Chapter 17
Mechanism of Neuroprotective Function of Taurine

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Abstract Taurine has potent protective function against glutamate-induced neuronal injury presumably through its function in regulation of intracellular free calcium level, $[Ca^{2+}]_i$. In this communication, we report that taurine exerts its protective function through one or more of the following mechanisms: 1. Inhibition of glutamate-induced calcium influx through L-, N- and P/Q-type voltage-gated calcium channels and NMDA receptor calcium channel; 2. Attenuation of glutamate-induced membrane depolarization; 3. Prevention of glutamate-induced apoptosis via preventing glutamate-mediated down-regulation of Bcl-2; 4. Prevention of cleavage of Bcl-2 by calpain. This action of taurine is due to its inhibition on glutamate induced calpain activation. Based on these observations, we propose that taurine protects neurons against glutamate-induced neurotoxicity in part, by preventing glutamate-induced membrane depolarization, elevation of $[Ca^{2+}]_i$, activation of calpain, reduction of Bcl-2 and apoptosis.

Abbreviations *VGCC*, voltage-gated calcium channel; *BME*, basal medium eagle; *div*, days in vitro; *EBSS*, Earle's balanced salt solution; *Glu*, Glutamate

17.1 Introduction

The physiological role of taurine (2-amino-ethanesulfonic acid), one of the most abundant amino acids in mammals, has received considerable attention since the reports that cats fed with a taurine deficient diet developed central retinal degeneration (Hayes et al. 1975) and cardiomyopathy (Pion et al. 1987). Taurine has been shown to be involved in many important physiological functions (Bianchi et al. 2006) e.g., as a trophic factor in the development of the CNS (Sturman 1993; Young 2004). It also serves in maintaining the structural integrity of the membrane (Moran et al. 1988), regulating calcium homeostasis (El Idrissi, 2006), as an osmolyte (Wade et al. 1988; Schaffer et al. 2000), as a neurotransmitter (Okamoto et al. 1983;

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Lin et al. 1985) and as a neuroprotector against Glu-induced neurotoxicity (Tang et al. 1996; Ward et al. 2006).

One important function of taurine is neuroprotection. Taurine has been shown to effectively prevent Glu-induced neuronal injury in cultured neurons (El Idrissi 2006; Chen et al. 2001; Tang et al. 1996). It is generally believed that the neuroprotective functions of taurine are due to its role in reducing the intracellular free Ca^{2+}, $[Ca^{2+}]_i$, concentration, and its anti-oxidative stress capacity (Chen et al. 2001; Schaffer et al. 2003). It was reported that taurine reduced Glu-induced elevation of $[Ca^{2+}]_i$ was through inhibition of Ca^{2+} influx via the reverse mode of the Na^+/Ca^{2+} exchanger (Chen et al. 2001). In addition to the Na^+/Ca^{2+} exchanger, we found taurine also inhibits various voltage-gated calcium channels (VGCC) including L-, N- and P/Q-type (Wu et al. 2005). We also found that taurine can protect neurons against Glu-induced apoptosis by preventing the activation of calpain, a calcium-dependent protease, after Glu stimulation.

17.2 Methods

17.2.1 Cell Culture and Experiments

Whole-brain primary neuronal cell cultures were prepared from fetal rat brains. Briefly, brains were dissected from 17-day fetal rats, kept in GME (BME supplemented with 20% fetal bovine serum). The brains were mechanically dissociated and cell suspension was centrifuged at 200 g for 3 minutes. The pellet obtained was resuspended in GME and plated in 24-well plates pre-coated with poly-d-lysine. For confocal microscopic study, 20 mm circular glass coverslips held by 35 mm dishes were used. Cells were allowed to adhere for hour in an incubator (37°C, 5% CO_2). The incubation medium was then replaced with serum-free BME.

Cultured neurons at 14 day in vitro (DIV) were used. For the Glu treatment group, cultured neurons were treated with 0.25 mM Glu for 10 minutes or 100 μM for 24 hours. For the taurine plus Glu group, cultured neurons were pre-incubated with 25 mM taurine for 10 minutes prior to the Glu stimulation.

17.2.2 Detection of Intracellular Calcium and ^{45}Ca Influx Study

Cultured neurons plated on 20 mm circular glass coverslips were used. After 14 DIV, the original media was replaced with Earle's balanced salt solution (EBSS) (116.4 mM NaCl, 5.4 mM KCl, 0.8 mM $MgSO_4$, 1.0 m M NaH_2CO_3, 1.8 m M $CaCl_2$, 5.6 m M glucose, pH 7.2). Cultures were equilibrated for 2 hours. Fluo-3 was added and further incubated for 30 minutes. After rinsing 3 times with EBSS to eliminate excessive dye, the coverslip was mounted on a customized perfusion chamber. The neurons were then treated with Glu alone, or in the presence of taurine and other compounds as described. The neurons were washed after each treatment.

The fluorescent dye was excited at 488 nm, and the changes in fluorescence were monitored using a computer connected to a confocal microscope.

The Ca^{2+} influx was assayed using ^{45}Ca. After 14 DIV, the cultures were washed twice with fresh EBSS, the media were replaced with fresh EBSS and incubated for 1 hour in the incubator. The media were changed to EBSS containing 55.5 KBq/ml $^{45}CaCl_2$, and the cultures were equilibrated for 10 minutes prior to a 10-minute exposure to 50 μM Glu. The uptake of ^{45}Ca was terminated by the removal of media, followed by 3 quick rinses with 1ml ice-cold 4 mM EGTA/0.9% NaCl. The cells were solubilized in 700 μl 0.3 M NaOH, and the radioactivity was determined using a liquid scintillation counter (the efficiency for ^{45}Ca is 95%).

17.2.3 Hoechst Staining for Nuclear Morphology

Nuclear morphology was detected by Hoechst 33342 staining 24 hours after initial treatment. Before dye application, cultures were washed twice with PBS and fixed for 10 minutes with 4% paraformaldehyde. After fixation, cultures were washed twice with PBS and exposed to Hoechst 33342 (2 mg/l) for 15 minutes. Cells with bright blue fragmented nuclei showing condensation of chromatin were identified as apoptotic cells.

17.2.4 Immunoblotting and DNA Electrophoresis

For immunoblotting, equal amount of protein samples were first separated on an SDS-PAGE and then blotted onto nitrocellulose membranes followed by a 2-hour blocking with 3% non-fat milk at room temperature. After a 2-hour incubation with the primary antibody and a 2-hour incubation with the secondary antibody at room temperature, the protein immuno-complex was visualized using ECL^{TM} detection reagents.

For DNA electrophoresis, 7 μg of genomic DNA was loaded onto 1.8% agarose gel containing ethidium bromide and run at 80 volts until the dye reached half of the gel. The DNA was then visualized using UV light.

17.3 Results

17.3.1 Effect of Taurine on Glu-Induced Neurotoxicity and Intracellular Calcium, $[Ca^{2+}]_i$, Elevation

Primary neuronal cell cultures of 14 DIV were treated with 250μM Glu in the presence or absence of 25 mM taurine. The neuronal damage was evaluated by LDH releasing assay. Glu stimulation caused cell damage in primary neuronal culture, as

indicated by the increased LDH release, and this increased LDH release was largely inhibited by taurine (Fig. 17.1a).

Intracellular calcium level was determined by confocal microscopy. As shown in Fig. 17.1b, compared with the control (panel A) which shows the basal level of intracellular free calcium (blue color), the application of 50 μM Glu markedly increased intracellular calcium level (panel B, bright red color). In the presence of 25 mM taurine, Glu failed to induce an increase in $[Ca^{2+}]_i$ (compare panel H with B), indicating that taurine blocks the Glu-induced $[Ca^{2+}]_i$ accumulation. The cultured neurons used remained viable as indicated by a sharp increase in $[Ca^{2+}]_i$ when they were treated with Glu again at the end of the experiment (panel J).

Furthermore, extracellular calcium influx into neurons was measured using ^{45}Ca. As shown in Fig. 17.1c, 50 μM Glu stimulation induced ^{45}Ca accumulation inside the neurons, and taurine, at concentrations of 25 mM and 5 mM, inhibited Glu-induced intracellular calcium accumulation.

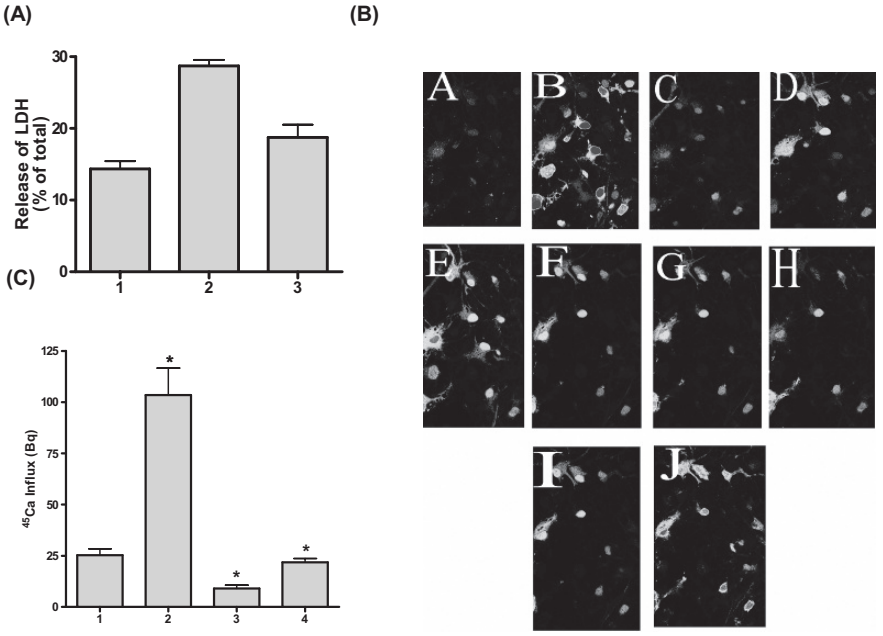

Fig. 17.1 (**a**) Effect of taurine on Glu-induced LDH release. 1. Control; 2. Glu; 3. Glu plus taurine. (**b**) Effect of taurine on Glu induced $[Ca^{2+}]_i$ accumulation (confocal). A. Baseline; B & J. Glu; C, F & I. After washing; D. Nifedipine; E. Nifedipine plus Glu; G. Taurine; H. Taurine plus Glu. Color coding indicates $[Ca^{2+}]_i$, red being the highest and blue the lowest C. Effect of taurine on Glu induced $[Ca2+]$i accumulation ($^{45}Ca^{2+}$ influx). 1. Control; 2. Glu; 3. Glu plus 25mM taurine; 4. Glu plus 5mM taurine

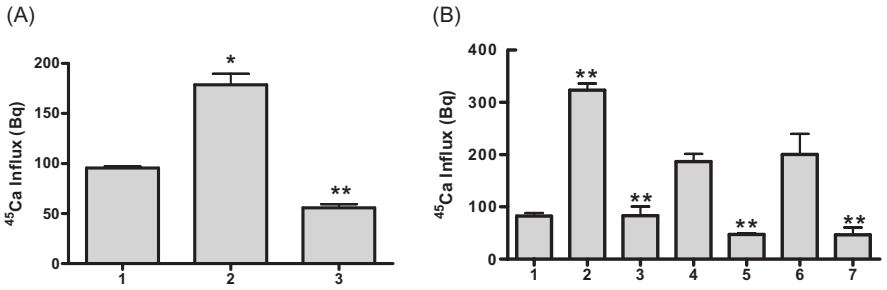

Fig. 17.2 (**a**) Effect of taurine on L-type VGCC-mediated calcium influx. 1. Control; 2. Bay K 8644; 3. Bay K 8644 plus taurine. (**b**) Effect of taurine on P/Q-, N-type VGCC-mediated calcium influx. 1. Control; 2. Glu; 3. Glu plus taurine; 4. P/Q-type VGCC (Glu plus channel blockers mixture); 5. Same as 4 plus taurine; 6. P/Q-type VGCC (Glu plus channel blockers mixture); 7. Same as 6 plus taurine

17.3.2 Effect of Taurine on Calcium Influx Through Various Voltage-Gated Calcium Channels (VGCCs)

Since extracellular calcium influx was confirmed, the effect of taurine on major types (including L-, P/Q- and N-type) of VGCCs was determined. In confocal microscopic study, nifedipine, a specific L-type VGCC blocker, inhibited Glu-induced intracellular calcium accumulation (Fig. 17.1b, compare panel E and B). As shown in Fig. 17.2a, Bay K 8644, a specific L-type VGCC activator, increased the $[Ca^{2+}]_i$ by 90%. However, when neurons were pretreated with taurine, the Bay K 8644-induced increase in $[Ca^{2+}]_i$ was completely inhibited suggesting that taurine blocks the calcium influx through L-type VGCC.

To study the effect of taurine on P/Q- and N-type VGCCs, the Glu-induced ^{45}Ca influx was conducted in the presence of a mixture of calcium channel blockers to inhibit all the major calcium channels except for the P/Q- or N-type VGCC. For example, P/Q-type VGCC was studied in the presence of a combination of nifedipine, N-conotoxin GVI A, 2,4-dichlorobenzamil, MK801 which blocks L-, N-type VGCCs, reverse mode of Na^+/Ca^{2+} exchanger and NMDA receptor, respectively. As shown in Fig. 17.2b, P/Q-type (column 4) and N-type (column 6) VGCCs contributed, to a similar extent, to Glu-induced calcium influx. Taurine blocked the calcium influx through both P/Q-type (column 5) and N-type (column 7) VGCCs.

17.3.3 Effect of Taurine on Calcium Influx Through NMDA Receptor Calcium Channel

Besides VGCCs, the NMDA receptor calcium channel represents another major calcium influx pathway. When the experiments were performed with regular EBSS (Mg^{2+} is present), calcium influx through the NMDA receptor calcium channel was completely blocked by taurine (Fig. 17.3 a column 3). When neurons were treated in

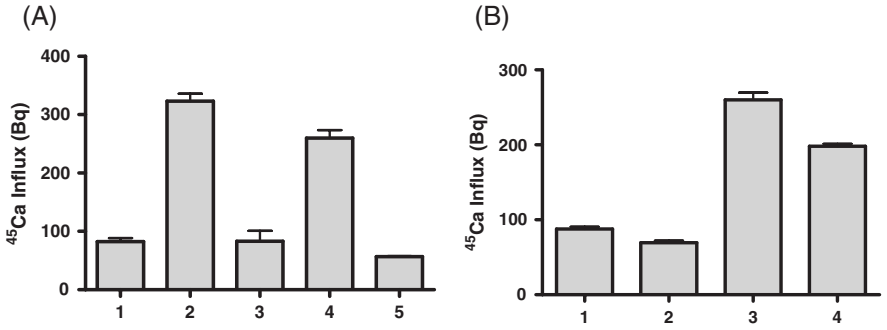

Fig. 17.3 (**a**) Effect of taurine on NMDA-mediated calcium influx in EBSS. 1. Control; 2. Glu; 3. Glu plus taurine; 4. NMDA calcium channel (Glu plus channel blockers mixture); 5. Same as 4 plus taurine. (**b**) Effect of taurine on NMDA-mediated calcium influx in Mg^{2+}-freeEBSS. 1. Control; 2. Taurine; 3. NMDA; 4. NMDA plus taurine

$Mg^{2+} - free$ EBSS media containing CNQX (a specific antagonist for AMPA/KA receptors), NMDA induced calcium influx, however, taurine failed to block the calcium influx through NMDA receptors (Fig. 17.3b, column 4). These results indicate that taurine does not act directly on NMDA receptors.

17.3.4 Effect of Taurine, Calpastatin on the Glu-Induced Nucleus Condensation

To study the effect of taurine on Glu-induced apoptosis, neuronal cell cultures at 12–14 DIV were treated with 50 μM Glu for 24 hours. Hoechst 33342 was used to show nuclear morphology. As shown in Fig. 17.4, compared with the control group (panel A), a 20-hour treatment of 50μM Glu induced nuclear condensation

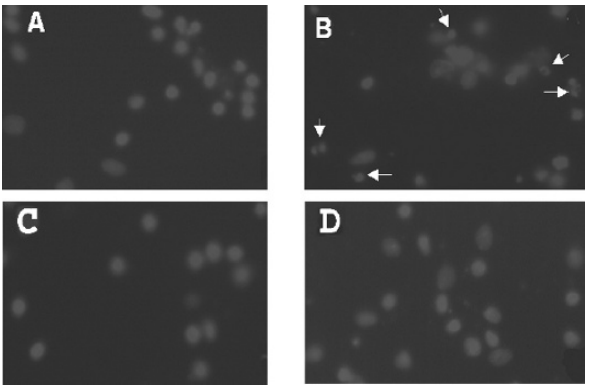

Fig. 17.4 Effect of taurine on the Glu-induced apoptosis: Hoechst 33342 staining. (**A**) Control; (**B**) Glu; (**C**) Glu plus taurine. (**D**) Glu plus calpastatin. Arrows indicate the condensed nuclei

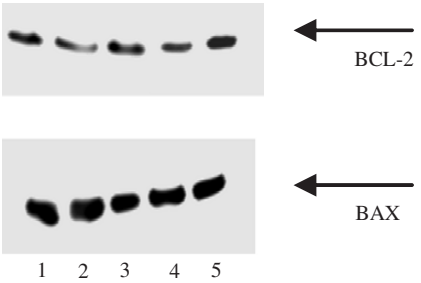

Fig. 17.5 Effect of taurine on the Glu-induced change in BCL-2 and BAX. 1. Control; 2. Glu; 3. Glu plus taurine; 4. Glu; 5.Glu plus calpastatin

(panel B), indicating that Glu stimulation induced apoptosis in primary neuronal cultures. The Glu-induced nuclear condensation was inhibited by calpastatin (panel D), a specific calpain inhibitor, suggesting the involvement of calpain, a calcium-dependent cysteine protease, in the Glu-induced apoptosis. The Glu-induced nuclear condensation was also prevented by the presence of taurine (panel C), suggesting that taurine can protect neurons against the Glu-induced apoptosis.

17.3.5 Effect of Taurine and Calpastatin on the Glu-Induced Change of BCL-2 and BAX

The BCL-2 family is a family of proteins involved in regulating apoptosis. Among these, BCL-2 antagonizes apoptosis, while BAX promotes the occurrence of apoptosis, and the balance between BCL-2 and BAX regulates apoptosis. Based on the immuno-blotting results (Fig. 17.5), the level BCL-2 was decreased by the Glu treatment (upper panel, lane 2 and 4). Interestingly, in the presence of either taurine or calpastatin, Glu-induced decrease of BCL-2 level was not observed (upper panel lane 3 and 5) indicating that the Glu-induced down-regulation of BCL-2 was prevented by taurine or calpastatin.

Contrary to BCL-2, the level of BAX was not affected by treatment of all 3 groups: Glu alone, Glu plus taurine, and Glu plus calpastatin (Fig. 17.5, lower panel).

17.3.6 Effect of Taurine and Calpastatin on the Glu-Induced Calpain Activation

It was reported that BCL-2 is a substrate of calpain, and we showed that calpastatin inhibited Glu-induced nuclear condensation in the primary neuronal cell culture. The effect of Glu on calpain activity was examined by measuring the cleavage of spectrin, a specific endogenous calpain substrate. The ratio of the cleaved to the total

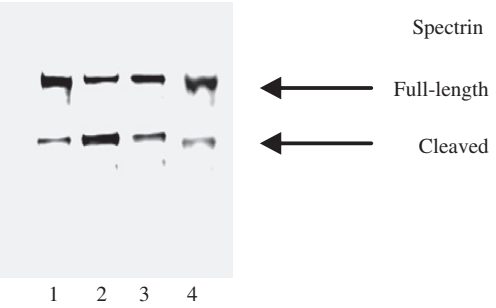

Fig. 17.6 Effect of taurine on the Glu-induced cleavage of spectrin. 1. Control; 2. Glu; 3. Glu plus taurine; 4. Glu plus calpastatin

spectrin increased by 2.5 folds (Fig. 17.6, lane 2) after Glu treatment compared to the control group, indicating the activation of calpain by Glu stimulation. Furthermore, the Glu-induced activation of calpain was largely inhibited by taurine (lane 3) and calpastatin (lane 4).

17.4 Discussion

Glu is the major excitatory amino acid neurotransmitter in the mammalian central nervous system. Glu plays an important role in neuronal differentiation, migration and survival in the developing brain (Ikonomidou et al. 1999; Behar et al. 1999; Hirai et al. 1999; Wu et al. 1996; Komuro and Rakic 1993) as well as in synaptic maintenance and plasticity (Wu et al. 1996). However, excessive extracellular Glu can cause cell damage, even cell death, by increasing intracellular free calcium. It has been well established that taurine protects neurons against Glu-induced neuronal damage in the primary neuronal culture. The neuroprotective effect of taurine is attributed to its functions in maintaining intracellular calcium homeostasis, membrane integrity (Pasantes-Morales and Cruz 1984; 1985) and as an antioxidant.

In our studies, neurons survived only in the presence of a high concentration of taurine, but not with a low concentration of taurine that failed to prevent the Glu-induced calcium influx (data not shown), suggesting an important role of taurine-mediated calcium homeostasis. We further found that taurine blocked calcium influx through L-, P/Q-, and N-type VGCCs, whose opening depends on the membrane depolarization. One interesting finding is that taurine blocked calcium influx through the NMDA receptor calcium channel only when regular EBSS with Mg^{2+} was used, but not with the use of Mg^{2+}-free EBSS. It is known that NMDA receptor is ligand- and membrane-potential dependent when $Mg^{2+}$is trapped in its channel pore and is only ligand-dependent when Mg^{2+} is absent. This finding implies that taurine does not act directly on the NMDA receptor, but via its effect on membrane potential. Interestingly, a report by Chen et al. (2001) that taurine inhibits calcium influx through the reverse mode of Na^{+}/Ca^{2+} exchanger (whose activity is

membrane potential-dependent) suggests that the neuroprotection of taurine is mediated by its function of preventing Glu-induced membrane depolarization as we also demonstrated previously (Wu et al. 2005). Here, we propose that taurine protects neurons against Glu excitotoxicity by preventing Glu-induced membrane depolarization, probably through its effect in opening of chloride channels and, therefore, preventing the Glu-induced increase in calcium influx and other downstream events.

The exposure to excessive Glu causes neuronal damage including both necrosis and apoptosis depending on the recovery of the mitochondrial function (Ankarcrona et al. 1995). It is reported that the Glu-induced apoptosis accounts for the neuronal degeneration in some neurological diseases such as Alzheimer's disease (Masliah et al. 1998) and Huntington's disease (Portera-Cailliau et al. 1995). In our study, we also found that taurine prevented Glu-induced DNA fragmentation and nuclear condensation, indicating that taurine can prevent the Glu-induced apoptosis. We also found that BCL-2 protein (an anti-apoptotic protein) level was down-regulated by Glu treatment, and this down-regulation was prevented in the presence of taurine. On the other hand, Glu stimulation caused no change in BAX protein (a pro-apoptotic protein) level. BAX can form homodimers, which attack mitochondria and lead to the release of cytochrome C, which in turn initiates the caspase cascade and apoptosis (Henshall et al. 2002). Since BCL-2 forms heterodimers with BAX to prevent mitochondria from attack by homodimers of BAX, the restoration of the balance of BCL-2/BAX by taurine protects neurons from apoptosis. Furthermore, we found that taurine treatment prevented Glu-induced cleavage of spectrin, a specific

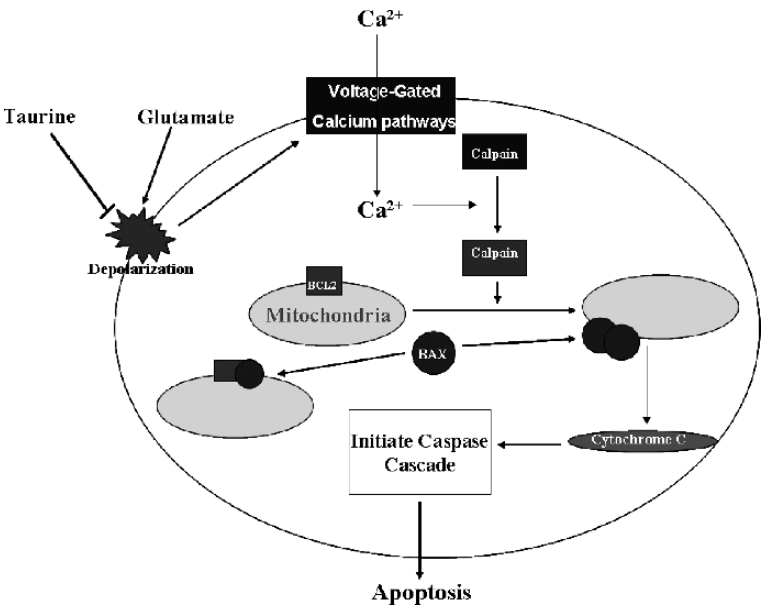

Fig. 17.7 A model depicting the pathway that taurine exerts its function against Glu-induced apoptosis (see discussion)

endogenous substrate of calpain, suggesting that taurine inhibits Glu-induced activation of calpain, a calcium-dependent cysteine protease. It was reported that BCL-2 is a substrate of calpain, therefore, taurine restores the balance of BCL-2/BAX by preventing Glu-induced activation of calpain. This was confirmed by the experiment with calpastatin, a specific calpain inhibitor, which also prevented the Glu-induced nuclear condensation and down-regulation of BCL-2. Here we propose the sequence of events leading from Glu stimulation to apoptosis and the mode of action of taurine in preventing Glu-induced apoptosis are as follows (Fig. 17.7): (1) Glu stimulation induces $[Ca^{2+}]_i$ elevation which in turn activates calpain; (2) The activated calpain cleaves BCL-2; (3) Glu stimulation also induces a conformational change of BAX resulting in formation and activation of homodimers of BAX; (4) With decreased protection from BCL-2, the homodimers of BAX target the mitochondria and lead to the release of cytochrome C; (5) Released cytochrome C activates Apaf-1 which in turn activates a downstream caspase cascade leading to apoptosis; (6) The anti-apoptotic function of taurine is due to its capability of preventing Glu-induced $[Ca^{2+}]_i$ elevation by preventing Glu-induced depolarization resulting in the blockade of all the downstream events.

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