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REVIEW ARTICLE

# Taurine and central nervous system disorders

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**Abstract** In the present era, investigators seek to find therapeutic interventions that are multifaceted in their mode of action. Such targets provide the most advantageous routes for addressing the multiplicity of pathophysiological avenues that lead to neuronal dysfunction and death observed in neurological disorders and neurodegenerative diseases. Taurine, an endogenous amino acid, exhibits a plethora of physiological functions in the central nervous system. In this review, we describe the mode of action of taurine and its clinical application in the neurological diseases: Alzheimer's disease, Parkinson's disease and Huntington's disease.

**Keywords** Taurine · Neuroprotective mechanisms · Alzheimer's disease · Parkinson's disease · Huntington's disease

## Introduction

Taurine (2-amino-ethanesulfonic acid) is a sulfur containing, free amino acid that is abundantly found in mammals with a concentration that is only exceeded by glutamic acid (Jacobsen and Smith 1968). It is derived from methionine and cysteine metabolism with cysteine sulfinic acid decarboxylase (CSAD) being the rate-limiting enzyme (Wu 1982; Hayes 1985). It is mostly found in excitable tissues such as the brain, retina, cardiac muscle and skeletal muscle (Reichelt and Edminson 1974; Macaione et al. 1974; Huxtable 1976, 1992; Saransaari and Oja 2000; Warskulat et al. 2004; Oja and Saransaari 2007). Although taurine was first discovered as a component of ox bile in 1827, it took more than a decade before investigators began to identify some of its physiological importance (Davison and Kaczmarek 1971; Oja and Lahdesmaki 1974; Oja et al. 1985; Pion et al. 1987).

Hayes et al. (1975) showed that a deficiency of taurine in both the body and the diet resulted in a neurological disorder of the eye. Studies on cats demonstrated that they do not synthesize taurine and that they must receive taurine from their diet. Hayes et al. (1975) demonstrated that cats fed a taurine-deficient diet developed central retinal degeneration. The developments of cardiomyopathy and growth retardation in other animal studies (Pion et al. 1987; Sturman 1993) have further highlighted the importance of taurine in the diet if it is not found endogenously in the body. By virtue of this recognition of the importance of taurine during development, taurine is now added to formula milk and may be especially important for preterm and low birth weight infants (Verner et al. 2007).

### Physiological role in central nervous system (CNS)

Taurine mediates a myriad of physiological functions (Huxtable 1989, 1992) in the CNS. In the CNS, taurine plays a role in neuromodulation (Kuriyama 1980; El Idrissi and Trenkner 2004; Banerjee et al. 2008),

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osmoregulation (Schaffer et al. 2000; Oja and Saransaari 2007), the maintenance of calcium homeostasis (Chen et al. 2001; Foos and Wu 2002; El Idrissi and Trenkner 1999, 2003; El Idrissi 2008), membrane stabilization (Moran et al. 1988; Schaffer et al. 1995), anti-oxidant function (Hagar 2004; Schaffer et al. 2009; Jong et al. 2012), anti-inflammatory processes (Miao et al. 2012; Sun et al. 2012), and neuroprotection (Chen et al. 2001; Wu et al. 2005; Leon et al. 2009; Junyent et al. 2010; Pan et al. 2010, 2011; Sun et al. 2011). Taurine is also seen as a key trophic factor during CNS development (Lima and Cubillos 1998; Hernandez-Benitez et al. 2010). Its neuroprotective effect is observed against L-glutamate-induced excitotoxicity, whereby it counteracts the glutamate-induced increase of intracellular calcium through L-, P/Q-, N-type voltage-gated calcium channels (VGCCs) and the *N*-methyl-D-aspartate (NMDA) receptor, thus preventing glutamate-induced membrane depolarization (Chen et al. 2001; Wu et al. 2005).

Although taurine is not definitively classified as a neurotransmitter, it fulfills most of the necessary criteria: it is associated with synaptic membrane structures (Kontro and Oja 1987) and both taurine and its synthesizing enzyme CSAD are co-localized in presynaptic neuronal terminals (Wu et al. 1979; Wu 1982; Magnusson et al. 1989); stimulated taurine release is both calcium dependent (at a potassium concentration up to 40 mM) and calcium independent (at a potassium concentration $> 40$ mM) (Philibert et al. 1989); taurine modulates neurotransmission by eliciting inhibitory neuronal transmission through $GABA_A$, and glycine receptors (Okamoto et al. 1983; Albrecht and Schousboe 2005; Wu et al. 2008) and it is taken up into the cell by a sodium-dependent taurine transporter (TauT) (Martin 1992; Kozlowski et al. 2008). Our previous studies (Wu et al. 1992a, b) have provided strong evidence of the existence of a specific taurine receptor. Our experiments and the later investigation by Frosini et al. (2003) demonstrated that the receptor is neither activated nor antagonized by structurally similar amino acids such as glutamate, gamma-amino butyric acid (GABA) and glycine.

Many neurological disorders and neurodegenerative diseases including Alzheimer's, Parkinson's and Huntington's diseases share a common fundamental pathophysiology of glutamate excitotoxicity, calcium imbalance or oxidative stress which individually or collectively results in cell death. Therefore, taurine's role as an inducer of inhibitory neurotransmission, an anti-oxidant, neuromodulator, regulator of calcium homeostasis and neuroprotectant makes it an ideal therapeutic agent for many of these diseases. This review will focus on previous and current studies of taurine's effect on the diseases mentioned above.

## Alzheimer's disease

Alzheimer's disease (AD) was first characterized by Alois Alzheimer in 1907 as a disease with progressive dementia and deteriorating cognitive functions (Alzheimer 1907). The symptoms are strongly correlated with synaptic degeneration and neuronal death in limbic structures such as the hippocampus (brain region responsible for short and long-term memory), the basal forebrain, the amygdala (brain region involved in emotion) and the associated cortex (http://www.nia.nih.gov/alzheimers/publication/alzheimers). Neurons in layer 2 of the entorhinal cortex and in the CA1 region of the hippocampus are more susceptible to AD's pathogenesis (MacDermott and Dale 1987). Symptoms of mild AD are short-term memory loss, difficulty in performing complex activities and confusion about familiar places. As atrophy of the cerebral cortex and hippocampus progress, there is a concurrent development of difficulty in speech, reasoning, sensory processing and conscious thought (http://www.nia.nih.gov/alzheimers/publication/alzheimers). The hallmarks of the disease are cerebral plaques consisting of $\beta$-amyloid peptides (A$\beta$s) and intracellular neurofibrillary tangles (NFTs), mainly composed of hyperphosphorylated tau (Braak and Braak 1998).

Cleavage of the transmembrane amyloid precursor protein (APP) by $\beta$-secretase (BACE: beta-site-APP-cleaving enzyme), followed by $\gamma$-secretase cleavage at its intramembrane region produces two principal forms of A$\beta$s: $A\beta_{40}$ ($A\beta_{1-40}$) and $A\beta_{42}$ ($A\beta_{1-42}$), depending on the cleavage site, with $A\beta_{40}$ (a soluble form) being the more common (Burdick et al. 1992; Haass and Selkoe 1993). An increase in the ratio of $A\beta_{42}$ to $A\beta_{40}$ due to a mutant variant of $\gamma$-secretase results in extracellular aggregates of the insoluble $A\beta_{42}$, which grow into fibrils and eventually $\beta$-pleated sheets, as observed in advanced amyloid plaques (Haass and De Strooper 1999; Haass 2004; Haass and Selkoe 2007). It is interesting that some authors (Selkoe 2002) describe the clinical presentation of AD symptoms as synaptic failure rather than a neurodegenerative disorder due to the initiation of neuronal death via synaptic dysfunction. In support of this line of thought, several investigations have shown soluble A$\beta$ triggering synaptic pruning in brain slices in vitro and causing cognitive impairment in the absence of neurodegeneration in animals (Roselli et al. 2005; Lesne et al. 2006; Haass and Selkoe 2007; Shankar et al. 2007, 2008). Furthermore, other researchers (Bitan et al. 2005; Wogulis et al. 2005; Hepler et al. 2006; Kuperstein et al. 2010) have provided evidence of a strong correlation between the density of accumulated soluble non-fibrilar A$\beta$ oligomers, synaptic loss and the severity of the disease. APP is not only located at the plasma membrane but also localized to the trans-Golgi

network, the endoplasmic reticulum (ER), endosomal, lysosomal and mitochondrial membrane (Xu et al. 1995; Yan et al. 1997; Kinoshita et al. 2003; Lustbader et al. 2004), thus sequential cleavage by BACE and $\gamma$-secretase can liberate A$\beta$s into the cytosol and in the respective organelles, accounting for intracellular A$\beta$s (Wertkin et al. 1993) and the potential disruption of the normal function of these organelles.

The other central feature of AD is NFTs, which are composed of the hyperphosphorylated form of the microtubule-associated protein, tau. It was reported that mutated tau was more heavily associated with familial forms of fronto-temporal dementia (Neumann et al. 2009) than to AD, resulting in tau receiving slightly less attention in the literature compared to A$\beta$. In addition, A$\beta$ dimers (the simplest form of the soluble oligomers) induce tau hyperphosphorylation (Jin et al. 2011), thus giving precedence to A$\beta$ pathology in AD.

## Neurochemical mechanisms of AD

The two major neurotransmitter systems affected by A$\beta$ oligomers are the basal forebrain cholinergic system and the glutamatergic system, both vital for the cognition and formation of memory (Size et al. 2001; Schliebs and Arendt 2006). Perturbation in these systems can easily lead to disruption in synaptic plasticity, which involves long-term potentiation (LTP) and long-term depression (LTD) (Bear and Abraham 1996), critical components of memory formation and cognition. It was reported that most patients with a clinical presentation of AD also showed a defect in the cholinergic system, characterized by a loss of cholinergic receptors or cholinergic neurons in the basal forebrain (Teaktong et al. 2004; Geula et al. 2008). It has been shown that A$\beta$s (pM − μM) induce synaptic failure by disturbing the cholinergic neurotransmission at various sites (Auld et al. 2002), including reducing the activity of choline acetyltransferase (ChAT; the enzyme involved in choline biosynthesis), decreasing acetylcholine's (ACh) intracellular concentration, and inhibiting ACh synaptic release and uptake (Hoshi et al. 1997; Kar et al. 1998; Vaucher et al. 2001; Pedersen et al. 1996).

There is a growing consensus that soluble non-fibrilar A$\beta$ mediates synaptic failure by indirect or direct interaction with one or more receptors. This was observed when chronic exposure to A$\beta$ resulted in its binding to the $Ca^{2+}$ permeable $\alpha$7-nicotinic acetylcholine receptor ($\alpha$7-nAcChR) (Oddo and LaFerla 2006), causing hyperactivity and the ensuing downregulation of extracellular signal-regulated kinase 2 (ERK2)/mitogen-activated protein kinase 1 (MAPK1). This results in the impairment of late phase LTP due to reduced phosphorylation of the downstream transcription factor, cAMP-regulatory element binding protein (CREB) (Dineley et al. 2001). It has been shown that A$\beta$ mediates both synaptic failure and excitotoxicity via glutamate receptors (NMDARs, AMPARs and mGluRs) (Chen et al. 2002; Texidó et al. 2011). Synaptic failure was observed when exposure to high concentrations of A$\beta_{40}$ downregulated key downstream molecules of the NMDAR-dependent LTP cascade, impairing LTP in the dentate gyrus (DG) and in the CA1 region of the hippocampus. LTD was also facilitated, potentiating synaptic failure (Chen et al. 2000, 2002). Impaired LTP was further diminished when A$\beta_{40}$ activated NMDAR, resulting in AMPAR (AMPAR also facilitates LTP) endocytosis (Gu et al. 2009). It was reported that A$\beta$ directly induced NMDAR hyperactivity, mediating neuronal excitotoxicity due to $Ca^{2+}$ influx through $Ca^{2+}$ permeable NMDARs, increasing intracellular $Ca^{2+}$ and deregulating $Ca^{2+}$ homeostasis (Texidó et al. 2011; Ferreira et al. 2012). Due to A$\beta$'s inhibition of the glutamate transporter, a high concentration of released glutamate was maintained in the synaptic cleft, resulting in a positive feed forward mechanism of excitotoxicity as postsynaptic NMDARs became hyperactive by glutamate (Mattson 1997; Harkany et al. 2000; Procter 2000).

## The role of taurine in AD

Due to the neurotoxic effect of A$\beta$ in AD, scientists have investigated potential targets that can either inhibit the aggregation of A$\beta$ or its production. Osmolytes interact with peptide backbone and amino acid side-chains; therefore, they could prevent misfolding and aggregation of proteins (Kumar 2009). Taurine, being an osmolyte, could inhibit $\beta$-amyloid aggregation. Santa-Maria et al. (2007) mixed A$\beta_{25-35}$ (the biologically active region of A$\beta_{1-42}$, with a higher capacity for self assembly) with taurine. They reported that taurine was a weak inhibitor of amyloid peptide aggregation, since aggregates were at a slightly lower level in the presence of taurine than in taurine's absence. Inspite of a weak inhibition of A$\beta$ aggregate formation, taurine, nevertheless, demonstrated its capacity to inhibit A$\beta$ aggregation. As discussed previously, A$\beta$ induces synaptic failure and causes the impairment of late phase LTP (Dineley et al. 2001), a critical phenomenon for memory formation and cognition (Bear and Abraham 1996). Del Olmo et al. (2003) demonstrated that taurine induced the synaptic potentiation and late phase LTP. They showed that taurine was able to recruit the cyclic adenosine monophosphate (cAMP), protein kinase A (PKA), phosphorylated CREB (pCREB) and protein synthesis pathway; a pathway intricately involved in late phase LTP (Frey et al. 1993; Winder et al. 1998; Schulz et al. 1999).

The previous section ("Neurochemical mechanisms of AD") focused on A$\beta$-induced excitotoxicity via neurotransmitter receptors, especially via direct interaction with

NMDAR, resulting in increased intracellular [$Ca^{2+}$] (Mattson 1997; Harkany et al. 2000; Procter 2000; Texidó et al. 2011; Ferreira et al. 2012). Intriguingly, A$\beta$ activation NMDAR is not only by a direct interaction with the receptor but also via A$\beta$'s ability to impair plasma membrane energetic pumps, $Na^+/K^+$ ATPase and $Ca^{2+}$ ATPase, or due to membrane lipid peroxidation resulting in pore formation with $Ca^{2+}$ channel-like activity, within the membrane (Kawahara and Kuroda 2000; Lin et al. 2001), consequently depolarizing the membrane (Goodman and Mattson 1994). This would ultimately result in an increase in intracellular $Ca^{2+}$ level. We and other investigators have established that taurine has a protective effect in cultured neurons against glutamate-induced excitotoxcity (Wu et al. 1987, 2000, 2005; Tang et al. 1996; El Idrissi and Trenkner 1999; Chen et al. 2001). Such observations from these studies have shown that taurine's neuroprotective mechanism is through the maintenance of intracellular calcium homeostasis via the inhibition of the $Na^+/Ca^{2+}$ exchanger reverse mode (Chen et al. 2001), inhibition of L-, P/Q-, N-type voltage-gated calcium channels (Wu et al. 2005), prevention of $Ca^{2+}$ influx through NMDA receptor calcium channels (Wu et al. 2009), inhibition of calcium release from the endoplasmic reticulum (Chen 2000), and the maintenance of intra-mitochondrial calcium homeostasis (El Idrissi 2008).

Taurine also protects against excitotoxicity by increasing inhibitory neurotransmission via $GABA_A$ and glycine receptor stimulation (Okamoto et al. 1983; Albrecht and Schousboe 2005; Wu et al. 2008). This neuroprotective role of taurine was observed against A$\beta$-induced excitotoxicity in chick retinal neurons (Louzada et al. 2004). These investigators showed that the neuroprotective effect was not mediated by taurine's interaction with the glutamate receptor, since neuroprotection could be blocked by the $GABA_A$ antagonist, picrotoxin and enhanced by its agonist, phenobarbital. The following year, the same group provided added evidence of taurine's ability to protect against A$\beta$-induced excitotoxicity. Using primary hippocampal and cortical neuronal cultures, they reported that neuronal death (approximately 45 % of neurons) caused by A$\beta$ (20 μM)-induced excitotoxicity was completely blocked by taurine (Paula-Lima et al. 2005).

Excessive intracellular [$Ca^{2+}$] results in ER stress, and mitochondrial dysfunction consequently potentiating the formation of reactive oxygen species (ROS), resulting in cell death. In the AD brain, A$\beta$ augments the deleterious effect of excessive $[Ca^{2+}]_i$ in both NMDAR-dependent and NMDAR-independent manner (discussed previously). Beta-amyloid itself forms free radical moieties, thereby increasing the level of ROS and potentiating oxidative stress (Hensley et al. 1994). Taurine through its anti-oxidant property (Hagar 2004; Schaffer et al. 2009; Jong et al. 2012) may be capable of protection against A$\beta$-induced neurotoxicity. There is also a strong link between apoptotic cell death and deposition of A$\beta$ as Gervais et al. (1999) observed that direct cleavage of APP by caspase-3 resulted in elevated levels of A$\beta$. It was demonstrated that synthetic A$\beta$ induced apoptosis in culture neurons (Loo et al. 1993) and that there were increases in caspase activity and DNA damage, as well as alterations in expression of apoptosis-related genes such as B-cell lymphoma-2 (Bcl-2) family members, prostate apoptosis response gene-4 (Par-4) and DNA damage response genes in brains of AD patients (Su et al. 1994; Masliah et al. 1998). In addition, mitochondrial dysfunction is reported in AD (for review see Takuma et al. 2005). Several lines of evidence (Takatani et al. 2004; Chen et al. 2009; Leon et al. 2009) have shown that taurine attenuates different apoptotic steps along the mitochondrion-mediated death cascade: a cascade that commences with the release of cytochrome *c* from the mitochondrion, through mitochondrial permeability transition (MPT) pores, the formation of an apoptosome due to the association of the released cytochrome *c* with apoptotic protease activity factor-1 (Apaf-1) and subsequent activation of caspase-9, which activates caspase-3 (seen as the final downstream killer in the cascade). An increase in the formation of Bcl-2/Bax (Bcl-2 associated protein X) heterodimers on the mitochondrion's membrane results in the decrease of cytochrome *c* release from the mitochondrion (Mikhailov et al. 2001). Using a glutamate-induced neuronal damage culture system, we (Leon et al. 2009) have recently observed that taurine is able to shift the ratio of Bcl-2: Bax in favor of cell survival by increasing the ratio of Bcl2 to Bax. Chen et al. (2009) provided evidence that taurine reduced the extent to which the MPT pores were opened, reduced the mitochondrial membrane potential and increased ATP production, preventing mitochondrial dysfunction. Takatani et al. (2004) demonstrated the inhibitory effect of taurine on the formation of the Apaf-1/caspase-9 complex (apoptosome). The inhibition of the apoptosome resulted in the attenuation of activated caspase-3 due to the inhibition of caspase-9 apoptosome-dependent activation (Takatani et al. 2004).

Another apoptotic pathway mediated by intracellular A$\beta$ is the p53-Bax pathway (Zhang et al. 2002), whereby p53, a site-specific transactivator of transcription activates the pro-apoptotic gene, Bax (Kern et al. 1991; Miyashita et al. 1994). Recently, it was reported that taurine inhibited p53 as well as the proapoptotic proteins: c-Jun N-terminal kinases (JNKs), mitogen-activated protein kinase (p38Mapk) and nuclear transcription factor kappa B (NF-kB) while activating the prosurvival phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathway in cardiac tissue (Das et al. 2011).

Based on the findings of the neuroprotective effect of taurine against excitotoxicity, disruption of calcium homeostasis, oxidative stress and apoptosis, the observation

that A$\beta$-induced neurotoxicity is mediated by these same conditions, and also the findings that the level of taurine was reduced in aged rodents as well as in the CSF of AD patients (Arai et al. 1984; Alom et al. 1991), we propose that a decrease in endogenous taurine might have shifted the balance from a protected neuronal environment to one that is vulnerable to cell death.

### Clinical trials

Birdsall (1998) reported that until 1998, there were no clinical trials for the use of taurine as a treatment for patient with Alzheimer's disease, and currently the situation remains the same. Taurine is lipophobic and an intact blood–brain barrier (BBB) prevents significant amount of exogenous taurine from entering the brain. In Alzheimer's disease, the integrity of the BBB is compromised as a result of amyloidogenesis, which disrupts tight junctions (Biron et al. 2011). A compromised BBB would allow free access of exogenous taurine to injured neurons and glia. Such a wealth of substantiating experimental evidence of taurine's protective role against AD's pathological conditions should provide the impetus for researchers to investigate the potential efficacy of taurine as a therapeutic treatment for AD in clinical trials.

## Parkinson's and Huntington's diseases

Both Parkinson's disease (PD) and Huntington's disease (HD) are motor disorders that involve the dysfunction of the basal ganglia (a group of subcortical nuclei involved in the control of movement). The basal ganglia includes the striatum (caudate/putamen), the globus pallidus with external segment (GPe) and internal segment (GPi), the subthalamic nucleus (STN), the thalamus, the pedunculopontine nucleus (PPN), and the substantia nigra pars reticulata/pars compacta (SNr/SNc). Connections of these subcortical nuclei form the basal ganglia circuitry loop (Fig. 1).

The neural circuitry of the basal ganglia represents a loop that is able to modulate behaviors; one such behavior is the initiation of movement. According to the classical model of basal ganglion function (Albin et al. 1989; Alexander and Crutcher 1990; Gerfen 1992), the striatum, the main input nucleus of the loop receives glutamatergic corticostriatal projection from the cortex and transmits this information to the output nuclei, GPi and the SNr via the direct pathway and the indirect pathway. The direct pathway originates from a subset of GABAergic striatal neurons, containing dynorphin as a co-neurotransmitter and express D1 dopamine receptors. Projections from this pathway directly innervate the SNr and GPi. The indirect pathway originates from a different subset of GABAergic striatal neurons, containing enkephalin as co-neurotransmitter and expressing D2 dopamine receptors. Projections from the indirect pathway innervate the GPe which send GABAergic projections to the STN. The STN sends glutamatergic projections back to GPe and to the output nuclei, SNr and GPi. GABAergic neurons from SNr and GPi innervate the motor thalamus which sends glutamatergic thalamocortical projections to the cortex, closing the loop. Activation of the direct pathway results in inhibition of GABAergic output nuclei, subsequently disinhibiting the thalamus which excites the cortex and facilitates movement via corticofugal projections to the brainstem and spinal cord. Activation of the indirect pathway results in inhibition of the GPe by GABAergic striatal neurons, subsequently disinhibiting the STN. A disinhibited STN sends glutamatergic projections to the GABAergic output nuclei, SNr and GPi, which inhibit the motor thalamus, resulting in a paucity of movement due to an unexcited cortex (Alexander and Crutcher 1990; DeLong 1990). Other systems overlying the basal ganglion are able to enhance or suppress movement by modulating the pathways. This is clearly seen with the dopaminergic system; dopaminergic neurons from the SNc activate D1-expressing neurons and D2-expressing neurons of the striatum. Activated D1 receptors excite the direct pathway, while activated D2 receptors inhibit the indirect pathway resulting in a net excitatory output from the basal ganglia that facilitate/enhance movement.

### Parkinson's disease

In PD, loss of dopaminergic neurons that project from the SNc to the striatum results in a net inhibitory output from the basal ganglia which impedes movement. The clinical representation of PD is hypokinetic movements, such as resting tremor, muscular rigidity, slowness of movement (bradykinesia) and failure in initiating movement (akinesia). As the disease progresses, defects in cognition such as dementia and sleep complications may arise. The neuropathological hallmarks of PD are (1) the degenerative loss of dopaminergic nigrostriatal neurons, (2) the presence of intra-cytoplasmic Lewy bodies (LBs) and (3) intra-axonal Lewy neurites (LNs) (Forno 1996). Both LBs and LNs are composed of fibrillary aggregated $\alpha$-synuclein (Spillantini et al. 1998). Alpha-synuclein is a normal brain protein found in the presynaptic axonal terminals (George et al. 1995). It is located in close association with synaptic vesicles, may modulate synaptic vesicular function, binds lipid membranes and is associated reversibly with components of the vesicular trafficking machinery (Jensen et al. 2000). Once mutated, soluble $\alpha$-synuclein misfolds, forming aggregates of $\beta$-pleated sheath, are seen in LBs and

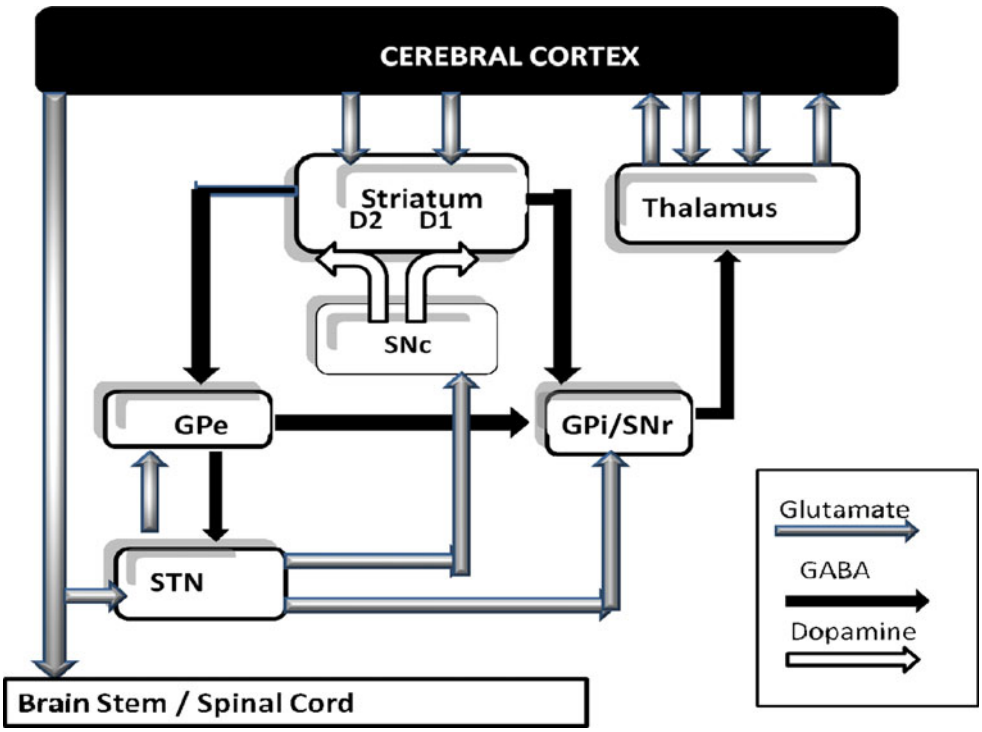


**Fig. 1** A simplified diagram, depicting the anatomical connections within the basal ganglia circuitry, according to the classical direct and indirect pathway model

LNs (Eliezer et al. 2001). With this conformational change, α-synuclein is endowed with a toxic gain of function, responsible for its neurotoxicity (Dauer et al. 2002). PD may also arise from other genetic mutations besides α-synuclein, such as parkin (Kitada et al. 1998), DJ-1 (Bonifati et al. 2003), PINK1 (Hofer and Gasser 2004) and LRRK2 (Zimprich et al. 2004).

*Neurochemical mechanisms of PD*

The development of Parkinson's-like symptoms by individuals who had accidently ingested 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Langston et al. 1983) provided the critical insight that environmental toxins may cause PD. The mode of MPTP's neurotoxicity also provided a tool for scientists to use in revealing the neurochemical/molecular mechanism of PD (Nicklas et al. 1987). Once in the cell, MPTP is oxidized by monoamine oxidase-B (MAO-B) to 1-methyl-4-phenylpyridinium ion (MPP+). MPP+ disrupts the mitochondrion's electron transport chain by inhibiting multienzyme complex I (NADH-ubiquinone reductase), resulting in decreased ATP production (Nicklas et al. 1987; Chan et al. 1991). These findings have prompted extensive research on the function of mitochondrial enzymes in PD. Documented data have shown a reduction in the activity of complex I, specifically in the substantia nigra of patients with Parkinson's disease (Parker et al. 1989; Schapira et al. 1990). Recent evidence has identified the physiological activity of complex I being maintained by DJ-1 and that a mutation in the DJ-1 gene, observed in PD, leads to an impaired complex I and mitochondrion fragmentation (Heo et al. 2012). Heo et al. (2012) also proposed that the mitochondrial membrane potential is maintained by sustaining complex I formation. It was reported that an over-expression of α-synuclein aggregates in GT1-7 cells resulted in morphological change in the mitochondrion (Hsu et al. 2000) and that PC. While PC 12 cells expressing mutated α-synuclein underwent mitochondrial depolarization and mitochondrion-mediated cell death (Smith et al. 2005).

Dopaminergic neurons in the SNc might be selectively more vulnerable to oxidative stress due to high levels of iron, auto-oxidation of melanin and the presence of dopamine (DA) itself. Dopamine, being prone to oxidation, produces DA quinone and ROS such as hydrogen peroxide ($H_2O_2$) and superoxide anion ($O_2^{\bullet -}$) during auto-oxidation and metabolism by MAO, respectively (Hastings 1995; Stokes et al. 1999; Maguire-Zeiss et al. 2005). Due to the high levels of iron in the SN (Koeppen 1995), $H_2O_2$ is converted to hydroxyl radical ($HO^{\bullet -}$) via the Fenton reaction (Youdim et al. 1989). Within this highly oxidative environment, anti-oxidants such as glutathione are impaired due to oxidation (Mytilineou et al. 2002). The production of ROS, if not reduced, as well as DA quinone can interfere with mitochondrial respiration and also open MPT pore (Berman and Hastings 1999).

Glutamate excitotoxicity in the SNc is not mediated by the usual excessive extracellular glutamate but by the

"indirect excitotoxic hypothesis" (Albin and Greenamyre 1992; Beal et al. 1993). The basis of this hypothesis is an attenuated bioenergetic activity due to reduced ATP production in a dysfunctional mitochondrion. Ionic and voltage gradients are therefore not maintained, causing plasma membrane depolarization, making the nigral dopaminergic neurons vulnerable to even physiological levels of glutamate (Novelli et al. 1988). Another source of glutamate excitotoxicity in the SNc is from a hyperactive STN. In PD, due to the loss of nigral dopaminergic input to the striatum in the basal ganglia circuitry (Fig. 1), the STN becomes hyperactivated and transmits hyperactive glutamatergic projections to the SNc (Smith et al. 1996). Initially this is beneficial, as it enhances the activity of the surviving nigral dopaminergic neurons (Shimo and Wichmann 2009), but eventually prolonged stimulation becomes toxic.

Smith et al. (2005) reported that the ER is stressed in PD and contributes to caspase-dependent apoptotic cell death. In their stable PC12 cell line with an inducible A53T alpha-synuclein mutation, they observed an elevated level of caspase-12 (an ER stress marker and initiator of caspase-dependent apoptosis), caspase-9 and caspase-3. When the level of caspase-12 was knocked down, with siRNA, cell survival was increased. The mitochondrion-mediated-death pathway was also observed to play a role in their model, since cyclosporine A, an inhibitor of the mitochondrial permeability transition (MPT), partially blocked cell death.

*The role of taurine in PD*

Several lines of evidence have implicated taurine as a neuromodulator in the nigrostriatal system (Bianchi et al. 1996; Ye et al. 1997). It was reported that taurine is at particularly high concentrations in the striatum (Palkovits et al. 1986) and the SN (Dray and Straughan 1976), and is observed in GABAergic terminals coming from the striatum to the SN (Della Corte et al.1990; Bianchi et al. 1998). It was shown that taurine modulated DA release and neuronal activity in the SN via the striatonigral pathway (Ruotsalainen and Ahtee 1996). Data from extracellular recordings of iontophoretically applied taurine showed taurine inhibiting SN firing in vivo (Dray and Straughan 1976), and it was reported that inhibition by taurine of the SNr was GABA receptor and glycine receptor-mediated (Ye et al. 1997). It was shown that pre-treatment with taurine (1 and 20 mM) attenuated MPP+ neurotoxicity in brain sections from the striatum, cortex, and corpus callosum (O'Byrne and Tipton 2000). This mechanism of protection was via the activation of $GABA_A$ receptor. O'Bryne and Tipton were able to identify the neuroprotective mechanism when the application of bicuculline ($GABA_A$ antagonist) blocked the protective effect of taurine, while muscimol ($GABA_A$ agonist) provided protection similar to taurine. They also reported that the taurine concentration of 20 mM was somewhat less effective than the concentration of 1 mM, an indication of taurine's biphasic response (Tang et al. 1996). These findings indicate that in PD (1) taurine could enhance the protection of dopaminergic cells in the SNc from both direct and indirect excitotoxicity and (2) by inhibiting the firing of GABAergic SNr cells (Ye et al. 1997), taurine could override the PD-induced hyperactive projection from the STN to the SNr, subsequently disinhibiting the motor thalamus and enhancing movement. Recently, Morales et al. (2007) reported that there was an extrasynaptic pool of taurine in the SN. They showed that the level of this pool of taurine was modulated by the cell's osmotic status and in particular, by levels of ATP and glutamate. They postulated that this could be another protective measure taken by the SN against swelling and eventual necrotic death (Morales et al. 2007).

Another avenue of protection by taurine in the PD brain is against oxidative stress. The SN is selectively vulnerable to oxidative stress due to $H_2O_2$ and $O_2^{\bullet -}$ production (Graham1978; Maguire-Zeiss et al. 2005) observed in patients of Parkinson's disease (Spencer et al. 1998). Auto-oxidation of DA is catalyzed by iron, which is of a high concentration within the SN (Jellinger 1999). Dawson et al. (2000) reported that taurine significantly reduced ferric iron and manganese-stimulated dopamine oxidation in vitro. Several lines of evidence (Vohra and Hui 2001; Hagar 2004) showed that in an oxidative environment, taurine was able to induce the activity of the endogenous anti-oxidants, catalase and glutathione peroxidase (GSH-Px). In this manner, taurine helps to scavenge ROS (Dickinson and Forman 2002).

The mitochondrial respiratory chain is disrupted in PD due to a mutated form of the DJ-1 gene, resulting in an impairment of complex I in the respiratory chain and eventually the opening of the MPT pore, initiating the mitochondrion-mediated death cascade (Heo et al. 2012). Recently, Jong et al. (2012) reported that taurine-conjugated $tRNA^{Leu(UUR)}$ (Kirino et al. 2004) in the mitochondrion is important for the encoding of proteins involved in the assembly of complex I of the electron transfer transport chain. The beneficial effect of taurine on the mitochondrion's respiratory chain resulted in reduced mitochondrial ROS (Jong et al. 2012). This report provided evidence that taurine could promote the normal functioning of complex I in PD with the subsequent increase in anti-oxidant protection. The multifaceted role of taurine provides a wide ranging neuroprotective scheme, demonstrated by the protection against mitochondrial ROS (Vohra and Hui 2001; Hagar 2004; Schaffer et al. 2009; Jong et al. 2012) as well as rectifying other mitochondrial pathology such as MPT pore opening which is reduced by taurine (Chen et al. 2009). The ER is stressed in PD, leading to caspase-

dependent apoptotic cell death via elevations of caspase-12 (Smith et al. 2005). We have shown that in the presence of taurine, the expression of both full-length caspase-12 and its activated form, cleaved caspase-12, was reduced (Pan et al. 2011).

It has been reported that there is age-related decline of taurine which correlated strongly with striatal dopamine loss (Dawson et al. 1999) and that there is a lower level of taurine in patients with PD than in control patients (Molina et al. 1997). This suggests that, similar to AD, the loss of taurine in PD could swing the scale towards neuronal degeneration. On the other hand, a report by Navneet et al. (2008) found that taurine was not protective against dopaminergic neuronal loss in a MPP+ animal model. They reported the dose of taurine (250 mg/kg, i.p.) used was similar to another study (Mankovskaya et al. 2000) that showed neuroprotection. Such conflict could arise from the difference in experimental paradigms and warrants more research in animal models of PD.

## Huntington's disease

Patients with HD exhibit hyperkinetic movements clinically presented as chorea: involuntary arrhythmic jerky movements of the upper and lower limbs or involuntary dance-like movements (Lanska 2000). This manifestation is due to the degeneration of striatal enkephalin-containing GABAergic neurons that project to GPe, subsequently inhibiting the indirect pathway of the basal ganglia (Fig. 1) and resulting in a net excitatory output to the motor thalamus (Reiner et al. 1988). The progressive stage of the disease is manifested in multiple body parts, which is gradually replaced by rigidity. Cognitive defects are also observed in the late stage of the disease, manifested as dementia. The hallmark of the disease is a mutation in the *huntingtin* or *IT15* gene resulting in an aberrant expansion (more than 35 in number; Andrew et al. 1993) of the trinucleotide (CAG) repeats which code for the amino acid glutamine in the N-terminal of the huntingtin protein (Htt) (Hs.DCR Group 1993). The expanded polyglutamine repeats alter the function of Htt, resulting in its toxicity. Mutated Htt (Exp-Htt) forms proteolysis-resistant aggregates that cannot be cleared by the ubiquitin–proteasome system (Bence et al. 2001; Venkatraman et al. 2004) altering the function of the ubiquitin–proteasome system (Bennett et al. 2007). Aggregates sequester transport proteins, Htts and transcription factors, thus disrupting neuronal function (Martindale et al. 1998; Kazantsev et al. 1999; Trushina et al. 2004).

### *Neurochemical mechanisms in HD*

Although the presence of extended polyglutamine repeats is characteristic of HD, the mechanisms underlying the pathology are still not clear. Observations that the expression of huntingtin protein, which is ubiquitously expressed throughout the body does not correlate with selected cerebral region targeted by the disease, suggests that a specific property of the striatal neurons confers selectivity to the degeneration in HD (Landwehrmeyer et al. 1995). The medium spiny neuron, containing GABA and enkephalin (ENK) are the most vulnerable of the striatal neurons (Richfield et al. 1995). It is reported that the disruption in energy metabolism and mitochondrion defects play a critical role in the mechanisms of the disease (Jenkins et al. 1993; Milakovic and Johnson 2005), and glucose metabolism is markedly reduced in the basal ganglia of patients with HD (Mazziotta et al. 1987; Kuwert et al. 1990). In support of this conclusion, studies with mitochondrial toxins that interfere with the mitochondrial respiratory chain have shown selective basal ganglia lesions (Ludolph et al. 1990; Brouillet et al. 1995). It was reported that 3-nitropropionic acid (3-NP) and malonate, two mitochondrial toxins that selectively inhibit succinate dehydrogenase (complex II) of the mitochondrial electron transfer chain, induced a clinical and pathological phenotype that closely resembles HD (Gu et al. 1996). One way in which Exp-Htt could affect mitochondrial function is by direct interaction with it. It was reported from subfractionation that mitochondria from the knock-in HD-mouse model had Exp-Htt associated with the mitochondrial outer membrane (Choo et al. 2004). Mitochondrial dysfunction leads to reduced ATP production and loss of bioenergetic activities that maintain the membrane's ionic and voltage gradients, resulting in depolarization and excitotoxicity even at non-toxic levels of glutamate (Beal et al. 1993).

Another way that Exp-Htt could interfere with mitochondrial function is by altering transcription (Brouillet et al. 1995). For instance, interacting with transcription factors, such as p53, Exp-Htt is able to activate the mitochondrion-mediated death cascade. The tumor suppressor, p53, in response to genotoxic injury, increases transcription of pro-apoptotic protein such as PUMA (Yu et al. 2001) and/or directly activates Bax at the mitochondria (Chipuk et al. 2004).

### *The role of taurine in HD*

Recently it was reported that taurine inhibited the tumor suppressor p53 (Das et al. 2011). Observations of taurine's neuroprotective effect were made in a 3-NP-induced animal model of HD (Tadros et al. 2005). The investigators assessed the level of GABA, oxidative stress activity, locomotor behavior and acoustic startle response. Pre-treated taurine (200 mg/kg daily for 3 days), increased striatal GABA concentration, decreased levels of malondialdehyde (MDA: a mitochondrial oxidative stress marker)

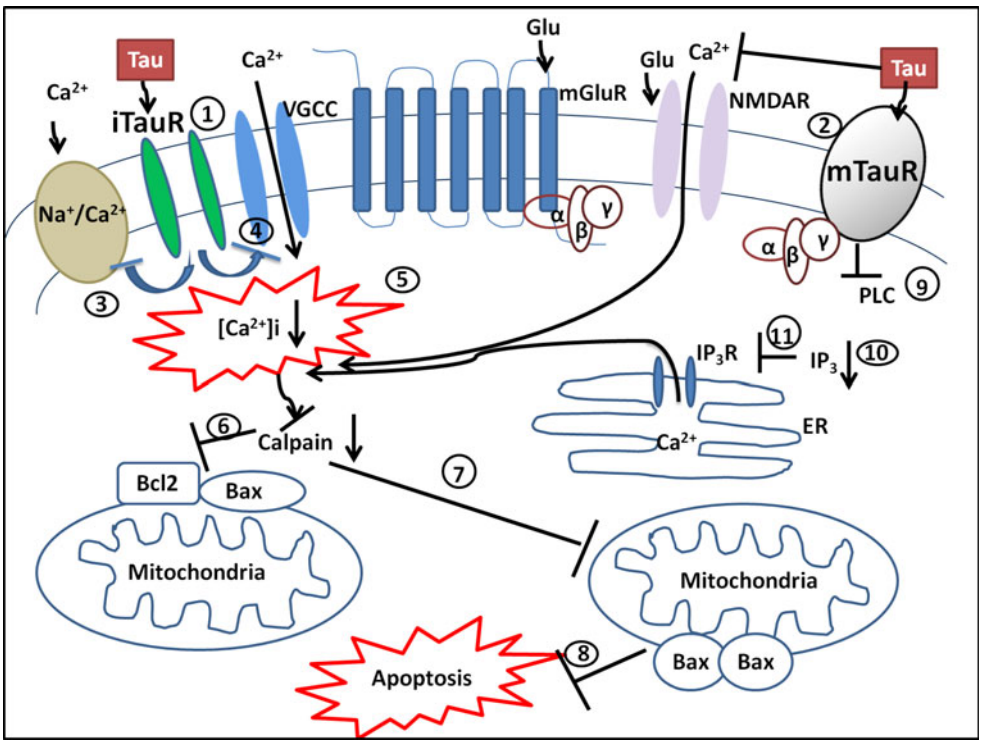


**Fig. 2** Schematic depiction of taurine neuroprotective mechanisms via putative taurine receptors. (*1*) Activated ionotropic taurine receptor (iTauR) and/or (*2*) metabotropic taurine receptor (mTauR) inhibits (*3*) the reverse mode of the sodium/calcium exchanger; (*4*) inhibition of voltage-gated calcium channels (VGCC) due to taurine-induced hyperpolarization, decreases (*5*) intracellular calcium. Reduction in intracellular calcium inhibits calpain, eliciting the inhibition of (*6*) calpain-induced cleavage of Bcl-2 and Bax. (*7*) Bax homodimer is inhibited, resulting in the inhibition of the (*8*) mitochondrion-mediated death cascade. (*9*) Phospholipase C (PLC) is inhibited by activated mTauR (mTauR: is coupled to inhibitory G-protein), resulting in (*10*) decreased $IP_3$ production, which attenuates (*11*) the release of calcium from the endoplasmic reticulum (ER) causing a reduction of ER stress and ER stress-mediated apoptosis

in the striatum, reduced locomotor hypoactivity and increased pre-pulse inhibition of startle response (Tadros et al. 2005). The increase in GABA level by taurine could be due to the inhibition of GABA transaminase (the catalysis for GABA degradation) (Sulaiman et al. 2003) or by an increase in the expression of the two isoforms of GAD (the rate-limiting synthesizing enzyme for GABA): GAD65 and GAD67 (El Idrissi and Trenkner 2004). Whichever is the central mechanism, the increase in striatal GABA by taurine would reduce the net excitatory output from the basal ganglia to the motor thalamus in HD (Fig. 1), resulting in the reduction of hyperactive movements.

Indirect excitotoxicity due to attenuated bioenergetics via mitochondrial dysfunction (Beal et al. 1993) is also observed in HD (Jenkins et al. 1993; Milakovic and Johnson 2005; Oliveira 2010). A decrease in enzymatic activity of succinate dehydrogenase (complex II) of the mitochondrial respiratory chain plays a critical role in attenuating cellular bioenergetics (Benchoua et al. 2006) and increasing oxidative stress (LaFontaine et al. 2000) in a rodent model of HD. Rivas-arancibia et al. (2001) demonstrated that taurine was protective against oxidative stress in rats given 3-NP (a mitochondrion toxin that selectively inhibits complex II). Wan et al. (2008) reported that taurine had a protective effect on mitochondrial enzymes, in the myocardium of rats with severe burns resulting in reduced mitochondrial oxidative stress. They also reported that succinate dehydrogenase was one of the mitochondrial enzymes being protected by taurine in their experimental model.

Owing to the polyglutamine's expansion in HD, the ER's protein homeostasis is impaired resulting in ER stress (Kouroku et al. 2002). It has been reported that there is an upregulation of C/EBP homologous protein (CHOP) and caspase-12 (both CHOP and caspase-12 are ER-stress markers and mediators of cell death) in experimental models expressing the polyglutamine expansion of Htt (Kouroku et al. 2002; Reijonen et al. 2008). The upregulation of CHOP is indicative of activation of the ER transmembrane stress sensors: inositol-requiring kinase 1 (IRE1), double-stranded RNA-activated protein kinase 1 (PKR)-like endoplasmic reticulum kinase (PERK), and activating transcription factor 6 (ATF 6) (Rao and Bredesen 2004), as well as the activation of corresponding

intracellular pathways (IRE1-, PERK-, ATF6-pathways) upstream of CHOP. We have demonstrated that taurine is protective against ER stress (Pan et al. 2011). Taurine inhibits the expression of CHOP by downregulating the expression of cleaved ATF6 by 50 %, resulting in the inhibition of the ATF6-pathway. It also inhibited the IRE1-pathway by reducing the expression of p-IRE1 (the activated form of IRE1) (Pan et al. 2011). Taurine also protects against caspase-mediated cell death by downregulating caspase-12, one of the ER stress markers (Pan et al. 2011).

### Clinical trials for PD and HD

Treatment for PD and HD remains a major challenge for both patients and clinicians. Advances in understanding the mechanisms underlying the neuropathology of the disease will significantly help in the development of targeted therapies. At present, there are no ongoing clinical trials reported for taurine in PD or HD.

## Concluding remarks

Taurine (2-amino-ethanesulfonic acid), an endogenous amino acid is found in very high concentrations in mammalian systems (Jacobsen and Smith 1968). It exhibits a plethora of physiological functions (Huxtable 1992), and in the CNS, it functions through multiple neuroprotective mechanisms: regulation of cellular osmolarity (Schaffer et al. 2000; Morales et al. 2007), anti-oxidant (Hagar 2004; Schaffer et al. 2009; Jong et al. 2012), neuromodulator of GABAergic transmission (O'Byrne and Tipton 2000; Wu et al. 2008), maintenance of calcium homeostasis (Chen et al. 2001; Foos and Wu 2002; El Idrissi and Trenkner 2003; El Idrissi 2008), inhibition of glutamate excitotoxicity (Chen et al. 2001; Wu et al. 2005; Paula-Lima et al. 2005), attenuation of endoplasmic reticulum stress (Pan et al. 2011), modulation of mitochondrial pore permeability (Chen et al. 2009), downregulation of a range of pro-apoptotic proteins while upregulating anti-apoptotic proteins (Su et al. 1994; Leon et al. 2009; Das et al. 2011) and downregulation of inflammatory mediators (Sun et al. 2012).

Although there is no cloned taurine receptor, several studies have provided strong evidence of the existence of a specific taurine receptor (Gleeson et al. 1987; Wu et al. 1990, 1992a, b; López-Colomé et al. 1991; Sung et al. 1996; Wu and Prentice 2010). In our previous studies (Wu et al. 1992a, b), we demonstrated that the receptor is neither activated nor antagonized by structurally similar amino acids such as glutamate, GABA and glycine. These observations were later supported by Frosini et al. (2003). There is also a strong possibility of there being two types of taurine receptor; an ionotrophic taurine receptor (Wu et al. 1992a, b) and a metabotrophic taurine receptor (Foos and Wu 2002). Other researchers have also demonstrated the existence of distinct types of taurine receptor (Kudo et al. 1988). We propose that taurine's neuroprotective effect against glutamate-induced apoptosis is in part mediated via these receptors (Fig. 2).

Many neurological disorders and neurodegenerative diseases, such as Alzheimer's, Parkinson and Huntington diseases, share a number of broad mechanisms—oxidative stress, mitochondrial dysfunction, excitotoxicity, calcium imbalance, inflammatory changes and apoptosis. Substantiating experimental data have provided evidence of taurine's protection against these pathophysiological mechanisms. Several reports demonstrate that the level of taurine is reduced in these diseases (Arai et al. 1984; Alom et al. 1991; Molina et al. 1997), indicating that the lack of taurine makes the neurophile more vulnerable. Taurine being an endogenous amino acid that is relatively inert and multifactorial in function, could be the ideal prophylactic target for these diseases. More clinical trials need to be carried out for taurine in order to validate taurine as a therapeutic agent for these diseases.

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