

Mechanisms Underlying Taurine Protection Against Glutamate-Induced Neurotoxicity

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ABSTRACT: Taurine appears to exert potent protections against glutamate (Glu)-induced injury to neurons, but the underlying molecular mechanisms are not fully understood. The possibly protected targets consist of the plasma membrane and the mitochondrial as well as endoplasmic reticulum (ER) membranes. Protection may be provided through a variety of effects, including the prevention of membrane depolarization, neuronal excitotoxicity and mitochondrial energy failure, increases in intracellular free calcium ($[Ca^{2+}]_i$), activation of calpain, and reduction of Bcl-2 levels. These activities are likely to be linked spatially and temporally in the neuroprotective functions of taurine. In addition, events that occur downstream of Glu stimulation, including altered enzymatic activities, apoptotic pathways, and necrosis triggered by the increased $[Ca^{2+}]_i$, can be inhibited by taurine. This review discusses the possible molecular mechanisms of taurine against Glu-induced neuronal injury, providing a better understanding of the protective processes, which might be helpful in the development of novel interventional strategies.

RÉSUMÉ: Mécanismes sous-jacent à l'effet protecteur de la taurine contre la neurotoxicité induite par le glutamate. La taurine peut exercer une protection puissante contre le dommage neuronal induit par le glutamate (Glu) mais les mécanismes moléculaires sous-jacents ne sont pas bien compris. Les cibles potentiellement protégées sont la membrane cellulaire, la membrane mitochondriale et celle du réticulum endoplasmique, sur lesquelles le fait d'exercer une protection au moyen de différents effets dont la prévention de la dépolarisation de la membrane, l'excitotoxicité et la défaillance énergétique mitochondriale, l'augmentation du calcium libre intracellulaire ($[Ca^{2+}]_i$), l'activation de la calpaïne et la diminution des niveaux de Bcl-2. Ces activités sont vraisemblablement liées au point de vue spatial et temporel dans les fonctions de neuroprotection qu'exerce la taurine. De plus, les événements qui surviennent en aval de la stimulation par le Glu dont une altération des activités enzymatiques et des voies apoptotiques et une nécrose induite par l'augmentation de ($[Ca^{2+}]_i$), peuvent être inhibées par la taurine. Dans cette revue, nous discutons des mécanismes moléculaires possibles de la taurine pour contrer le dommage neuronal induit par le Glu afin de mieux comprendre lequel pourrait être utile dans le développement de nouvelles stratégies d'intervention.

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Taurine (2-aminoethanesulfonic acid) is an abundant β -amino acid found in most mammalian tissues, such as the cardiac muscles and brain¹. Taurine has an important role in certain aspects of mammalian development, especially as a trophic factor in the development of the central nervous system (CNS)^{2,3}. The physiological role of taurine has received considerable attention since the finding that cats fed a diet deficient in taurine develop central retinal degeneration⁴, skeletal muscle disorders⁵ and cardiomyopathy^{6,7}. These pathologic conditions could be reversed if taurine intervention was given within a critical time window⁸.

The notion that taurine is a neurotransmitter in the mammalian CNS has been supported by following lines of evidence: 1. The presence of a specific enzyme, namely cysteine/cysteine sulfinic acid decarboxylase, responsible for taurine biosynthesis in the brain⁹. 2. Release of taurine has been shown to be either calcium independent or calcium dependent¹⁰. 3. Taurine has been shown to elicit neuronal hyperpolarization, presumably through its action of opening the chloride channels in neurons of the hippocampus¹¹, cerebellum¹², and anteroventral cochlear nucleus¹³. 4. The presence of specific taurine receptors has been demonstrated¹⁴. 5. The presence of a taurine transporter system for inactivation of its function has also been reported¹⁵.

In summary, taurine may primarily be accepted as a neurotransmitter in the mammalian CNS.

Taurine can be synthesized from methionine and cysteine within the liver^{16,17}. Although mammals are able to synthesize taurine endogenously, taurine biosynthesis is high in rodents and low in humans. As a consequence, dietary taurine uptake is the major method of taurine supply in humans, and dietary deficiency may induce problems in physiological processes¹⁸. The whole-body taurine content then is derived in three different ways: (1) direct taurine intake from the diet; (2) kidney reabsorption; and (3) taurine *de-novo* synthesis by the liver and alternative tissues¹⁸. In addition, taurine has been shown to have many other important physiologic functions, including maintenance of the structural integrity of plasma membrane¹⁹,

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modulation of calcium homeostasis²⁰, antioxidant activity²¹, modulation of synaptic activity in the brain^{2,3,22}, anticonvulsant activity²³, osmoregulatory activity^{24,25}. The protection of neurons against glutamate (Glu)-induced excitotoxicity has been considered as its essential action²⁶. Clinically, taurine has been used with varying degrees of success in the treatment of various conditions, including cardiovascular diseases, epilepsy and other seizure disorders, macular degeneration, hepatic disorders, cystic fibrosis, stroke, Alzheimer's disease, Huntington's disease, and brain ischemia²⁷⁻³¹.

Glutamate is the major excitatory neurotransmitter in the mammalian CNS³² and plays important roles in neuronal differentiation, migration, and survival in the developing brain³³⁻³⁵, as well as in synaptic maintenance and plasticity³⁶. Activation of Glu receptors results in extracellular calcium influx and mobilization of additional calcium from intracellular stores²⁰. However, excessive stimulation by Glu causes cell damage, and even cell death, in a phenomenon known as neuronal excitotoxicity^{33,34,37}. Intense glutamatergic insult may induce a loss of cellular homeostasis with acute mitochondrial dysfunction leading to massive energy failure³⁸. Milder glutamatergic insults, however, cause cell death ascribed to various cell death pathways, including a gamut of molecular players cysteine proteases, mitochondrial endonucleases, peroxynitrite, poly ADP ribose polymerase and glyceraldehyde phosphate dehydrogenase in excitotoxic neurodegeneration³⁹.

An important function of taurine is that it is neuroprotective⁴⁰. It is generally believed that taurine protects neurons against Glu-induced neurotoxicity by preventing Glu-induced membrane depolarization, excitotoxicity, increases in level of intracellular free calcium ($[Ca^{2+}]_i$), mitochondrial energy failure, activation of calpain, reduction of Bcl-2 levels, and apoptosis⁴¹. These phenomena are probably linked spatially and temporally in the neuroprotective functions of taurine. However, there is a lack of information regarding the specific impacts of taurine on intracellular signaling and cell death pathways, particularly *in vivo*. A better understanding of the molecular process underlying the neuroprotective function of taurine against Glu-induced neuronal injury would facilitate the development of novel interventional strategies to protect against neurotoxicity.

Taurine and membranes

Taurine acts through several mechanisms to limit the degree of lipid peroxidation (LP) and membrane damage. Recent studies have shown that preliminary treatment with taurine decreases the rates of lipid peroxide formation and lactate accumulation in the brain, and restores membrane Na^+ , K^+ -ATPase activity during acute severe hypoxia⁴². Hypoxia-induced activation of LP has been reported by many researchers^{43,44}. It has also been proposed that increased cytosolic Ca^{2+} is responsible for LP activation in various tissues under hypoxic conditions. The regulation of membrane Na^+ , K^+ -ATPase activity by taurine explains the effects of taurine on the membrane binding of Ca^{2+} and the modification of the membrane lipid order, conformation, and dynamics. Taurine is also observed to act as an antioxidant of peroxynitrite to decrease LP and thus affect liver plasma membrane Na^+ , K^+ -ATPase by restoring its activity⁴⁵. Furthermore, taurine deficiency has been implicated in disturbances of the lipid membrane structure and

membrane fatty acid composition⁴⁶. Taurine is also known to interact with specific plasma membrane proteins⁴⁷ and to prevent phospholipase-mediated and oxidation-mediated membrane damage through its membrane stabilizing activity⁴⁸, while membrane damages were considered as an inevitable result of Glu-induced excitotoxicity.

Furthermore, Wu et al⁴⁹ have shown that taurine protects neurons against Glu excitotoxicity by direct preventing Glu-induced membrane depolarization. Taurine affects the opening of chloride channels by interactions with γ -aminobutyric acid (GABA)_A receptors¹³, glycine receptors⁵⁰ or taurine receptors⁴⁹, thereby preventing the Glu-induced increase in calcium influx and other downstream events. This hypothesis, that taurine inhibits the Glu-induced calcium influx by affecting membrane potential, is supported by several observations^{49,51}. First, taurine inhibits calcium influx through various voltage-gated calcium channels (VGCCs). Second, taurine does not directly inhibit calcium influx through NMDA receptor calcium channels unless Mg^{2+} is present, which renders the NMDA receptor depolarization-dependent. Third, taurine inhibits Glu-induced membrane depolarization in cultured neurons.

Taurine and mitochondria

Mitochondria have two major functions: the production of cellular energy and the sequestration of calcium ions. They also play key roles in the regulation of calcium homeostasis and apoptosis⁵²⁻⁵⁵. Glu excitotoxicity begins with excessive calcium influx through the L-, N-, and P/Q-type VGCC and NMDA receptor calcium channels, leading to intracellular calcium overload, which can activate the release of cytochrome c and activate caspases, thereby leading to apoptosis^{56,57}. Conversely, the release of cytochrome c impairs mitochondrial function, as cytochrome c is one of the components of the oxidative phosphorylation chain. Impairment of mitochondrial function disrupts ATP synthesis, and a lack of ATP leads to dysfunction of ion channels, resulting in irreversible mitochondrial dysfunction and, ultimately, cell death^{49,58,59}.

The mitochondrial pathway of apoptosis is involved in the excitotoxic response to Glu and, as such, the response to cellular stress induces the mitochondrial pathway though the initial action of caspase-9^{60,61}. Furthermore, imbalances between Bcl-2 and Bax lead to the formation of Bax homodimers, which target the mitochondria and cause the release of cytochrome c, resulting in the activation of apoptotic protease activity factor-1 (Apaf-1), which in turn activates the caspase cascade that leads to apoptosis⁶². Moreover, Glu-induced neuronal necrosis is preceded by a rapid increase in the cytoplasmic free calcium concentration⁶³, in which mitochondria play an important role by releasing internal free calcium.

Recent studies have confirmed that pre-treatment of cerebellar granule cells with taurine significantly counteracts Glu excitotoxicity²⁰. This counteraction is mediated through regulation of cytoplasmic $[Ca^{2+}]_i$ and intra-mitochondrial calcium homeostasis, as determined by Fluo-3 and ⁴⁵Ca²⁺ uptake assays. Furthermore, overall mitochondrial function is increased in the presence of taurine, as assessed by tests for rhodamine accumulation by mitochondria and total cellular ATP levels⁶⁴. Taurine also increases the capacity of mitochondria to sequester calcium when the cells are stimulated and the level of

cytoplasmic calcium is drastically increased. Thus, taurine reduces Glu excitotoxicity through both the enhancement of mitochondrial function and the regulation of intracellular (cytoplasmic and intra-mitochondrial) calcium homeostasis²⁰. The functional consequence of regulating $[Ca^{2+}]_i$ is that the mitochondria are protected from the damaging effects of calcium overload and subsequent neuronal death. The role of taurine in modulating mitochondrial calcium homeostasis may be of particular importance under pathologic conditions characterized by excessive calcium overload^{20,64}.

Mitochondrial protection by taurine may not be merely a consequence of calcium regulation during excitotoxicity. Taurine could have a trophic role for neuronal cells through the enhancement of their mitochondrial functions and, thus, their bioenergetic capacity. Consistent with this, taurine has been identified as a survival-promoting factor for cerebellar granule cells⁴⁴. In addition, taurine serves as a regulator of mitochondrial protein synthesis, thereby enhancing electron transport chain activity and protecting the mitochondria against excessive superoxide generation^{42,43}. The major components of superoxide generation in the mitochondria are complexes I and III, and it is widely accepted that slowing electron flux through the respiratory chain diverts electrons from complexes I and III to an alternate acceptor, such as oxygen. Taurine prevents the diversion of electrons into superoxide generation by improving the functioning of the electron transport chain.

Takatani et al^{54,65} have demonstrated that taurine prevents ischemia-induced apoptosis of cardiomyocytes, and that this is accompanied by the inactivation of caspase-9 and caspase-3. Taurine treatment inhibited Apaf-1/caspase-9 apoptosome formation without preventing mitochondrial dysfunction under ischemic conditions. To act as a neuroprotectant, taurine must interact with targets linked to calcium and mitochondrial metabolism²⁰ or downregulate components of the apoptosis cascade, such as caspase-3^{55,66} and caspases-8 and -9⁶⁷. *In vivo* taurine has been demonstrated to protect the brain against experimental stroke in a dose-dependent manner⁵⁵, and taurine could reduce ischemic brain injury by blocking mitochondria-mediated cell death pathways by inhibiting the activation of calpain and caspase-3, reducing the degradation of α II-spectrin, and attenuating necrotic and apoptotic cell death in the penumbra and core⁶⁸.

Therefore, these two functions for taurine: enhancement of mitochondrial function and regulation of intracellular (cytoplasmic and mitochondrial) calcium homeostasis, and possibly others functions, probably participate in neuronal survival and protection against Glu excitotoxicity. Therefore, taurine may serve as an endogenous neuroprotective molecule against mitochondrial dysfunction.²⁰

Taurine and endoplasmic reticulum (ER) membranes

The ER is an important subcellular organelle that is responsible for intracellular calcium homeostasis, protein secretion and lipid biosynthesis⁶⁹⁻⁷¹, and there is increasing evidence that ER stress plays a crucial role in hypoxia/ ischemia-induced cell dysfunction^{72,73}. Cerebral hypoxia and/or ischemia result in a decrease of glucose and oxygen which in turn induce the release of Glu at the presynaptic level. The high levels of Glu and the subsequent activation of glutamatergic postsynaptic

receptors are the main components in a cascade of sequential molecular events that culminates the death of neurons^{63,74}. Pan et al^{75,76} recently demonstrated that taurine may exert its protective effect on cortical neurons through suppression of ER stress induced by Glu. When neurons are exposed to Glu, the homeostasis in neuronal cultures is disturbed, initiating dimerization and autophosphorylation of ER membrane proteins, kinase-like ER kinase (PERK) and inositol requiring enzyme 1 (IRE1). Transcription factor 6 (ATF6) (P90) is activated by limited proteolysis after its translocation from the ER to the Golgi apparatus to form cleaved ATF6 (P50). All of these three pathways induce up-regulation of C/EBP homologous protein (CHOP) which would initiate cell death. Taurine treatment greatly inhibits ATF6 and IRE1 pathways after Glu over a longer time frame. In contrast, activation of the initiation of PERK pathway is delayed by taurine under conditions of brief Glu exposure⁷⁵.

Taurine and intracellular calcium homeostasis

The $[Ca^{2+}]_i$ is maintained by calcium sequestration into internal calcium storage pools, as well as by pumping out of calcium to the extracellular space by a calcium-ATPase at a sub-micromolar concentration. When neurons are stimulated by Glu, the $[Ca^{2+}]_i$ is increased due to an influx of calcium from extracellular sources via various calcium channels, as well as by the release of calcium from the internal calcium storage pools^{49,77}.

Taurine has been shown to be involved in the regulation of calcium homeostasis in many tissues, including the heart^{6,7}, brain⁷⁸, and retina⁷⁹, as well as in cultured myocardial cells⁸⁰, cultured spiral ganglion neurons, the outer hair cells of the inner ear^{81,82}, and cultured neuronal cells^{20,44,54}. The primary mechanism of the neuroprotective activity of taurine is thought to be its action in regulating calcium homeostasis, i.e., preventing or reducing Glu-induced increases in $[Ca^{2+}]_i$ ^{44,83}, which is supported by many other findings.

It has been reported that taurine may inhibit calcium influx through the reverse mode of the Na^+/Ca^{2+} exchanger, the activity of which is membrane potential-dependent⁸³. The function of the Na^+/Ca^{2+} exchanger is to move Ca^{2+} out of cell at the resting membrane potential; the exchanger reverses mode to facilitate Ca^{2+} influx under depolarizing conditions, such as Glu stimulation⁸⁴. The effect of taurine on the Na^+/Ca^{2+} exchanger is, in part, due to its membrane stabilizing activity, which suggests that the neuroprotective activity of taurine is linked to its ability to prevent Glu-induced membrane depolarization⁸⁵.

Recent studies have shown that when Glu-induced membrane depolarization is abolished by taurine, as measured with a voltage-sensitive dye, VGCC activity is also suppressed⁸⁶. In addition to its action on membrane potential, taurine may inhibit channel activity through its effect on protein phosphorylation⁴⁹. It has been known that Glu stimulation activates metabotropic Glu receptors, which activate phospholipase C (PLC), resulting in an increase in inositol triphosphate (IP_3) formation and IP_3 -mediated Ca^{2+} release from internal Ca^{2+} storage pools. When the metabotropic taurine receptors (mTauR) are activated by taurine, the coupled inhibitory G-proteins (G_o/G_i) are activated, resulting in the inhibition of VGCCs. Furthermore, activation of mTauR by taurine leads to inhibition of PLC activity, resulting in

a reduction in IP₃ formation and, consequently, IP₃-mediated release of Ca²⁺ from the internal pools²¹.

Furthermore, taurine inhibits various VGCCs, including the L, N, and P/Q types⁸⁶. The NMDA receptor calcium channel represents a major calcium influx pathway. Taurine completely blocks calcium influx through the NMDA receptor calcium channel, and rather than acting directly on the NMDA receptor, taurine exerts this effect by influencing the membrane potential⁴¹. Taurine also maintains [Ca²⁺]_i by inhibiting the Glu-induced release of calcium from the intracellular pools, supported by the finding that the Glu-induced increase in [Ca²⁺]_i in the absence of extracellular Ca²⁺ is inhibited by taurine²¹. Metabotropic Glu receptors were also reported to conversely participate in the regulation of taurine release⁸⁷. Under various cell-damaging conditions, including ischemia, hypoxia and hypoglycemia, taurine release is enhanced⁴⁰. The increase in extracellular taurine upon excessive stimulation of Glu receptors and under cell-damaging conditions may serve as an important protective mechanism against excitotoxicity, being particularly effective in the immature brain^{87,88}.

Taurine protection against neuronal death

Glutamate-induced neuronal death is initiated by increases in [Ca²⁺]_i and sodium levels, and these are followed by the activation of catabolic enzymes, such as proteases⁴³, phospholipases and endonucleases, the protein kinase and lipid kinase cascades, energy compromise, and the formation of ROS, leading to necrosis or apoptosis⁷⁶. Some of these events induced by Glu overexcitation occur early and lead to rapid cell damage, while other factors, such as energy compromise and ROS formation, initiate a more delayed cell death process.

Both necrosis and apoptosis are involved in Glu-induced neuronal cell death^{47,48}. One of the mechanisms of Glu-induced cell death involves calcium overload, which is known to induce mitochondrial dysfunction⁵⁸, ER stress⁷⁵, oxidative stress⁸⁹, and activation of proteases, including calpain^{21,90}. As Ca²⁺ overload triggers the release of more Glu, overactivation of the Glu receptors spreads among the neurons and further causes the release of additional calcium from intracellular stores⁷⁷, thereby exacerbating excitotoxicity and contributing to the neuronal loss. Mechanisms behind Glu-induced apoptosis are: increased [Ca²⁺]_i following Glu stimulation, which in turn activates calpain; activation of calpain decreases the Bcl-2/Bax ratio and further results in the release of cytochrome c from impaired mitochondrial that leads to apoptosis^{56,57,62}. Impairment of mitochondrial function disrupts ATP synthesis, and the consequent shortage of ATP leads to dysfunction of ion channels, resulting in intracellular ion derangements and subsequent cell death by necrosis²⁰.

Taurine has been shown to prevent neuronal cell apoptosis and necrosis associated with Glu-induced excitotoxicity⁸⁶. Taurine may exert its neuroprotective function through both extracellular and intracellular mechanisms to inhibit the Glu-induced increase in [Ca²⁺]_i²⁰. The extracellular mechanism involves the inhibition of calcium influx through various calcium channels, including the VGCC, as well as through NMDA-mediated calcium channels⁴⁹. This property of taurine is attributed to its suppression of Glu-mediated depolarization through the opening of the chloride channel^{13,91}. In addition,

taurine antagonizes oxygen/glucose deprivation and reperfusion-induced edema, and these activities are dependent upon taurine transport into the cells and GABA_A receptor activation and involve the activity of volume-sensitive outwardly rectifying Cl⁻ channels⁹².

The intracellular action of taurine may be related to its protection of mitochondrial function from calcium overload and subsequent inhibition of calpain activation and all downstream events under excitatory conditions. It has been reported that Glu-induced activation of calpain directly promotes the caspase cascade by influencing the Bcl-2/Bax ratio⁸⁶. Furthermore, taurine treatment prevents Glu-induced cleavage of spectrin, a specific endogenous substrate of calpain, which suggests that taurine inhibits Glu-induced activation of calpain, a calcium-dependent cysteine protease⁴¹. Since Bcl-2 is a substrate of calpain, taurine protects neurons from apoptosis by inhibiting Glu-induced activation of calpain and preserving the Bcl-2/Bax ratio⁸⁶. These authors have also pointed out that taurine modulates the survival/death kinase pathway equilibrium in the context of Glu stimulation.

Several studies have shown that taurine is neuroprotective against a variety of disorders^{44,49,83}. The sequence of events that leads from Glu stimulation to apoptosis and the mode of action of taurine in preventing Glu-induced apoptosis can be summarized as follows:

1. Taurine prevents Glu-induced DNA fragmentation and nuclear condensation⁴¹;
2. Taurine suppresses the endoplasmic reticulum stress induced by Glu^{25,75};
3. Taurine attenuates Glu-induced membrane depolarization^{49,50};
4. Taurine prevents Glu-induced apoptosis by preventing Glu-mediated down-regulation of Bcl-2⁸⁶; inhibition on Glu-induced activation of calpain prevents cleavage of Bcl-2 by calpain.⁴¹;
5. Taurine protects neurons from apoptosis by restoring the balance of Bcl-2/Bax⁴¹;
6. Taurine inhibits apoptosis by preventing the formation of the Apaf-1/caspase-9 apoptosome⁵⁴;
7. Taurine prevents Glu toxicity by blocking calcium overload-mediated apoptosis²¹ and by reducing oxidative stress-linked apoptosis⁴³;
8. The anti-apoptotic function of taurine is linked to its ability to prevent the Glu-induced increase in [Ca²⁺]_i through blocking Glu-induced depolarization, resulting in the blockade of all the downstream events⁴¹.

CONCLUSIONS

There is compelling evidence that the neuroprotective effect of taurine is attributed to its functions in maintaining intracellular calcium homeostasis, membrane integrity, mitochondrial function, ER stress and as an antioxidant. This schema is depicted in the Figure and is offered as a working hypothesis. Events that occur downstream of Glu stimulation, including altered enzymatic activities, apoptotic pathways, and necrosis triggered by increased [Ca²⁺]_i, may be inhibited by taurine. However, we still have limited knowledge on the specific effects of taurine on intracellular signaling and cell death pathways and the molecular mechanisms underlying its

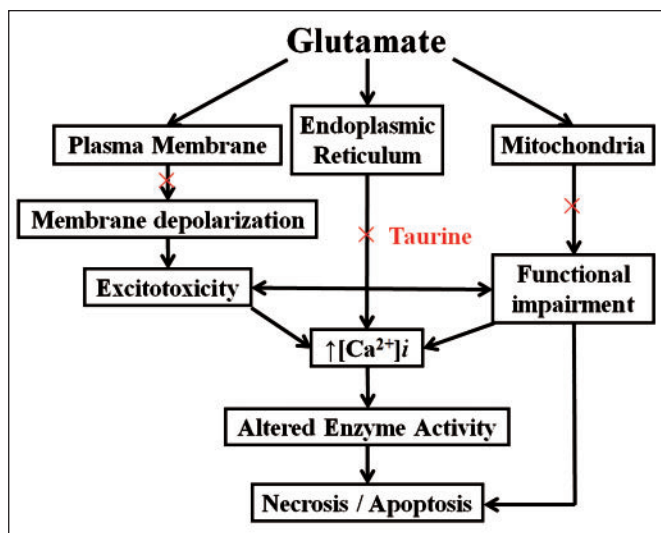


Figure: Schematic simplified overview of hypothesized pathophysiological mechanisms in the neuroprotective function of taurine (Tau) against Glu-induced neurotoxicity. Taurine protects neurons against Glu-induced neurotoxicity by preventing Glu-induced membrane depolarization, ER stress, mitochondrial energy failure and increased intracellular calcium levels. Increased intracellular calcium levels result in altered enzyme activities and together these activate directly or indirectly apoptotic pathways, or irreversible neuronal damage. The downstream events triggered by increased $[Ca^{2+}]_i$ leading from Glu stimulation, can be inhibited by taurine.

actions. We also know little about the possible taurine receptors when participate in protective against excitotoxicity. In particular, its critical roles in neuronal protection and underlying molecular mechanisms need to be carefully evaluated in relation to human neurological diseases. Further investigation of upstream signals controlling excitotoxicity afforded by taurine, and which cause hyperactivity of glu receptors under disease conditions may provide new insights on the mechanisms contributing to Glu-induced neurodegenerative diseases in humans, thereby unveiling novel strategies for therapy.

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