increased Bcl-2 expression and reduced Bax expression under HG but in presence of perifosine, taurine had not so good effect. Similarly, TUNEL assay showed that taurine decreased apoptosis in HT-22 cells exposed to HG however, perifosine blocked anti-apoptotic activity of taurine and in this case apoptosis was not ameliorated so better as without perifosine. This result confirmed our assumption that taurine ameliorated apoptosis in HT-22 cells exposed to HG via regulating Akt/Bad pathway.

Based on our results it can be concluded that taurine protected HT-22 cells against HG induced apoptosis. It can predict that taurine may have protective effect against apoptosis in hippocampus induced by hyperglycemia. However, further in vivo studies have to be conducted to confirm this prediction.

5 Conclusion

HG can increase apoptosis in HT-22 cells leading to death of the cells via apoptosis and taurine may control this apoptosis by modifying Akt/Bad pathway. Hence, taurine may be helpful in dealing with memory loss in diabetes.

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References

- Baynes JW (1991) Role of oxidative stress in development of complications in diabetes. *Diabetes* 40(4):405–412
- Chinenye S, Uloko AE, Ogera AO, Ofoegbu EN, Fasanmade OA, Fasanmade AA, Ogbu OO (2012) Profile of Nigerians with diabetes mellitus—Diabcare Nigeria study group (2008): results of a multicenter study. *Indian J Endocrinol Metabol* 16(4):558
- Chuhwak E, Pam S (2007) Diabetes co-existing with chronic liver disease: clinical features and response to therapy. *Niger J Med: J Natl Assoc Resid Doct Niger* 16(2):156–160
- Das J, Sil PC (2012) Taurine ameliorates alloxan-induced diabetic renal injury, oxidative stress-related signaling pathways and apoptosis in rats. *Amino Acids* 43(4):1509–1523
- Datta SR, Dudek H, Tao X, Masters S, Fu H, Gotoh Y, Greenberg ME (1997) Akt phosphorylation of BAD couples survival signals to the cell-intrinsic death machinery. *Cell* 91(2):231–241
- De Luca A, Pierno S, Camerino DC (2015) Taurine: the appeal of a safe amino acid for skeletal muscle disorders. *J Transl Med* 13(1):243

- Eustache F, Desgranges B, Giffard B, de la Sayette V, Baron JC (2001) Entorhinal cortex disruption causes memory deficit in early Alzheimer's disease as shown by PET. *Neuroreport* 12(4):683–685
- Garchon HJ, Luan JJ, Eloy L, Bédossa P, Bach JF (1994) Genetic analysis of immune dysfunction in non-obese diabetic (NOD) mice: mapping of a susceptibility locus close to the Bcl-2 gene correlates with increased resistance of NOD T cells to apoptosis induction. *Eur J Immunol* 24(2):380–384
- Hajializadeh Z, Nasri S, Kaeidi A, Sheibani V, Rasouljan B, Esmaeili-Mahani S (2014) Inhibitory effect of Thymus caramanicus Jalas on hyperglycemia-induced apoptosis in in vitro and in vivo models of diabetic neuropathic pain. *J Ethnopharmacol* 153(3):596–603
- Hanke J (2000) Apoptosis and occurrence of Bcl-2, Bak, Bax, Fas and FasL in the developing and adult rat endocrine pancreas. *Anat Embryol* 202(4):303–312
- Hawkins CL, Davies MJ (2001) Generation and propagation of radical reactions on proteins. *Biochimica et Biophysica Acta (BBA)-Bioenergetics* 1504(2–3):196–219
- Hizoh I, Haller C (2002) Radiocontrast-induced renal tubular cell apoptosis: hypertonic versus oxidative stress. *Investig Radiol* 37(8):428–434
- Kaeidi A, Esmaeili-Mahani S, Abbasnejad M, Sheibani V, Rasouljan B, Hajializadeh Z, Pasban-Aliabadi H (2013) Satureja khuzestanica attenuates apoptosis in hyperglycemic PC12 cells and spinal cord of diabetic rats. *J Nat Med* 67(1):61–69
- Kim KS, Kim JY, Lee BG, You JS, Chang KJ, Chung H, Hwang YC (2012) Taurine ameliorates hyperglycemia and dyslipidemia by reducing insulin resistance and leptin level in Otsuka Long-Evans Tokushima fatty (OLETF) rats with long-term diabetes. *Exp Mol Med* 44(11):665–673
- Kondapaka SB, Singh SS, Dasmahapatra GP, Sausville EA, Roy KK (2003) Perifosine, a novel alkylphospholipid, inhibits protein kinase B activation. *Mol Cancer Ther* 2(11):1093–1103
- Li ZG, Zhang W, Grunberger G, Sima AA (2002) Hippocampal neuronal apoptosis in type 1 diabetes. *Brain Res* 946(2):221–231
- Maher S, Condron CEM, Bouchier-Hayes D, Toomey D (2005) Taurine attenuates CD3/interleukin-2-induced T cell apoptosis in an in vitro model of activation-induced cell death (AICD). *Clin Exp Immunol* 139(2):279–286
- McCrimmon RJ, Ryan CM, Frier BM (2012) Diabetes and cognitive dysfunction. *Lancet* 379(9833):2291–2299
- Ojo O, Brooke J (2015) Evaluating the association between diabetes, cognitive decline and dementia. *Int J Environ Res Public Health* 12(7):8281–8294
- Pop-Busui R, Sullivan KA, Van Huysen C, Bayer L, Cao X, Towns R, Stevens MJ (2001) Depletion of taurine in experimental diabetic neuropathy: implications for nerve metabolic, vascular, and functional deficits. *Exp Neurol* 168(2):259–272
- Rahmeier FL, Zavalhia LS, Tortorelli LS, Huf F, Géa LP, Meurer RT, da Cruz Fernandes M (2016) The effect of taurine and enriched environment on behaviour, memory and hippocampus of diabetic rats. *Neurosci Lett* 630:84–92
- Rashid K, Das J, Sil PC (2013) Taurine ameliorate alloxan induced oxidative stress and intrinsic apoptotic pathway in the hepatic tissue of diabetic rats. *Food Chem Toxicol* 51:317–329
- Reagan LP (2012) Diabetes as a chronic metabolic stressor: causes, consequences and clinical complications. *Exp Neurol* 233(1):68–78
- Revsin Y, Rekers NV, Louwe MC, Saravia FE, De Nicola AF, De Kloet ER, Oitzl MS (2009) Glucocorticoid receptor blockade normalizes hippocampal alterations and cognitive impairment in streptozotocin-induced type 1 diabetes mice. *Neuropsychopharmacology* 34(3):747–758
- Srivastava RM, Varalakshmi C, Khar A (2008) The ischemia-responsive protein 94 (Irp94) activates dendritic cells through NK cell receptor protein-2/NK group 2 member D (NKR-P2/NKG2D) leading to their maturation. *J Immunol* 180(2):1117–1130
- Steenbergen C, Afshari CA, Petranka JG, Collins J, Martin K, Bennett L, Murphy E (2003) Alterations in apoptotic signaling in human idiopathic cardiomyopathic hearts in failure. *Am J Phys Heart Circ Phys* 284(1):H268–H276

- Stevens M, Lattimer S, Kamijo M, Van Huysen C, Sima A, Greene D (1993) Osmotically-induced nerve taurine depletion and the compatible osmolyte hypothesis in experimental diabetic neuropathy in the rat. *Diabetologia* 36(7):608–614
- Stranahan AM, Arumugam TV, Cutler RG, Lee K, Egan JM, Mattson MP (2008) Diabetes impairs hippocampal function through glucocorticoid-mediated effects on new and mature neurons. *Nat Neurosci* 11(3):309–317
- Takatani T, Takahashi K, Uozumi Y, Matsuda T, Ito T, Schaffer SW, Azuma J (2004) Taurine prevents the ischemia-induced apoptosis in cultured neonatal rat cardiomyocytes through Akt/caspase-9 pathway. *Biochem Biophys Res Commun* 316(2):484–489
- Tonoli C, Heyman E, Roelands B, Pattyn N, Buyse L, Piacentini MF, Meeusen R (2014) Type 1 diabetes-associated cognitive decline: a meta-analysis and update of the current literature. *J Diabetes* 6(6):499–513
- Verdile G, Fuller SJ, Martins RN (2015) The role of type 2 diabetes in neurodegeneration. *Neurobiol Dis* 84:22–38
- Vieira ER, Mendy A, Prado CM, Gasana J, Albatineh AN (2015) Falls, physical limitations, confusion and memory problems in people with type II diabetes, undiagnosed diabetes and prediabetes, and the influence of vitamins A, D and E. *J Diabetes Complicat* 29(8):1159–1164
- Zhang WJ, Tan YF, Yue J, Vranic M, Wojtowicz J (2008) Impairment of hippocampal neurogenesis in streptozotocin-treated diabetic rats. *Acta Neurol Scand* 117(3):205–210