

Chapter 2

Taurine and Its Neuroprotective Role

Neeta Kumari, Howard Prentice, and Jang-Yen Wu

Abstract Taurine plays multiple roles in the CNS including acting as a neuro-modulator, an osmoregulator, a regulator of cytoplasmic calcium levels, a trophic factor in development, and a neuroprotectant. In neurons taurine has been shown to prevent mitochondrial dysfunction and to protect against endoplasmic reticulum (ER) stress associated with neurological disorders. In cortical neurons in culture taurine protects against excitotoxicity through reversing an increase in levels of key ER signaling components including eIF-2-alpha and cleaved ATF6. The role of communication between the ER and mitochondrion is also important and examples are presented of protection by taurine against ER stress together with prevention of subsequent mitochondrial initiated apoptosis.

2.1 Introduction

Taurine, or 2-aminoethanesulfonic acid, is a sulfonic acid which is derived from cysteine and it is one of the few naturally occurring sulfonic acids. Taurine is widely distributed in animal tissues and one of the most abundant amino acid in mammals. Taurine plays several crucial roles including modulation of calcium signaling, osmoregulation, and membrane stabilization. However, despite extensive study, the mechanisms of action of taurine are not well understood. Based on past studies taurine has appeared as a promising agent for treating several neurological disorders including Alzheimer's disease, Huntington's disease, and stroke because of its ability to prevent apoptosis and its capacity to act as an antioxidant.

N. Kumari • H. Prentice (✉) • J.-Y. Wu (✉)
Department of Biomedical Science, Charles E. Schmidt College of Medicine,
Florida Atlantic University, 777 Glades Road, Boca Raton, FL 33431, USA
e-mail: neetazephyr@gmail.com; hprentic@fau.edu; jwu@fau.edu

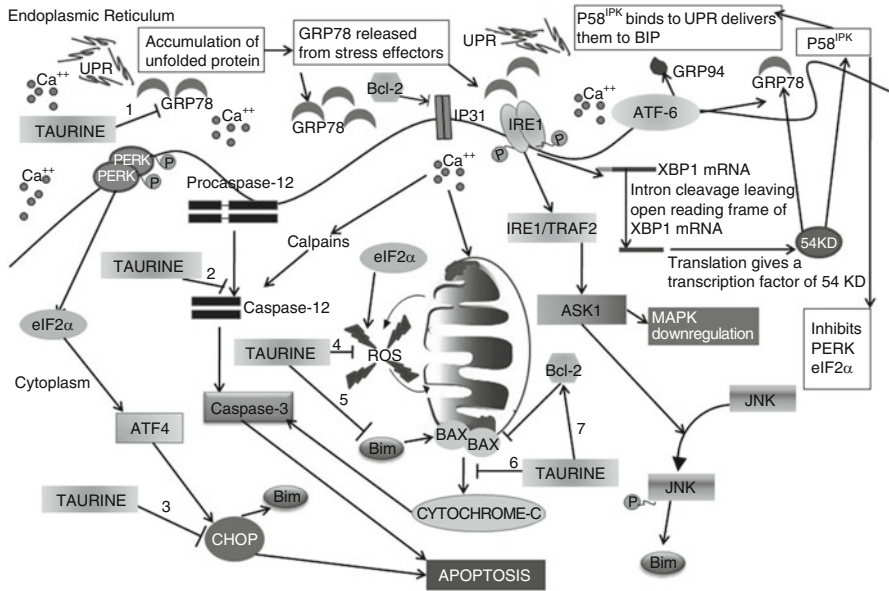


Fig. 2.1 Diagram showing the mode of action of taurine in alleviating the apoptosis induced by ER stress and mitochondrial dysfunction. The sites of action of taurine regulation are indicated as follows: (1) decreased Grp78, (2) decreased caspase 12, (3) decreased CHOP, (4) decreased ROS levels, (5) decreased Bim, (6) decreased cytochrome C release, and (7) increased Bcl-2

In this chapter, we will focus on the neuroprotective role of taurine. There has been extensive research demonstrating that taurine has a unique protective role and that it can downregulate several stress-associated proteins and increase neuronal survival under conditions of glutamate-induced cytotoxicity, mitochondrial stress, and endoplasmic reticulum (ER) stress (Fig. 2.1).

2.2 Taurine and Its Receptors

The taurine-synthesizing enzyme cysteine sulfinic acid decarboxylase (CSAD) in the brain was first identified and purified (Wu 1982) and then localized in the hippocampus (Taber et al. 1986), cerebellum (Chan-Palay et al. 1982b; Chan-Palay et al. 1982a), and the retina (Chan-Palay et al. 1982b; Chan-Palay et al. 1982a; Wu et al. 1985). Taurine fulfills most of the criteria as a neurotransmitter as the molecule is released from neurons in a calcium-dependent manner and binds to specific receptors postsynaptically (Lin et al. 1985a; Lin et al. 1985b; Wu and Prentice 2010; Wu et al. 1985). Taurine is of great interest as a potential neuroprotectant preventing excitotoxicity caused by glutamate which is a major excitatory neurotransmitter in the CNS. Part of the effect of taurine in neuroprotection involves

preventing calcium entry into neurons through its action on L, P/Q, and N-type calcium channels and NMDA-R calcium channels (Wu et al. 2005). The mechanisms by which taurine modulates voltage-gated calcium channels may involve binding to GABA/glycinergic receptors resulting in hyperpolarization. Under conditions of excessive calcium entry taurine can downregulate this process. Taurine acts as an agonist of GABA and glycine receptors increasing the duration of chloride channel conductance (for review, Wu and Prentice 2010). Besides taurine binding to GABAergic or glycinergic receptors, we have previously reported that there are also taurine-specific receptors because blocking agents specific to GABA and glycine receptors were found to exert only a minimal effect on taurine receptor binding in neurons (Wu et al. 1992). Taurine is also important for regulating osmotic stress, a cellular response that is reduced though taurine's action on blocking sodium/calcium exchangers, K(ATP) channels, voltage-gated calcium channels, and fast acting sodium channels (Takatani et al. 2004a).

2.3 Role of Taurine in Mitochondrial Dysfunction

Mitochondria are highly sensitive to oxidative damage and there is much evidence of a cytoprotective role of taurine towards mitochondria in addition to other organelles within the cell. In mitochondria, taurine has been shown to be a key regulator of levels of superoxide production and of oxidative phosphorylation since taurine deficiency results in oxidative stress in mitochondria through respiratory chain impairment. Many taurine-conjugated products are functionally involved in energy metabolism and cholesterol metabolism (Schuller-Levis and Park 2003; Yokogoshi et al. 1999). One of the key products is 5-taurinomethyluridine-tRNA^{leu} (UUR) which is involved in stabilization of U-G pairing in an anticodon loop transfer RNA (tRNA) responsible for efficient decoding of UUG (Kurata et al. 2008). Taurine deficiency lowers the taurinomethyluridine-tRNA^{leu} encoded protein synthesis disabling efficient assembly of respiratory chain components (Schaffer et al. 2009).

Superoxide generation is the result of the diversion of electrons to acceptor oxygen from the respiratory chain (Jong et al. 2011a; Jong et al. 2011b). Mitochondrial DNA mutations can cause mitochondrial dysfunction which has been found to be the primary cause of several kinds of mitochondrial disease. Some key studies have demonstrated that these mutated mt tRNAs are the result of the absence of posttranscriptional taurine-dependent modifications leading to the molecular pathogenesis of mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) and a second disease, myoclonus epilepsy, associated with ragged red fibers (MERRF) (Suzuki et al. 2002). In an investigation of the protective role of taurine in a rat model of stroke it was shown that taurine can preserve mitochondrial function and prevent the cell death mediated by the mitochondrial pathway of apoptosis (Sun et al. 2011).

2.4 Role of Taurine in Endoplasmic Reticulum Stress

The accumulation of misfolded proteins leading to endoplasmic reticulum stress (ER stress) interferes with neuronal signaling and induces neuronal cell death. Under such conditions of neuronal stress the unfolded protein response (UPR) becomes activated to restore normal cellular function by activating three signaling systems: PERK (PKR-like endoplasmic reticulum kinase), IRE 1 (inositol-requiring enzyme 1), and ATF 6 (activation transcription factor 6) which then regulate protein synthesis during ER stress at both the transcriptional and posttranscriptional levels (Harding et al. 2003; Kaufman 1999). In addition to misfolding of proteins, calcium overload and oxidative stress all can lead to endoplasmic reticulum stress (Lai et al. 2007). The accumulation of unfolded proteins within the ER lumen leads to dissociation of GRP 78 (glucose-regulated protein 78) from PERK, IRE1, and ATF 6, respectively, which is the initiating step in activation of these signaling molecules and their downstream signaling counterparts (Bertolotti et al. 2000; Shen et al. 2002). The primary function of PERK, IRE1, and ATF 6 is to activate signaling events to overcome ER stress but under severe conditions of stress when the UPR system fails to restore correct protein folding and processing capacity PERK, IRE 1, and ATF 6 can also activate apoptosis, not directly, but by activating downstream pro-death components including CHOP, JNK, and caspases (Anand and Babu 2012; Higo et al. 2010; Sokka et al. 2007) (Fig. 2.1).

Taurine is effective in reducing ER stress in a number of neural systems including PC12 cell cultures, primary neuronal cultures, and human neuroblastoma cell lines. Taurine exerts its neuroprotective function in part by restoring the integrity of the structure and function of the ER. Treatment with taurine under conditions of oxidative stress, excitotoxicity, or hypoxic stress results in a decrease in levels of expression of a number of ER stress proteins including Grp 78, CHOP/GADD153, p-IRE and p-eI0046–2 alpha protein, and caspase-12, as well as a decreased ratio of cleaved ATF6 and full-length ATF6 and a decreased ratio of Bax/Bcl2 (Pan et al. 2011; Pan et al. 2010) (Fig. 2.1).

2.5 Role of Taurine in Apoptosis

Taurine has the ability to downregulate several of the molecules that trigger apoptosis. In a recent study on neuronal cell cultures taurine treatment resulted in decreased levels of the Bax to Bcl-2 ratio after exposure to glutamate (Leon et al. 2009). Taurine was able to prevent the decline in Bcl-2 expression in these cultures in the presence of glutamate (Leon et al. 2009). A major route by which taurine can regulate apoptosis is by decreasing intracellular free calcium through inhibiting different types of calcium channels (Leon et al. 2009) and also by increasing of Ca^{2+} levels in mitochondria (Taranukhin et al. 2010) (Fig. 2.1).

Furthermore beyond its reported antioxidant roles there is substantial evidence that taurine can act on apoptotic components and will help to restore the cellular

Bcl-2 pool. Previous studies have shown that taurine can prevent release of cytochrome c from mitochondria and also suppress the assembly of the Apaf 1/caspase-9 apoptosome complex preventing caspase-9 activation (Takatani et al. 2004b). Further studies investigating this pathway revealed that taurine regulates the interaction of Apaf 1 and caspase-9 through Akt (Takatani et al. 2004a).

In an investigation of morphine-induced toxicity in C6 glioma cells taurine reversed the depletion of Bcl-2 levels in conjunction with increasing the activities of superoxide dismutase, catalase, and glutathione peroxidase (Taranukhin et al. 2010). Thus taurine contributed to preventing the oxidative insult that resulted in morphine-induced apoptosis (Zhou et al. 2011).

2.6 Role of Taurine in Neurological Diseases

In stroke the loss of blood supply leads to ischemic stress which is characterized by an increase in intracellular free calcium, elevated reactive oxygen species, and the development of acidosis. Previous studies have shown the ability of taurine to maintain neuronal calcium homeostasis and to prevent neuronal cell death occurring through necrosis or apoptosis as well as through ER stress (Mantopoulos et al. 2011; Zhang et al. 2010). In stroke patients it is reported that plasma concentrations of taurine are increased (Ghandforoush-Sattari et al. 2011). Further studies are examining the extent to which taurine levels may be a biomarker for recovery in stroke. In experimental stroke administration of taurine can protect in a dose-dependent manner through mechanisms that include up-regulation of calpastatin and down-regulation of calpain and caspase-3 (Sun et al. 2009). In a recent analysis of the effects of taurine on inflammatory markers 22 h after a 2 h transient brain ischemia it was shown that both poly (ADP-ribose) polymerase (PARP)- and nuclear-factor-kappa-B (NF-kB)-driven expression of inflammatory mediators was suppressed by taurine (Sun et al. 2012). Specifically taurine administration resulted in decreased levels of tumor necrosis factor-alpha, interleukin-i-beta, inducible nitric oxide synthase, and intracellular adhesion molecule-1.

A rat model of Huntington's disease resulting from striatal lesions induced by the mitochondrial toxin 3-NP has been employed for an investigation of the protective effects of taurine. It was found that pretreatment with taurine significantly protected against the behavioral deficits in this model and increased locomotor activity (Tadros et al. 2005).

In spinal cord injury, the neutrophils that migrate to the site of injury have been shown to contain high taurine concentrations. Using a spinal cord compression model, treatment with taurine was shown to inhibit expression of the pro-inflammatory cytokine IL-6 and to decrease phosphorylation of STAT3 and expression of COX2. In the taurine-fed mice there was a reduced accumulation of neutrophils in addition to recovery of function of the mouse hind-limb (Nakajima et al. 2010).

In epilepsy an imbalance in amino acid content in epileptic foci is found which is characterized by low concentrations of glutamate and taurine and high levels of glycine (Guilarte 1989). Administration of taurine rectifies this imbalance of amino acids through alterations in membrane fluidity and activation of membrane enzymes and transporters including the sodium/calcium exchanger (Jong et al. 2011b). Several studies report that taurine can reverse epileptic symptoms (Junyent et al. 2011; Junyent et al. 2010) and in the KA experimental model increased taurine levels have been reported (Baran 2006). Using a KA mouse model of epilepsy it was recently demonstrated that administration of taurine 12 h before KA administration elicited a reduction or even a disappearance of cellular and molecular KA-derived effects.

Elevated calcium in neurons is strongly linked to seizure activity and a recent study addressed the effects of taurine treatment in mice on the expression of proteins in the hippocampus associated with calcium regulation. Taurine inhibited CaMKII activity in hippocampus which may be related to its neuroprotective effect. Other calcium-binding proteins including calbindin-D28k, calretinin, and parvalbumin were also increased in expression within the same time frame as the previously reported anticonvulsant effect of taurine (Junyent et al. 2010).

2.7 Communication Between the ER and Mitochondrion

Communication between the ER and mitochondrion may play an important role in regulating intracellular free calcium levels. In stressed conditions the ER can trigger signaling events that result in cytochrome C release from the mitochondrion. An integral protein of the ER membrane BAP 31 (B-cell-associated protein 31) is a caspase cleavage product which has been shown to induce mitochondrial fission through ER-derived calcium signals that enhance cytochrome C release (Rutter and Rizzuto 2000). Once released, cytochrome C can translocate to ER where it binds with IP3R and causes a sustained increase in cytosolic calcium levels (Boehning et al. 2003; Wang and El-Deiry 2004). ER stress resulting from the accumulation of unfolded proteins is associated with several neurological diseases including Alzheimer's disease, Parkinson's disease, and cerebral stroke. It is likely that in these disease conditions an increase in intracellular free calcium can lead to ER stress and that ER stress may also be responsible for triggering mitochondrial dysfunction and subsequent apoptosis. Therapeutic interventions controlling ER stress may therefore have potential for preventing apoptotic responses. In a study on the effect of taurine against transient focal cerebral ischemia one proposed protective mechanisms of taurine against ischemia was through blocking the mu-calpain and caspase-3-mediated apoptotic cell death pathways (Sun and Xu 2008). Taurine has been shown in a number of studies to diminish the damaging effects of ER stress. In a recent study on *C. elegans* exposed to the ER stress inducer tunicamycin it was found that taurine treatment was able to enhance longevity, mobility, and fecundity of the organism (Kim et al. 2010).

2.8 Conclusion

In summary, taurine exerts its neuroprotective function minimally through its action at both the mitochondrial and ER levels by decreasing the expression and/or the activity of Grp78, caspase-12, CHOP, ROS levels, Bim, and cytochrome C release and increasing the level of Bcl-2. The details of the mechanism at each step need further investigation.

References

- Anand SS, Babu PP (2012) Endoplasmic reticulum stress and neurodegeneration in experimental cerebral malaria. *Neurosignals*. doi:[10.1159/000336970](https://doi.org/10.1159/000336970)
- Baran H (2006) Alterations of taurine in the brain of chronic kainic acid epilepsy model. *Amino Acids* 31:303–307
- Bertolotti A, Zhang Y, Hendershot LM et al (2000) Dynamic interaction of BiP and ER stress transducers in the unfolded-protein response. *Nat Cell Biol* 2:326–332
- Boehning D, Patterson RL, Sedaghat L et al (2003) Cytochrome c binds to inositol (1,4,5) trisphosphate receptors, amplifying calcium-dependent apoptosis. *Nat Cell Biol* 5:1051–1061
- Chan-Palay V, Lin CT, Palay S et al (1982a) Taurine in the mammalian cerebellum: demonstration by autoradiography with [3H]taurine and immunocytochemistry with antibodies against the taurine-synthesizing enzyme, cysteine-sulfinic acid decarboxylase. *Proc Natl Acad Sci USA* 79:2695–2699
- Chan-Palay V, Palay SL, Wu JY (1982b) Sagittal cerebellar microbands of taurine neurons: immunocytochemical demonstration by using antibodies against the taurine-synthesizing enzyme cysteine sulfinic acid decarboxylase. *Proc Natl Acad Sci USA* 79:4221–4225
- Ghandforoush-Sattari M, Mashayekhi SO, Nemati M, Ayromlou H (2011) Changes in plasma concentration of taurine in stroke. *Neurosci Lett* 496:172–175
- Guilarte TR (1989) Regional changes in the concentrations of glutamate, glycine, taurine, and GABA in the vitamin B-6 deficient developing rat brain: association with neonatal seizures. *Neurochem Res* 14:889–897
- Harding HP, Zhang Y, Zeng H et al (2003) An integrated stress response regulates amino acid metabolism and resistance to oxidative stress. *Mol Cell* 11:619–633
- Higo T, Hamada K, Hisatsune C et al (2010) Mechanism of ER stress-induced brain damage by IP(3) receptor. *Neuron* 68:865–878
- Jong CJ, Azuma J, Schaffer S (2011a) Mechanism underlying the antioxidant activity of taurine: prevention of mitochondrial oxidant production. *Amino Acids* 42:2223–2232
- Jong CJ, Azuma J, Schaffer SW (2011b) Role of mitochondrial permeability transition in taurine deficiency-induced apoptosis. *Exp Clin Cardiol* 16:125–128
- Junyent F, Porquet D, de Lemos L et al (2011) Decrease of calbindin-d28k, calretinin, and parvalbumin by taurine treatment does not induce a major susceptibility to kainic acid. *J Neurosci Res* 89:1043–1051
- Junyent F, Romero R, de Lemos L et al (2010) Taurine treatment inhibits CaMKII activity and modulates the presence of calbindin D28k, calretinin, and parvalbumin in the brain. *J Neurosci Res* 88:136–142
- Kaufman RJ (1999) Stress signaling from the lumen of the endoplasmic reticulum: coordination of gene transcriptional and translational controls. *Genes Dev* 13:1211–1233
- Kim HM, Do C-H, Lee DH (2010) Taurine reduces ER stress in *C. elegans*. *J Biomed Sci* 17(Suppl 1): S1–S26

- Kurata S, Weixlbaumer A, Ohtsuki T et al (2008) Modified uridines with C5-methylene substituents at the first position of the tRNA anticodon stabilize U.G wobble pairing during decoding. *J Biol Chem* 283:18801–18811
- Lai E, Teodoro T, Volchuk A (2007) Endoplasmic reticulum stress: signaling the unfolded protein response. *Physiology* (Bethesda) 22:193–201
- Leon R, Wu H, Jin Y et al (2009) Protective function of taurine in glutamate-induced apoptosis in cultured neurons. *J Neurosci Res* 87:1185–1194
- Lin CT, Song GX, Wu JY (1985a) Is taurine a neurotransmitter in rabbit retina? *Brain Res* 337:293–298
- Lin CT, Song GX, Wu JY (1985b) Ultrastructural demonstration of L-glutamate decarboxylase and cysteinesulfinic acid decarboxylase in rat retina by immunocytochemistry. *Brain Res* 331: 71–80
- Mantopoulos D, Murakami Y, Comander J, Thanos A, Roh M, Miller JW, Vavvas DG (2011) Tauroursodeoxycholic acid (TUDCA) protects photoreceptors from cell death after experimental retinal detachment. *PLoS One* 6(9)
- Nakajima Y, Osuka K, Seki Y et al (2010) Taurine reduces inflammatory responses after spinal cord injury. *J Neurotrauma* 27:403–410
- Pan C, Giraldo GS, Prentice H, Wu J-Y (2010) Taurine protection of PC12 cells against endoplasmic reticulum stress induced by oxidative stress. *J Biomed Sci* 17(Suppl 1):S1–S17
- Pan C, Prentice H, Price AL, Wu J-Y (2011) Beneficial effect of taurine on hypoxia- and glutamate-induced endoplasmic reticulum stress pathways in primary neuronal culture. *Amino Acids* 43:845–855. doi:10.1007/s00726-011-1141-6
- Rutter GA, Rizzuto R (2000) Regulation of mitochondrial metabolism by ER Ca²⁺ release: an intimate connection. *Trends Biochem Sci* 25:215–221
- Schaffer SW, Azuma J, Mozaffari M (2009) Role of antioxidant activity of taurine in diabetes. *Can J Physiol Pharmacol* 87:91–99
- Schuller-Levis GB, Park E (2003) Taurine: new implications for an old amino acid. *FEMS Microbiol Lett* 226:195–202
- Shen J, Chen X, Hendershot L, Prywes R (2002) ER stress regulation of ATF6 localization by dissociation of BiP/GRP78 binding and unmasking of Golgi localization signals. *Dev Cell* 3:99–111
- Sokka A-L, Putkonen N, Mudo G et al (2007) Endoplasmic reticulum stress inhibition protects against excitotoxic neuronal injury in the rat brain. *J Neurosci* 27:901–908
- Sun M, Gu Y, Zhao Y et al (2011) Protective functions of taurine against experimental stroke through depressing mitochondria-mediated cell death in rats. *Amino Acids* 40:1419–1429
- Sun M, Xu C (2008) Neuroprotective mechanism of taurine due to up-regulating calpastatin and down-regulating calpain and caspase-3 during focal cerebral ischemia. *Cell Mol Neurobiol* 28(4):593–611
- Sun M, Zhao Y, Gu Y, Xu C (2009) Inhibition of nNOS reduces ischemic cell death through down-regulating calpain and caspase-3 after experimental stroke. *Neurochem Int* 54(5–6): 339–346
- Sun M, Zhao Y-M, Gu Y, Xu C (2012) Therapeutic window of taurine against experimental stroke in rats. *Transl Res* 160:223–229. doi:10.1016/j.trsl.2012.02.007
- Suzuki T, Suzuki T, Wada T et al (2002) Taurine as a constituent of mitochondrial tRNAs: new insights into the functions of taurine and human mitochondrial diseases. *EMBO J* 21:6581–6589
- Taber KH, Lin CT, Liu JW et al (1986) Taurine in hippocampus: localization and postsynaptic action. *Brain Res* 386:113–121
- Tadros MG, Khalifa AE, Abdel-Naim AB, Arafa HMM (2005) Neuroprotective effect of taurine in 3-nitropropionic acid-induced experimental animal model of Huntington's disease phenotype. *Pharmacol Biochem Behav* 82:574–582
- Takatani T, Takahashi K, Uozumi Y et al (2004a) Taurine prevents the ischemia-induced apoptosis in cultured neonatal rat cardiomyocytes through Akt/caspase-9 pathway. *Biochem Biophys Res Commun* 316:484–489. doi:10.1016/j.bbrc.2004.02.066
- Takatani T, Takahashi K, Uozumi Y et al (2004b) Taurine inhibits apoptosis by preventing formation of the Apaf-1/caspase-9 apoptosome. *Am J Physiol Cell Physiol* 287:C949–C953

- Taranukhin AG, Taranukhina EY, Saransaari P et al (2010) Neuroprotection by taurine in ethanol-induced apoptosis in the developing cerebellum. *J Biomed Sci* 17(Suppl 1):S1–S12
- Wang S, El-Deiry WS (2004) Cytochrome c: a crosslink between the mitochondria and the endoplasmic reticulum in calcium-dependent apoptosis. *Cancer Biol Ther* 3:44–46
- Wu H, Jin Y, Wei J et al (2005) Mode of action of taurine as a neuroprotector. *Brain Res* 1038: 123–131
- Wu J-Y, Prentice H (2010) Role of taurine in the central nervous system. *J Biomed Sci* 17(Suppl 1):S1–S6
- Wu JY (1982) Purification and characterization of cysteic acid and cysteine sulfinic acid decarboxylase and L-glutamate decarboxylase from bovine brain. *Proc Natl Acad Sci USA* 79:4270–4274
- Wu JY, Lin CT, Thalmann R et al (1985) Immunocytochemical and physiological identification of taurine neurons in the mammalian CNS. *Prog Clin Biol Res* 179:261–270
- Wu J-Y, Tang XW, Tsai WH (1992) Taurine receptor: kinetic analysis and pharmacological studies. *Adv Exp Med Biol* 315:263–268
- Yokogoshi H, Mochizuki H, Nanami K et al (1999) Nutrient interactions and toxicity dietary taurine enhances cholesterol degradation and reduces serum and liver cholesterol concentrations in rats fed a high-cholesterol diet. *J Nutr* 129:1705–1712
- Zhang B, Yang X, Gao X (2010) Taurine protects against bilirubin-induced neurotoxicity in vitro. *Brain Res* 1320:159–167
- Zhou J, Li Y, Yan G et al (2011) Protective role of taurine against morphine-induced neurotoxicity in C6 cells via inhibition of oxidative stress. *Neurotox Res* 20:334–342