Role of taurine in the central nervous system

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Abstract
Taurine demonstrates multiple cellular functions including a central role as a neurotransmitter, as a trophic factor in CNS development, in maintaining the structural integrity of the membrane, in regulating calcium transport and homeostasis, as an osmolyte, as a neuromodulator and as a neuroprotectant. The neurotransmitter properties of taurine are illustrated by its ability to elicit neuronal hyperpolarization, the presence of specific taurine synthesizing enzyme and receptors in the CNS and the presence of a taurine transporter system. Taurine exerts its neuroprotective functions against the glutamate induced excitotoxicity by reducing the glutamate-induced increase of intracellular calcium level, by shifting the ratio of Bcl-2 and Bad ratio in favor of cell survival and by reducing the ER stress. The presence of metabotropic taurine receptors which are negatively coupled to phospholipase C (PLC) signaling pathway through inhibitory G proteins is proposed, and the evidence supporting this notion is also presented.

Introduction
Taurine, 2-amino-ethanesulfonic acid, is one of the most abundant amino acids in mammals [1]. The physiological role of taurine has received considerable attention since the reports that cats fed a taurine deficient diet developed central retinal degeneration [2] and cardiomyopathy [3]. Now, taurine has been shown to be involved in many important physiological functions [for review, see [4]] e.g., as a trophic factor in the development of the CNS [5] and, for instance, kittens from the taurine-depleted mothers exhibit a delay in the migration of cells in the cerebellum and in the visual cortex [5]. It also serves in maintaining the structural integrity of the membrane [6], regulating calcium binding and transport [7,8], as an osmolyte [9,10], a neuromodulator [11], a neurotransmitter [12-18] and a neuroprotector against L-glutamate (L-Glu)-induced neurotoxicity [19,20]. In this article, the role of taurine in the central nervous system (CNS) as a neurotransmitter, a neuro-protective agent and a potent regulator for intracellular calcium homeostasis will be reviewed.

Taurine as a neurotransmitter
In general, a substance can be accepted as a neurotransmitter if it has fulfilled the following set of criteria: firstly, the substance and/or its synthesizing enzyme has to be present in the suspected neuron, preferably it is concentrated at the nerve terminal; secondly, it is released upon stimulation in a calcium-dependent manner; thirdly, it elicits proper physiological response; fourthly, a specific receptor is present and fifthly, an inactivation mechanism is present to terminate the action of the suspected neurotransmitter. The following lines of evidence have supported the notion that taurine is a neurotransmitter in the mammalian CNS: 1. The presence of a specific enzyme responsible for taurine biosynthesis in the brain, namely, cysteic/cysteine sulfinic acid decarboxylase (CAD/CSAD) which is distinctly different from the GABA-synthesizing enzyme, L-glutamate decarboxylase (GAD) was reported [21,22]. Immunocytochemical studies have revealed the localization of CAD/CSAD in the cell body, dendrite as well as in the nerve terminal [13][17][18][23][24-26]; 2. Release of taurine has been shown to be either calcium dependent or calcium independent [13]; 3. Taurine has been shown to elicit neuronal hyperpolarization presumably through its action by opening the chloride channels in the cerebellum [27] and in the hippocampus [14]; 4. The presence of a specific taurine receptor has been...
demonstrated. Previously we reported the presence of specific taurine receptors which have Kd in nM range and are distinctly different from GABA\(_A\), GABA\(_B\) and glycine receptors since the agonists or antagonists of these receptors have little effect on the binding of taurine to taurine receptors [28]. Similar observations were recently reported by Frosini et al [29]; 5. The presence of a taurine transporter system for inactivation of its function has also been reported [30]. In fact, taurine transporters have been cloned [31] and taurine transporter knock-out transgenic mice have been established [32]. In summary, taurine has fulfilled most if not all of the criteria to be accepted as a neurotransmitter in the mammalian CNS.

Regulation of intracellular calcium homeostasis

It is known that the level of intracellular free calcium, \([\text{Ca}^{2+}]_i\), is maintained at sub-micromolar concentration by calcium sequestering into internal calcium storage pools e.g., mitochondria, endoplasmic reticulum (ER) as well as pumping out to the extracellular space by calcium-ATPase. When neurons are stimulated by glutamate, the \([\text{Ca}^{2+}]_i\) level is elevated due to influx of calcium from extracellular sources through various calcium channels including NMDA receptors, voltage-gated calcium channels (VGCC) such as L-, N- and P/Q-type, reverse mode of Na\(^+\)/Ca\(^{2+}\) exchanger as well as release of calcium from the internal calcium storage pools. However, in the presence of taurine, glutamate-induced increase of \([\text{Ca}^{2+}]_i\) is markedly reduced as shown in Fig 1.

We [33] and El Idrissi & Trenkner [20] reported that one of the pathways by which taurine reduced glutamate-induced elevation of \([\text{Ca}^{2+}]_i\) is through inhibition of Ca\(^{2+}\) influx via the reverse mode of Na\(^+\)/Ca\(^{2+}\) exchanger. At the resting membrane potential, Na\(^+\)/Ca\(^{2+}\) exchanger functions to move Ca\(^{2+}\) out of the cell. However, under depolarizing conditions such as under glutamate stimulation, it reverses its function to facilitate Ca\(^{2+}\) influx [34]. The effect of taurine on Na\(^+\)/Ca\(^{2+}\) exchanger has been suggested to be in part due to in part its membrane stabilizing activity [35]. It has been shown that phospholipid N-methylation is associated with a decrease in Na\(^+\)/Ca\(^{2+}\) exchanger activity [36]. Hence, taurine-mediated reductions in phospholipid N-methyltransferase activity enhance efflux of Ca\(^{2+}\) through the Na\(^+\)/Ca\(^{2+}\) exchanger and lower tissue Ca\(^{2+}\) content. Taurine also promotes Ca\(^{2+}\) efflux via the Na\(^+\)/Ca\(^{2+}\) exchanger by increasing \([\text{Ca}^{2+}]_i\) in the vicinity of the exchanger. [35]. In addition to Na\(^+\)/Ca\(^{2+}\) exchanger, taurine also inhibits the release of Ca\(^{2+}\) from internal pools [37] as well as inhibits various voltage-gated calcium channels (VGCC) such as L-, N- and P/Q-type [38]. Although osmotic stress and taurine treatment were reported to affect various channels such as the Na\(^+\)/Ca\(^{2+}\)

![Figure 1](https://example.com/image.png)

**Figure 1** Effect of taurine on glutamate induced \([\text{Ca}^{2+}]_i\) accumulation (A) confocal study - A. Baseline; B & J. Glutamate; C, F & I. After washing; D. Nifedipine; E. Nifedipine plus glutamate; G. Taurine; H. Taurine plus glutamate. Color coding indicates \([\text{Ca}^{2+}]_i\), red being the highest and blue the lowest. (B). Accumulation of \(45\text{Ca}^{2+}\) influx - 1. Control; 2. Glutamate; 3. Glutamate plus 25mM taurine; 4. Glutamate plus 5mM taurine.

The ATP-sensitive K\(^+\) channel, the L-type VGCC and the fast Na\(^+\) channel [39], we believe that in neuronal systems, the effect of taurine on various calcium channels is likely due to a combination of counteraction of glutamate-induced depolarization by taurine as well as receptor-mediated G-protein coupled events. This notion is supported by the following observations: First of all, recently we have shown that when glutamate-induced membrane depolarization is abolished by taurine as measured by voltage-sensitive dye, the VGCC activity is also suppressed [38]. Secondly, Kaczmarek [40] reported that exposure of isolated bag cell neurons to activators of
A. Effect of taurine on PLC activity; B. A proposed model for the mode of action of taurine on the IP3 pathway.

A. Effect of taurine on PLC activity.

1. Control, 2. 0.25 mM Glu, 3. 25 mM taurine, 4. 25 mM taurine plus 0.25 mM Glu, 5. 10 μM carbachol. The error bar indicates the standard deviation with N=3. Briefly, 3H-inositol was used as precursor for [3H]-phosphoinositides (PI). Hydrolysis of [PI] to inositol phosphates, [IP]n, is an index of PLC activity. The experiments were performed as described previously [45]. Primary neuronal cultures in 35 mm dishes were first labeled with 8μCi of [3H, U]-inositol for 24 hours. The cells were washed with fresh medium containing 2 mM LiCl (to prevent IP3 dephosphorylation) and exposed to either Glu, taurine, or carbachol (a muscarinic cholinergic receptor agonist known to stimulate PLC), as indicated. Phosphoinositides, [PI], and inositol phosphates, [IP]n, were determined from the organic phase and aqueous phase, respectively as described [45]. The results are expressed as the ratio of [IP]n to [PI]. The results show that taurine reduces the production of basal level of [IP]n by 20% (column 3) and Glu-stimulated increase of [IP]n production by 40% (column 4). This coupled with the above results suggest that taurine may reduce the basal level or Glu-induced increase of poly-PI turnover through its inhibitory effect on PLC via inhibitory G-proteins e.g. Gi/Go-like proteins.

B. A proposed model for the mode of action of taurine on the IP3 pathway.

Diagram illustrating that taurine’s action on taurine receptors results in an inhibition of PLC activity causing a reduction in IP3 formation thus reducing IP3 mediated release of calcium from internal stores.
protein kinase C caused an increase in the amplitude of voltage-dependent calcium current. Since taurine can prevent protein phosphorylation, such as of its own synthesizing enzyme, CSAD [41], it is reasonable to believe that taurine also can prevent glutamate-induced VGCC activation by inhibiting phosphorylation of these channel proteins. Thirdly, previously we reported the presence of specific taurine receptors which have Kd in nM range and are distinctly different from GABA\text{A}, GABA\text{B}, glycine and glutamate receptors since the agonists or antagonists of these receptors have little effect on the binding of taurine to taurine receptors [42]. Similar observations were also reported by Frosini et al [29]. Furthermore, the binding of taurine to taurine receptors is inhibited by GTP or its non-hydrolyzable GTP analog, [\gamma-S]-GTP, in a dose-dependent manner [43]. It is believed that binding of GTP to the \alpha-subunit of G-protein promotes the dissociation of G-protein from the receptors resulting in the conversion of receptors back to their low affinity conformation. Fourthly, the inhibitory effect of GTP on taurine receptor binding disappeared once G-proteins were removed from the receptors by treating the membranes with a low concentration of Triton X-100 [43]. Fifthly, Glu-induced elevation of [Ca\text{2+}]i in the absence of extracellular Ca\text{2+} is inhibited by taurine suggesting that taurine inhibits the Glu-induced release of Ca\text{2+} from the internal pools [37]. It is of interest that GABA\text{B} receptor agonists such as baclofen were reported to inhibit a variety of VGCCs including L-, N- and P/Q-type VGCC through GABA\text{B} receptor-coupled inhibitory G-proteins, G\text{o} and G\text{i} [44]. Here we propose that similar to the GABA\text{B} receptors, when the metabotropic taurine receptors (mTauR) are activated by taurine, the coupled inhibitory G-proteins e.g. G\text{o}/G\text{i} are then activated resulting in inhibition of VGCCs. Furthermore, we propose that mTauR are negatively coupled to phospholipase C (PLC) through inhibitory G-proteins, e.g. G\text{o}/G\text{i} analogous to the GABA\text{B} receptors which are negatively coupled to adenylyl cyclase through inhibitory G-proteins [44]. Activation of taurine receptors by taurine would lead to inhibition of PLC activity (Fig 2), resulting in reduction in IP3 formation and hence IP3-mediated release of Ca\text{2+} from the internal pools.

**Taurine as a neuroprotective agent**

One important function of taurine is its neuro-protective function. We [19,33] as well as others [20] have shown that taurine can effectively prevent glutamate-induced neuronal injury in cultured neurons. In addition, we have...
also demonstrated that taurine can protect against H$_2$O$_2$-induced cell injury in PC12 cell cultures by reducing H$_2$O$_2$-induced ER stress (Pan et al 2010, in this issue). It is generally believed that taurine’s neuroprotective functions are due to its role in reducing intracellular free Ca$^{2+}$ concentration, [Ca$^{2+}$], and its anti-oxidative stress capacity [33,35]. We have recently shown that taurine can shift the ratio of the anti-apoptotic protein, Bcl-2 and the subsequent release of cytochrome C and the apoptosis cascade [38]. The sequence of events by which that taurine exerts its neuroprotective function can be summarized as follows:

1. Taurine reduces glutamate-induced elevation of [Ca$^{2+}$], by inhibiting calcium influx from various calcium channels including the reverse mode of Na$^+$/Ca$^{2+}$ exchanger, various voltage-gated calcium channels (VGCC) such as L-, N- and P/Q-type, and glutamate NMDA receptors.

2. Taurine inhibits phosphorylation of VGCC resulting in decrease of calcium influx 3. Taurine also reduces the release of calcium from the internal storage pools presumably due to inhibition of phospholipase C.

3. Taurine inhibits glutamate-induced activation of calpain and the subsequent hetero-dimerization of Bcl-2 and Bax protein resulting in inhibition of release of cytochrome C and the apoptosis cascade (Fig 3).

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Competing interests

The authors declare that they have no competing interests.

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References

1. Jacobsen JS, Smith LH: Biochemistry and physiology of taurine and taurine derivatives. Physiol Rev 1988, 48:424-511.
2. Haynes KC, Carey RE, Schmidt SY: Retinal degeneration associated with taurine deficiency in the cat. Science 1975, 188:949-951.
3. Pion PD, Kletleson MD, Rogers QR, Morris JR: Myocardial failure in cats associated with low plasma taurine: A reversible cardiomyopathy. Science 1987, 237:764-766.
4. Huxtable RJ: Expanding the circle 1975-1999: sulfur biochemistry and insights on the biological functions of taurine. Adv Exp Med Biol 2000, 483:1-25.
5. Sturman JA: Taurine in development. Physiol Rev 1993, 73:119-147.
6. Moran J, Salazar P, Pasantes-Morales H: Effect of tocopheryl and taurine on membrane fluidity of retinal rod outer segments. Experimental Eye Research 1988, 45:769-776.
7. Lazarewicz JW, Noremborg K, Lehmman A, Hamberger A: Effects of taurine on calcium binding and accumulation in rabbit hippocampal and cortical synaptosomes. Neurochem Int 1985, 7:421-428.
8. Lombardini JB: Effects of taurine on calcium ion uptake and protein phosphorylation in rat retinal membrane preparations. J Neurochem 1985, 45:268-275.
9. Solia JM, Henraz G, Herreras O, Lerma J, Del Rio RM: Does taurine act as an osmoregulatory substance in the rat brain. Neurosci Lett 1988, 91:53-58.
10. Wade JV, Olsen JP, Samson FE, Nelson SR, Pazdernik TL: A possible role for taurine in osmoregulation within the brain. J Neurochem 1988, 51:740-745.
11. Kuriyama K: Taurine as a neuromodulator. Fed Proc 1980, 39:2680-2684.
12. Okamoto K, Kimura H, Sakai Y: Evidence for taurine as an inhibitory neurotransmitter in cerebellar stellate interneurons: Selective antagonism by TAG (6-aminomethyl-3-methyl-4H,1,2-benzothiazidine-1,1-dioxide). Brain Res 1983, 265(1):163-168.
13. Lin C-T, Su Y,T, Song G-X, Wu J-Y: Is taurine a neurotransmitter in rabbit retina? Brain Res 1985, 337:293-296.
14. Taber TC, Lin C-T, Song G-X, Thalman RH, Wu JY: Taurine in the rat hippocampus-localization and postsynaptic action. Brain Res 1986, 386:113-121.
15. Cunningham R, Miller RF: Taurine: Its selective action on neuronal pathways in the rabbit retina. Brain Res 1976, 117:341-345.
16. Mandel P, Pasantes-Morales H, Urban PF: Taurine, a putative transmitter in retina. Transmitters in the Visual Process Oxford: Pergamon, OxfordBoringst, 1979, 89-105.
17. Lin C-T, Li H-Z, Wu J-Y: Immunocytochemical localization of L-glutamate decarboxylase, gamma aminobutyric acid transaminase, cysteine-sulfinic acid decarboxylase, aspartate aminotransferase and somatotatin in rat retina. Brain Res 1983, 270:273-283.
18. Lin C-T, Song G-X, Wu J-Y: Ultrastructural demonstration of L-glutamate decarboxylase and cysteine-sulfinic acid decarboxylase in rat retina by immunocytochemistry. Brain Res 1985, 331:71-80.
19. Tang XW, Deupree DL, Sun Y, Wu J-Y: Biphaseic effect of taurine on excitatory amino acid-induced neurotoxicity. Taurine: Basic and Clinical Aspects New York: Plenum Publishing Co.R. J. Huxtable RJ, Azuma J, Nakagawa M, Kuriyama K, Bala A. 1996, 499-506.
20. El Edrisi A, Trenkner E: Growth factors and taurine protect against excitotoxicity by stabilizing calcium homeostasis and energy metabolism. J Neurosci 1999, 19:9459-9468.
21. Wu J-Y, Moss LG, Chen MS: Tissue and regional distribution of cysteic acid decarboxylase in bovine brain. A new assay method. Neurochem Res 1979, 4:201-212.
22. Wu J-Y: Purification and characterization of cysteic/cysteine sulfonic acids decarboxylase and L-glutamate decarboxylase in bovine brain. Proc Natl Acad Sci USA 1982, 79:4270-4274.
23. Chan-Palay V, Lin CT, Palay S, Yamamoto M, Wu J-Y: Taurine in the mammalian cerebellum: Demonstration by autoradiography with [3H] taurine and immunocytochemistry with antibodies against the taurine-synthesizing enzyme, cysteine-sulfonic acid decarboxylase. Proc Natl Acad Sci USA 1982, 79:2695-2699.
24. Chan-Palay V, Palay SL, Li C, Wu J-Y: Sagittal cerebellar micro-bands of taurine neurons: Immunocytochemical demonstration by using antibodies against the taurine-synthesizing enzyme cysteine sulfonic acid decarboxylase. Proc Natl Acad Sci USA 1982, 79:4221-4225.
25. Magnusson KR, Madri JA, Clements JR, Wu J-Y, Larson AA, Betz AJ: Co-localization of taurine- and cysteine sulfonic acid decarboxylase-like immunoreactivity in the cerebellum of the rat with the use of a novel monoclonal antibody against taurine. J Neurosci 1988, 8(12):4551-4554.
26. Magnusson KR, Clements JR, Wu J-Y, Betz AJ: Co-localization of taurine- and cysteine sulfonic acid decarboxylase-like immunoreactivity in the hippocampus of the rat. Synapse 1989, 4:53-69.
27. Okamoto K, Kimura H, Sakai Y. Taurine-induced increase of the Cl- anion with a monoclonal antibody against taurine. Br J Pharmacol 1992, 106:1319-323.
28. Wu J-Y, Tang XW, Tsai WH: Taurine receptor: kinetic analysis and pharmacological studies. Adv Exp Med Biol 1992, 315:263-268.
29. Frosini M, Sesti C, Saponara S, Ricci L, Valeri M, Palmi M, Marchetti F, Sbaraglia G. A specific taurine recognition site in the rabbit brain is responsible for taurine effects on thermoregulation. Br J Pharmacol 2003, 139:487-494.
30. Chesney RW, Zelikovic I, Jones DP, Budreau A, Jolly K: The renal transport of taurine and the regulation of renal sodium-chloride-dependent transporter activity. Pediatr Nephrol 1990, 4(4):399-407.

31. Han X, Budreau AM, Chesney RW: Molecular cloning and functional expression of an LLC-PK1 cell taurine transporter that is adaptively regulated by taurine. Adv Exp Med Biol 1998, 442:261-268.

32. Warskulat U, Borsch E, Reinehr R, Monnighoff I, Buchczyk D, Donner M, Flogel U, Kappert G, Soboll S, Beer S, Pfeffer K, Marschall HU, Gabrielsen M, Amyry-Moghadam M, Ottersen OP, Diener HP, Haussinger D: Chronic liver disease is triggered by taurine transporter knockout in the mouse. FASEB J 2006, 20(3):574-576.

33. Chen WQ, Nguyen M, Carr J, Lee YJ, Jin H, Foos T, Hsu CC, Davis KM, Schloss Jv, Wu J-Y: Role of taurine in regulation of intracellular calcium level and neuroprotective function in cultured neurons. J Neurosci Res 2001, 66:612-619.

34. Takuma K, Matsuda T, Hashimoto H, Asano S, Baba A: Cultured rat astrocytes possess Na\(^+\)-Ca\(^{2+}\) exchanger. Glia 1994, 12:336-342.

35. Schaffer S, Azuma J, Takahashi K, Mozaffari M: Why is taurine cytoprotective? Taurine S London: Kluwer Academic/Plenum PublishersLombardini J B, Schaffer S, Azuma J. 2003, 307-321.

36. Hamaguchi T, Azuma J, Schaffer S: Interaction of taurine with methionine: inhibition of myocardial phospholipids methyltransferase. J Cardiovasc Pharmacol 1991, 18:224-230.

37. Chen WQ: Mode of action of taurine. Ph.D. dissertation University of Kansas 2000.

38. Leon R, Wu H, Jin Y, Wei J, Buddhalal C, Prentice H, Wu JY: Protective function of taurine in glutamate-induced apoptosis in cultured neurons. J Neurosci Res 2009, 87(5):1185-1194.

39. Schaffer S, Takahashi K, Azuma J: Role of osmoregulation in the actions of taurine. Amino Acids 2020, 19:527-546.

40. Kaczmarek LK: Phorbol esters, protein phosphorylation and the regulation of neuronal ion channels. J Exp Biol 1986, 124:375-392.

41. Tang XW, Hsu CC, Schloss Jv, Faiman MD, Wu E, Yang C-Y, Wu J-Y: Protein phosphorylation and taurine biosynthesis in vivo and in vitro. J Neuroscience 1997, 17:6947-6951.

42. Wu J-Y, Tang XW, Tsai WH: Taurine receptor: Kinetic analysis and pharmacological studies. Taurine: Nutritional Value and Mechanisms of Action New York: Plenum Publishing Co.Lombardini JB, Schaffer SW, Azuma J. 1992, 263-268.

43. Foos Tm, Wu J-Y: The role of taurine in the central nervous system and the modulation of intracellular calcium homeostasis. Neurochem Res 2002, 27:21-26.

44. Kaupmann K, Huggett K, Heid J, Flor PJ, Bischoff S, Mickel SJ, McMaster G, Angst C, Bittiger H, Froestl W, Bettler B: Expression cloning of GABA\(_{A}\) receptors underscores similarity to metabotropic glutamate receptors. Nature 1997, 386:239-246.

45. Lee YY, Deupree DL, Chen SC, Kao LS, Wu J-Y: Role of Ca\(^{2+}\) in AMPA-mediated polyphosphoinositides turnover in primary neuronal cultures. J Neurochem 1994, 62:2325-2332.

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