

Effects and Mechanisms of Taurine as a Therapeutic Agent

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Abstract

Taurine is an abundant, β -amino acid with diverse cytoprotective activity. In some species, taurine is an essential nutrient but in man it is considered a semi-essential nutrient, although cells lacking taurine show major pathology. These findings have spurred interest in the potential use of taurine as a therapeutic agent. The discovery that taurine is an effective therapy against congestive heart failure led to the study of taurine as a therapeutic agent against other disease conditions. Today, taurine has been approved for the treatment of congestive heart failure in Japan and shows promise in the treatment of several other diseases. The present review summarizes studies supporting a role of taurine in the treatment of diseases of muscle, the central nervous system, and the cardiovascular system. In addition, taurine is extremely effective in the treatment of the mitochondrial disease, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), and offers a new approach for the treatment of metabolic diseases, such as diabetes, and inflammatory diseases, such as arthritis. The review also addresses the functions of taurine (regulation of antioxidation, energy metabolism, gene expression, ER stress, neuromodulation, quality control and calcium homeostasis) underlying these therapeutic actions.

Key Words: Taurine, Cytoprotection, Neurodegenerative diseases, Antioxidation, ER stress, MELAS

INTRODUCTION

Taurine is a β -amino acid found in very high concentration in most cells, with levels particularly high in excitable tissues. Although taurine possesses many functions in mammals, its cytoprotective actions have attracted the most attention, as they dramatically alter the health and nutritional status of various species. Because taurine regulates fundamental events in the cell, while altering the balance between life and death, interest in taurine's physiological functions has grown. These findings have provided impetus for the use of taurine in infant formula, nutritional supplements and energy drinks. It also has stimulated research into its potential therapeutic uses. Although most of those studies have focused on taurine-mediated reversal of pathology in animals, there have been attempts to translate the basic science findings into clinical applications. Results of many clinical studies have been encouraging, suggesting a promising future for taurine therapy (Ginguay *et al.*, 2016). Equally promising are studies showing the nutritional value of taurine (McCarty, 2013). In some species, such as the cat and fox, taurine is an essential nutrient (Schmidt *et al.*, 1976;

Novotny *et al.*, 1991; Ito *et al.*, 2008; Ripps and Shen, 2012). Not only does taurine deficiency cause pathology in those animals but it also shortens their lifespan (Ito *et al.*, 2014a; Park *et al.*, 2014). By contrast, taurine is classified as a conditionally essential nutrient or a functional nutrient in man (Gaul, 1986, 1989; Bouckenoghe *et al.*, 2006). Although humans are incapable of synthesizing large amounts of taurine, the retention of taurine by human tissues is greater than that of cats or fox. Thus, unlike cats, humans do not readily develop overt signs of taurine deficiency although parenteral feeding can be associated with taurine deficiency (Arrieta *et al.*, 2014). Nonetheless, human studies have revealed the nutritional value of taurine. Particularly noteworthy is a World Health Association study involving 50 population groups in 25 different countries throughout the world, which reports that elevated dietary taurine consumption is associated with decreased risk of hypertension and hypercholesterolemia (Yamori *et al.*, 2004; Sagara *et al.*, 2015). Taurine supplementation is also linked to diminished body mass index (Yamori *et al.*, 2010) and reduced levels of inflammation markers in obese women (Rosa *et al.*, 2014). Thus, the cytoprotective actions of taurine contribute

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to an improvement in the clinical and nutritional health of humans. The present review discusses the mechanisms underlying the cytoprotective activity of taurine, the influence of taurine on a wide range of diseases and the nutritional value of taurine supplementation.

MECHANISMS UNDERLYING THE CYTOPROTECTIVE ACTIVITY OF TAURINE

Antioxidant activity

Recent studies have uncovered novel mechanisms responsible for taurine-mediated cytoprotection (Table 1). One of the primary mechanisms of taurine cytoprotection appears to involve its antioxidant activity, which is mediated by three distinct events. First, taurine is a proven anti-inflammatory agent that neutralizes the neutrophil oxidant, hypochlorous acid. The product of the reaction between taurine and hypochlorous acid, taurine chloramine, also interferes with the inflammatory process (Kim and Cha, 2014; Marcinkiewicz and Kontny 2014). Second, taurine diminishes the generation of superoxide by the mitochondria (Jong *et al.*, 2012; Schaffer *et al.*, 2014a). In normal mitochondria, taurine forms a conjugate with a uridine residue of tRNA^{Leu(UUR)}. Because the modified uridine residue is located in the Wobble position of the anticodon, the

conjugation reaction is capable of enhancing the interaction of the AAU anticodon of tRNA^{Leu(UUR)} with the UUG codon of mitochondrial mRNAs. However, in certain mitochondrial diseases, the formation of the taurine conjugate is diminished, an effect that suppresses the expression of specific mitochondria encoded proteins, such as NADH-ubiquinone oxidoreductase chain 6 (ND6) (Schaffer *et al.*, 2014a). ND6 is a subunit of complex I that is required for maximal complex I activity and the proper assembly of the complex. Therefore, a reduction in ND6 biosynthesis decreases complex I activity, the utilization of NADH by the respiratory chain and mitochondrial ATP generation but it increases the generation of superoxide by the respiratory chain (Jong *et al.*, 2012; Schaffer *et al.*, 2016; Shetewy *et al.*, 2016). It is widely accepted that mitochondrial oxidative stress damages macromolecules within the mitochondria, but more importantly it is capable of triggering the mitochondrial permeability transition (permeabilization of the inner mitochondrial membrane) and mitochondria-dependent apoptosis (Ricci *et al.*, 2008, Shetewy *et al.*, 2016). This sequence of events can be disrupted by taurine treatment. In the mitochondrial disease, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), the formation of the taurine conjugate is impaired. Taurine therapy provides a source of substrate for the taurine conjugation reaction, thereby restoring mitochondrial protein biosynthesis, improving

Table 1. Mechanisms underlying cytoprotective actions of taurine to improve clinical and nutritional health of humans

Cytoprotection	Functions of Taurine
Antioxidation	Anti-inflammation by neutralization of hypochlorous to produce taurine chloramine (Kim and Cha, 2014; Marcinkiewicz and Kontny, 2014) Diminishes superoxide by conjugating with uridine of tRNA ^{Leu(UUR)} in mitochondria (Jong <i>et al.</i> , 2012; Schaffer <i>et al.</i> , 2014a) Generates ATP by encoding mitochondrial ND6 protein (Jong <i>et al.</i> , 2012; Schaffer <i>et al.</i> , 2016; Shetewy <i>et al.</i> , 2016) Prevents mitochondrial membrane permeability and apoptosis (Ricci <i>et al.</i> , 2008, Shetewy <i>et al.</i> , 2016) Benefits mitochondrial disease, MELAS by providing substrate for taurine conjugation (Rikimaru <i>et al.</i> , 2012; Schaffer <i>et al.</i> , 2014b)
Energy metabolism	Activates complex I and NADH sensitive enzymes by reducing NADH/NAD ⁺ ratio during glycolysis (Schaffer <i>et al.</i> , 2016) Restores fatty acid oxidation by increasing PPARα levels (Schaffer <i>et al.</i> , 2016) Conjugates bile acids to facilitate lipid absorption by intestines (Schaffer <i>et al.</i> , 2016)
Gene expression	Changes transcription profile of metabolism-related genes (Park <i>et al.</i> , 2006) Modulates genes to induce longevity (Ito <i>et al.</i> , 2014a) Changes transcription factors (Schaffer <i>et al.</i> , 2016) Modulates protein phosphorylation and cell signalling (Lombardini, 1996; Ramila <i>et al.</i> , 2015)
ER stress	Attenuates ER stress by improving protein folding (Ito <i>et al.</i> , 2015a) Ameliorates stroke brain injury by inhibiting ER stress (Gharibani <i>et al.</i> , 2015) Protects neurons in stroke and Alzheimer's disease (Prentice <i>et al.</i> , 2015)
Neuromodulation	Protects CNS by agonizing GABA _A , glycine and NMDA receptors (El Idrissi and L'Amoreaux, 2008; Chan <i>et al.</i> , 2013) Decreases seizures by binding with GABA _A receptor (L'Amoreaux <i>et al.</i> , 2010) Protects against seizures by elevating glutamic acid decarboxylase (El Idrissi and L'Amoreaux, 2008)
Quality control	Protects cardiomyocytes by activating ubiquitin-proteasome system and autophagy (Jong <i>et al.</i> , 2015) Attenuates toxin-mediated autophagy (Li <i>et al.</i> , 2012; Bai <i>et al.</i> , 2016)
Ca ²⁺ homeostasis	Protects heart and brain during myocardial infarction and stroke by diminishing Ca ²⁺ overload (Li <i>et al.</i> , 2012; Bai <i>et al.</i> , 2016) Taurine loss during ischemia-reperfusion protects heart by reducing hypoxia-induced Ca ²⁺ overload (Schaffer <i>et al.</i> , 2002) Taurine depletion leads to cardiomyopathy due to reduced activity of SR Ca ²⁺ ATPase (Ramila <i>et al.</i> , 2015) Protects brain neurons during epilepsy by inducing Ca ²⁺ binding proteins (Junyent <i>et al.</i> , 2010) Protects neurons against glutamate excitotoxicity by reducing glutamate-induced elevation of [Ca ²⁺] _i (Wu <i>et al.</i> , 2005)
Osmoregulation	Serves as an organic osmolyte (Schaffer <i>et al.</i> , 2002)

mitochondrial function and reducing superoxide generation (Rikimaru *et al.*, 2012; Schaffer *et al.*, 2014b). In support of this theory, it has been shown that promoters of mitochondrial oxidative stress, including ozone, nitrogen dioxide, bleomycin, amiodarone, arsenic, iron, Adriamycin and catecholamines, to name a few, respond favorably to taurine therapy, (Schaffer *et al.*, 2009). Third, reactive oxygen species (ROS) generated by the mitochondria can damage antioxidant enzymes that are capable of preventing oxidative stress. Because the activity of some of the antioxidant enzymes is sensitive to oxidative damage, taurine may limit oxidative stress by preventing damage to those sensitive enzymes.

Effect on energy metabolism

Taurine deficiency-mediated impairment of complex I activity also affects energy metabolism, largely through elevations in the NADH/NAD⁺ ratio, which regulate energy metabolism by feedback inhibiting key dehydrogenases. The citric acid cycle is very sensitive to increases in the NADH/NAD⁺ ratio, as three NADH sensitive enzymes (α -ketoglutarate dehydrogenase, isocitrate dehydrogenase and citrate synthase) are subject to inhibition by elevations in the NADH/NAD⁺ ratio. For example, oxidation of pyruvate by the taurine deficient heart falls, as elevations in the NADH/NAD⁺ ratio inhibits pyruvate dehydrogenase activity and causes a deficiency in pyruvate, arising from the massive conversion of pyruvate to lactate (Schaffer *et al.*, 2016). Thus, despite stimulation of glycolysis, glucose oxidation is significantly reduced in the taurine deficient heart, dramatically decreasing the contribution of glucose metabolism toward overall ATP biosynthesis. The rate of taurine biosynthesis by the liver is low in humans, therefore, the major source of taurine in humans is the diet. For many years, diets rich in seafood were considered an excellent source of taurine, with meat containing some but less taurine than seafood. However, the recent introduction of taurine-containing supplements, such as Bacchus-D and Red Bull, provides an alternative source of taurine. The supplements have proven to be effective therapeutic agents, at least in the case of heart failure. According to Jeejeebhoy *et al.* (2002), taurine is deficient in hearts of patients suffering from heart failure. Restoration of taurine levels in these patients through supplementation leads to improved contractile function. This study reinforces the view that taurine supplements are important therapeutic agents. However, the largest decline in energy metabolism occurs in fatty acid oxidation, which falls in part because of a decrease in citric acid cycle flux. Also suppressing fatty acid oxidation in taurine deficiency are the low levels of the transcription factor, PPAR α (Schaffer *et al.*, 2016). PPAR α regulates several proteins and enzymes involved in fatty acid metabolism, with the most important being the long chain fatty acyl carnitine transporter complex (Schaffer *et al.*, 2016). Another factor affecting lipid metabolism is taurine deficiency-mediated reductions in bile acid biosynthesis, as bile acids facilitate the absorption of lipids by the intestines (see section on atherosclerosis).

Regulation of gene expression

Park *et al.* (2006) were the first investigators to recognize that taurine treatment triggers genetic changes. More recently, Ito *et al.* (2014a) have identified several taurine sensitive genes that contribute to a wide range of cellular functions (cell cycle progression, cell signaling, death and survival, amino acid metabolism, protein biosynthesis, protein folding and

aging). Taurine-mediated changes in transcription factor content have also been reported (Schaffer *et al.*, 2016). Although taurine is known to modulate protein phosphorylation and cell signaling (Lombardini, 1996; Ramila *et al.*, 2015), it remains to be determined if alterations in protein phosphorylation are involved in taurine-mediated genetic changes.

Modulation of ER stress

Another important mechanism of taurine cytoprotection is attenuation of endoplasmic reticular (ER) stress. ER stress is an important regulatory mechanism designed to restore ER function and re-establish a balance between protein degradation and protein biosynthesis/folding. When a cell experiences excessive ER stress, pathways are stimulated that can kill the cell. A common initiator of ER stress is the accumulation of defective proteins, whose levels increase as a result of improper protein folding, inadequate protein degradation or ER dysfunction. To restore ER function and the balance between protein degradation and protein biosynthesis/folding, unfolded or misfolded proteins activate three stress sensors (PERK, ATF6 and IRE1) that initiate distinct pathways known as the unfolded protein response (UPR) pathways. Together, the UPR pathways are capable of suppressing protein biosynthesis, enhancing protein degradation, generating chaperones to improve protein folding and initiating either autophagy or apoptosis. During a stroke, taurine decreases glutamate toxicity, thereby reducing both oxidative stress and calcium overload. However, taurine also suppresses two of the three UPR pathways. Although the mechanisms underlying the actions of taurine against ER stress and the UPR pathways remain to be determined, it is relevant that taurine deficiency is associated with ER stress (Ito *et al.*, 2015a). It has been proposed that taurine might alter protein folding, either by reducing oxidative stress or providing a better osmotic environment for protein folding (Ito *et al.*, 2015a). The initial studies describing the effect of taurine on ER stress used cellular and animal models of stroke (Gharibani *et al.*, 2013, 2015). According to the authors of those studies, ER stress, along with oxidative stress and mitochondrial dysfunction, are characteristic features of stroke and neurodegenerative diseases, including Alzheimer's, Huntington's and Parkinson's diseases (Prentice *et al.*, 2015). During stroke, massive amounts of the neurotransmitter, glutamate, are released which overstimulates postsynaptic neurons leading to a neuroexcitotoxic response, characterized by oxidative stress, calcium overload, ER stress and in some cases cell death (Prentice *et al.*, 2015).

Taurine as an inhibitory neuromodulator

Although ER stress assumes an important role in the cytoprotective actions of taurine in the central nervous system (CNS), another important mechanism affecting the CNS is the neuromodulatory activity of taurine. Toxicity in the CNS commonly occurs when an imbalance develops between excitatory and inhibitory neurotransmitters. GABA is one of the dominant inhibitory neurotransmitters, therefore, reductions in either the CNS levels of GABA or the activity of the GABA receptors can favor neuronal hyperexcitability. Taurine serves as a weak agonist of the GABA_A, glycine and NMDA receptors (El Idrissi and L'Amoreaux, 2008; Chan *et al.*, 2013). Therefore, taurine can partially substitute for GABA by causing inhibition of neuronal excitability. However, the regulation of the GABA_A receptor by taurine is complex. While acute taurine

administration activates the GABA_A receptor, chronic taurine feeding promotes the downregulation of the GABA_A receptor (L'Amoreaux *et al.*, 2010) and the upregulation of glutamate decarboxylase, the rate-limiting step in GABA biosynthesis (El Idrissi and L'Amoreaux, 2008). Therefore, complex interactions within the GABAergic system, as well as in the glycine and NMDA receptors, largely define the actions of taurine in the CNS.

Regulation of quality control processes

Taurine also regulates quality control processes, such as the ubiquitin-proteasome system and autophagy. These processes either rejuvenate damaged cells and subcellular organelles or eliminate them through degradation or cell death. In taurine deficient cells, a reduction in the activity of the proteasome leads to an accumulation of ubiquitinated proteins, an effect abolished by the mitochondrial specific antioxidant, mitoTEMPO (Jong *et al.*, 2015). Taurine deficiency is also associated with diminished autophagy, a condition that allows damaged cells and organelles to accumulate (Jong *et al.*, 2015). Inactivation of these quality control processes is extremely damaging to cells and tissue. However, excessive autophagy is also damaging because it can elevate cell death. Although there have only been a few studies examining the effect of taurine treatment on autophagy, the actions of taurine are compatible with its cytoprotective activity, as taurine attenuates toxin-mediated autophagy (Li *et al.*, 2012; Bai *et al.*, 2016).

Modulation of Ca²⁺ homeostasis

Excessive accumulation of Ca²⁺ by the heart and brain during a myocardial infarction or stroke, is also cytotoxic. Not only does high [Ca²⁺]_i activate proteases and lipases, but it also initiates the mitochondrial permeability transition, an event that permeabilizes the inner mitochondrial membrane and provokes the release of pro-apoptotic factors from the mitochondria that kill the cell (Rasola and Bernadi, 2011; Shet-ewy *et al.*, 2016). Taurine protects the cell by diminishing Ca²⁺ overload through three mechanisms (Schaffer *et al.*, 2014b; Prentice *et al.*, 2015). First, the loss of taurine from cells during an ischemia-reperfusion insult appears to be mediated by the taurine transporter, as taurine loss is also accompanied by the loss of Na⁺ from the cell. Consequently, upon taurine release, less Na⁺ is available for Ca²⁺ entry via the Na⁺/Ca²⁺ exchanger, which minimizes the degree of Ca²⁺ overload (Schaffer *et al.*, 2002). Second, taurine indirectly regulates the activity of the sarcoplasmic reticular Ca²⁺ ATPase, which is responsible for maintaining cytosolic Ca²⁺ homeostasis through the removal of Ca²⁺ from the cytosol (Ramila *et al.*, 2015). This action of taurine involves alterations of protein phosphorylation, however, the mechanism by which taurine modulates protein phosphorylation has not been ascertained and warrants further study. Third, taurine treatment is associated with changes in the presence of calbindin D28k, calretinin and parvalbumin (Junyent *et al.*, 2010). Fourth, taurine inhibits glutamate-induced Ca²⁺ influx through the L-, P/Q- and N-type voltage gated Ca²⁺ channels, as well as the NMDA receptor channel (Wu *et al.*, 2005).

Osmoregulation

The concentration of taurine within most cells is quite high. In response to elevations in an osmotic load, intracel-

lular taurine levels increase while they decrease in response to hypo-osmotic stress. These are important mechanisms to protect the cell from excessive stretching in response to osmotic imbalances. Because taurine serves as an organic osmolyte, it also modulates the levels of other osmolytes, such as Na⁺, which not only carries a charge (unlike taurine which is a neutral zwitterion) but is also involved in many important cellular functions, such as transport and membrane potential (Schaffer *et al.*, 2002). In the kidney, taurine serves as a weak diuretic and natriuretic agent, important properties for normal renal function.

TAURINE-MEDIATED PROTECTION AGAINST PATHOLOGY AND DISEASE

Effect of taurine on the central nervous system

Stroke: Stroke, whose incidence is on the rise, is presently a leading cause of death and disability. Under pathological conditions, such as ischemic stroke and hypo-osmotic stress, taurine is released from various cells in the central nervous system (CNS) and function as a neuroprotective agent (Albrecht and Schousboe, 2005). For many brain areas, concentrations of taurine are below 1 mM, which are adequate to activate glycine receptors but not most GABA receptors; the GABA receptors of the ventrobasal thalamus are an exception, as they exhibit especially high affinity for taurine. Taurine plays an important role in neuronal development in the cerebral cortex (Furukawa *et al.*, 2014). Although concentrations of taurine below 1 mM do not activate the GABA receptor in many regions of the CNS, taurine deficiency leads to impaired GABAergic inhibition in the striatum, a condition associated with the development of a disease mimicking hepatic encephalopathy (Sergeeva *et al.*, 2007).

A major cause of cellular damage and death during stroke is the release of large amounts of glutamate, which overstimulate glutamate receptors, resulting in hyper-excitability (Prentice *et al.*, 2015). Among the damaging events associated with glutamate toxicity are calcium overload, oxidative stress, ATP depletion and mitochondrial dysfunction (Abramov and Duchan, 2008; Prentice *et al.*, 2015). The combination of calcium excess and oxidative stress is capable of triggering the mitochondrial permeability transition and the release of pro-apoptotic factors that initiate mitochondrial apoptosis. Apoptosis can also be initiated by caspase 12, CHOP (C/EBP homologous protein) and JNK, which are end products of unfolded protein response (UPR) pathways that arise from ER stress. Interestingly, taurine is also released from brain slices in response to glutamate receptor stimulation (Saransaari and Oja, 2010). The release of taurine helps counteract the adverse effects of glutamate toxicity by reducing [Ca²⁺]_i, increasing the Bcl-2/Bad ratio and suppressing ER stress (Wu and Prentice, 2010). Moreover, taurine reduces cell swelling in rat brain cortical slices subjected to a hypoxic-reoxygenation insult (Ricci *et al.*, 2009). However, it remains to be determined whether taurine-mediated increases in ATP generation and suppression of mitochondrial ROS generation might also contribute to the reductions in the severity of stroke. There is reason to believe that the mitochondrial actions of taurine should reverse stroke-mediated suppression of complex I activity. Taurine might also attenuate another source of ROS in stroke, namely those from NADPH oxidase (Abramov *et al.*,

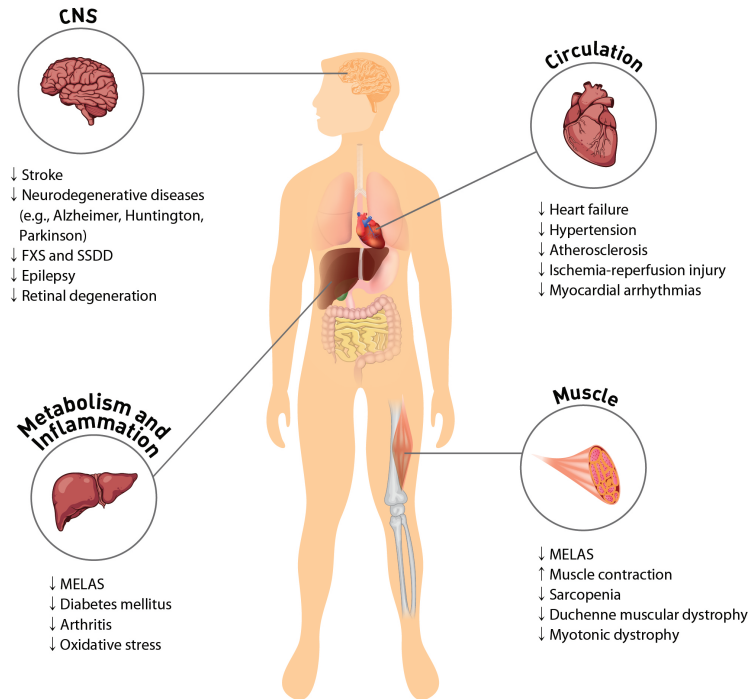


Fig. 1. Taurine-mediated protection against pathology and disease. High concentrations of taurine in most cells regulate physiological function of excitable tissues and mitochondria. Taurine protects CNS by decreasing ER stress and antagonizing neurotransmitter receptors of GABA_A, glycine and NMDA. Protection of the cardiovascular system by taurine occurs through regulation of cell signaling, such as Ca²⁺ transport, ROS generation and protein phosphorylation. Supplementation of taurine ameliorates symptoms of MELAS and diabetes mellitus. The anti-inflammatory activity of taurine involves either the formation of taurochloramine in neutrophils or the attenuation of nitric oxide and prostaglandin E2 in inflammatory diseases, such as rheumatoid arthritis and osteoarthritis. Taurine depletion or taurine transporter KO leads to cardiac and skeletal muscle dysfunction. Taurine prevents sarcopenia in aged person by minimizing gradual muscle loss. CNS: central nervous system; FXS: fragile X syndrome; SSDD: succinic semialdehyde dehydrogenase deficiency; MELAS: mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes.

2007), as taurine treatment is known to reduce the levels of the substrate, NADPH (Schaffer *et al.*, 2016) and mediate the downregulation of Nox2/Nox4 (Han *et al.*, 2016). Using an animal model of focal cerebral ischemia, Gharibani *et al.* (2015) found that the combination of taurine and a NMDA partial antagonist (5-methyl-N,N-diethylthiolcarbamate-sulfoxide) reduced apoptosis and ER stress while the partial antagonist alone exhibited no neuroprotection.

While there is abundant evidence that taurine is effective in treating stroke in animals (Menzie *et al.*, 2013), only a few studies have addressed its effect on the risk of stroke in humans. In a prospective-case study based on the New York University Women's Health Study, which examined 14,274 women, no association was observed between serum taurine levels and stroke risk (Wu *et al.*, 2016). However, among non-smokers there may be a link that deserves further consideration, particularly in light of evidence that the incidence of stroke was reduced 90% in a genetic model of stroke (stroke-prone spontaneously hypertensive rats) fed a diet rich in taurine (Yamori *et al.*, 2009). Clearly, clinical studies examining the effectiveness of taurine against stroke in humans is warranted (Fig. 1).

Neurodegenerative diseases, such as Alzheimer's, Huntington's and Parkinson's disease: The neurodegenerative diseases share many of the pathological features of stroke caused by glutamate-mediated activation of N-methyl-D-aspartate (NMDA) receptors, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) ionotropic glutamate recep-

tors and metabotropic glutamate receptors (Hara and Snyder, 2007). A major cause of cell death from glutamate-mediated hyperexcitability in neurodegenerative diseases appears to involve the collapse of the mitochondrial membrane potential (Abramov and Duchen, 2008). Activation of glutamate receptors leads to calcium overload and an increase in ROS production. Because mitochondrial function is adversely affected by neurodegeneration, one would expect that mitochondrial ROS generation should be a major cause of cellular damage. Indeed, respiratory chain defects have been detected in degenerative diseases, although the site of the defect is disease specific, with Parkinson's disease affecting complex I, Huntington's disease affecting complex II and Alzheimer's disease affecting complex IV (Damiano *et al.*, 2010; Alleyne *et al.*, 2011). Interestingly, one of the animal models of Parkinson's disease is generated by treating rodents with the complex I inhibitor, rotenone (Cannon *et al.*, 2009). Taurine deficiency and rotenone actions are similar, as both lead to reductions in complex I activity, inhibition of NADH dehydrogenase activity, reductions in respiratory activity and elevations in NADH. Because a primary physiological function of taurine is the maintenance of complex I activity, there is reason to believe that taurine therapy should reduce the severity of Parkinson's disease (Alkholifi *et al.*, 2015). Indeed, it has recently been reported that reduced plasma taurine content is associated with motor severity in Parkinson's disease (Zhang *et al.*, 2016). Moreover, a single blind, randomized, controlled study

of 47 patients with Parkinson's disease revealed effectiveness in reducing excessive sleepiness upon treatment with the taurine analog, homotaurine (Ricciardi *et al.*, 2015).

Fragile X Syndrome and succinic semialdehyde dehydrogenase deficiency: Fragile X syndrome is a genetic disease characterized by behavioral disorders and moderate to severe intellectual disabilities. The learning deficit (memory retention) of the fragile X mouse responds favorably to chronic oral administration of taurine (0.05% w/v) for 4 weeks, an effect seemingly linked to taurine's GABAergic activity (Neuwirth *et al.*, 2015).

Succinic semialdehyde dehydrogenase (SSADH) deficiency is a rare autosomal genetic disease involving a key enzyme in GABA catabolism. Patients with SSADH deficiency showed symptoms such as ataxia, hypotonia, language deficits, and intellectual disability. Nearly half of the SSADH patients suffer from seizures. Because the disease is associated with disruption of GABA homeostasis, the effect of taurine therapy on symptoms of the disease before and after treatment have been examined. In a single case study of a 2-year old boy, taurine therapy (200 mg/kg/day) for 12 months improved social behavior, coordination and activity (Saronwala *et al.*, 2008). However, in a subsequent open-label study of 18 SSADH deficient subjects administered taurine (50-200 mg/kg/day) for a period up to one year there was no major improvement in adaptive behavior with taurine (Pearl *et al.*, 2014). Clearly, a controlled, randomized double-blind study of a larger number of patients receiving either placebo or taurine therapy is warranted.

Epilepsy: Imbalances between excitatory and inhibitory neurotransmitters underlie the mechanism of seizures. Taurine is an abundant amino acid in the brain, where it serves as an inhibitory neuromodulator (Oja and Saransaari, 2013). Although taurine levels can suppress specific types of seizures, taurine deficiency is not required for initiation of seizures. In animal studies, taurine administration has been found to abolish seizures evoked by a wide range of stimulants, including [D-Ala, Met]-enkephalinamide, opioids, kainite, isoniazid, picrotoxin, penicillin and hypoxia. Nonetheless, clinical trials examining the effect of taurine treatment on human epilepsy have been mixed, with only about 1/3 of the patients responding favorably to taurine therapy (Barbeau and Donaldson, 1974; Bergamini *et al.*, 1974; Konig *et al.*, 1977; Rumpl *et al.*, 1977; Mantovani and DeVivo 1979; Airaksinen *et al.*, 1980).

The dominant inhibitory neurotransmitter in the brain is GABA, therefore, regulation of neuroexcitability by GABA plays a prominent role in preventing neuronal hyperexcitability and seizures (L'Amoreaux *et al.*, 2010). Taurine serves as an agonist of the GABA_A receptor, an action that enhances chloride influx into postsynaptic neurons, which causes hyperpolarization that inhibits hyperexcitability. Suppression of kainic acid, isoniazid and picrotoxin-mediated seizures has been attributed to the actions of taurine on the GABAergic system (El Idrissi *et al.*, 2003; El Idrissi and L'Amoreaux, 2008; Junyent *et al.*, 2009; L'Amoreaux *et al.*, 2010). Like GABA, glycine is a major inhibitory neurotransmitter that activates chloride conductance and hyperpolarizes neurons. The inhibitory neuromodulator activity of taurine also extends to the glycine receptor, as the binding of taurine to the glycine receptor evokes chloride current and suppresses neuronal firing (Wu *et al.*, 2008).

Retinal degeneration: The landmark studies showing

that taurine is an essential nutrient for cats focused on the link between taurine deficiency and the development of photoreceptor loss and retinal degeneration (Schmidt *et al.*, 1976; Hayes *et al.*, 1975). More recently, Hadj-Said *et al.* (2016) found that taurine deficiency also causes nuclear ganglion cell degeneration and loss. Moreover, the anti-epileptic agent, vigabatrin, can provoke retinal degeneration, including both photoreceptor and ganglion cell loss, accompanied by taurine deficiency (Heim and Gidal, 2012; Froger *et al.*, 2014). In two patients with succinic semialdehyde dehydrogenase deficiency exhibiting abnormal ERGs at baseline and after 6 months of vigabatrin treatment, taurine therapy partially prevents retinal damage triggered by vigabatrin treatment (Horvath *et al.*, 2016). Because taurine is required for normal retinal ganglion cell survival (Froger *et al.*, 2012), it has been proposed that taurine therapy may serve an important role in the prevention of retinal degeneration (Froger *et al.*, 2014).

Effect of taurine on the cardiovascular system

Congestive heart failure: Taurine has been approved for the treatment of congestive heart failure in Japan (Azuma *et al.*, 1992). Like other heart failure medication, taurine not only diminishes the common symptoms of congestive heart failure (breathlessness on exertion and edema) but also eliminates or decreases the need for administering other heart failure medication, such as digoxin (Azuma *et al.*, 1992). Although taurine exerts a mild positive inotropic effect on the hypodynamic heart and promotes natriuresis and diuresis, the major therapeutic effect of chronic taurine administration appears to involve a reduction in the actions of norepinephrine and angiotensin II, which are known to decrease myocardial performance through elevations in afterload pressure, ventricular remodeling and fluid remodeling (Ito *et al.*, 2014b). Taurine is effective in reducing the adverse actions of norepinephrine through its ability to both decrease catecholamine overflow (through alterations in Ca²⁺ transport) and diminish cell signaling (through changes in Ca²⁺ transport, ROS content and protein phosphorylation). Although recent studies have shown that taurine therapy improves exercise capacity of patients with heart failure (Ahmadian *et al.*, 2017), it remains to be determined whether taurine supplementation also reduces the risk of developing overt heart failure in the general population. Moreover, the possibility that taurine supplementation might lower the mortality rate of heart failure patients has not been examined. There is reason to believe that taurine might prolong lifespan of heart failure patients because it elevates high energy phosphate content of the heart, which is an important determinant of mortality among patients suffering from congestive heart failure (Schaffer *et al.*, 2016).

Hypertension: Supplementation with taurine prevents the development of hypertension in several animal models (Fujita and Sato, 1986; Ideishi *et al.*, 1994; Dawson *et al.*, 2000; Harada *et al.*, 2004; Hagar *et al.*, 2006; Hu *et al.*, 2009). In those models, taurine-mediated reductions in blood pressure appear to be mediated by a combination of diminished [Ca²⁺]_i, oxidative stress, sympathetic activity and inflammatory activity, as well as an improvement in renal function (Sato *et al.*, 1991; Dawson *et al.*, 2000; Harada *et al.*, 2004; Hagar *et al.*, 2006; Mozaffari *et al.*, 2006; Hu *et al.*, 2009; Han and Chesney, 2012; Maia *et al.*, 2014; Katakawa *et al.*, 2016).

Two recent clinical studies support the view that taurine therapy reduces blood pressure in hypertensive subjects

(Katakawa *et al.*, 2016; Sun *et al.*, 2016). Katakawa attributed the beneficial effects of taurine therapy against hypertension in humans to improved endothelial function secondary to a decline in oxidative stress. By comparison, Sun *et al.* (2016) focused on the vasodilatory effects of pre-hypertensive patients receiving taurine therapy. The most important feature of the study reported by Sun *et al.* (2016) was its size and design, as it is a single-center, double-blind, randomized, placebo-controlled trial of 120 pre-hypertensive subjects aged 18-75 with systolic pressure varying from 120-139 mm Hg and diastolic pressure from 80-89 mm Hg. After administration of taurine (1.6 g/day) for 12 weeks, systolic pressure of the pre-hypertensive subjects was reduced 7.2 mm Hg and diastolic pressure fell 4.7 mm Hg while pre-hypertensive subjects treated with placebo exhibited no significant reduction in blood pressure over the same treatment period (Sun *et al.*, 2016). The taurine effect was greater in pre-hypertensive subjects with higher blood pressure than with the subjects with lower blood pressure at the time of initial taurine administration. The administration of taurine resulted in a 1.5-fold increase in plasma taurine concentration, an effect correlated with the improvement in blood pressure. This observation was consistent with an earlier epidemiological study by Yamori *et al.* (2010), who found that individuals with elevated amounts of taurine intake exhibit lower blood pressure values than individuals consuming less taurine. Moreover, Ogawa *et al.* (1985) had previously observed that plasma taurine content is reduced in essential hypertension. The human studies are consistent with animal studies showing that taurine deficiency accelerates the onset of hypertension in rats lacking a kidney and maintained on a high salt diet (Mozaffari *et al.*, 2006). Moreover, a negative correlation has been detected between plasma taurine content and blood pressure in spontaneously hypertensive rats (Nara *et al.*, 1978). In their clinical study, Sun *et al.* (2016) attributed the taurine-mediated reduction in blood pressure to improved flow- and nitroglycerin-mediated dilation, a change not observed in the placebo treated group. In addition to elevating plasma taurine content, the taurine treated group exhibited elevated H₂S content, the latter that promotes hypotension by inhibiting transient receptor potential channel 3 (TRPC3)-induced signaling in the vasculature. Further studies are warranted to compare the importance of H₂S content on blood pressure control relative to the other common regulators of vascular function, such as Ca²⁺, neurohumoral factors and nitric oxide.

Atherosclerosis: Atherosclerosis is the primary cause of pathology in stroke, myocardial infarction and peripheral artery disease. The process of atherosclerosis is complex, involving multiple factors and steps (Moore and Tabas, 2011). One of the key steps in the initiation of atherosclerosis is the uptake of the cholesterol-enriched lipoprotein, LDL, by the intima of the arterial wall. Also recruited in the arterial wall are monocytes, which normally exhibit little adhesion to endothelial cells and are not readily accumulated by smooth muscle. However, upon exposure to inflammatory factors and chemoattractants (chemokines), monocytes begin to adhere to endothelial cells, where they are taken up by the intima of the arterial wall. Upon exposure to factors, such as macrophage-colony factor, most of the monocytes in the early atheromata are differentiated into macrophages. Within the intima, LDL can undergo oxidation and glycation, which individually enhance the uptake of the lipoprotein by macrophages. While the uptake and han-

dling of LDL by macrophages is considered an early event in the formation of foam cells, it is now apparent that there are multiple pathways involved in foam cell formation and atherosclerosis (Moore and Tabas, 2011).

Taurine treatment diminishes atherogenesis through several possible mechanisms. First, in most, but not all studies, taurine supplementation accelerates the regression in serum cholesterol levels in atherogenic animals (Petty *et al.*, 1990; Murakami *et al.*, 1996, 2010). During the regression period, hepatic cholesterol levels fall more rapidly in taurine treated animals, largely because of an increase in 7 α -hydroxylase activity, which accelerates the degradation of cholesterol. Because there is a correlation between lower serum cholesterol and the dose of taurine used during treatment, the upregulation of the CYP7A1 gene in the liver is thought to regulate serum cholesterol levels (Yokogoshi *et al.*, 1999; Lam *et al.*, 2006; Murakami *et al.*, 2010). At the same time, taurine treatment is associated with diminished activity of 3-hydroxy-3-methylglutaryl CoA reductase, the rate-limiting step of cholesterol biosynthesis (Bellentani *et al.*, 1987). Second, exposure of hepatic cells for 24 hrs with medium containing taurine leads to a decline in the biosynthesis of cholesterol esters and triglycerides. Because the hepatic content of triglycerides and cholesterol esters is a determinant of lipoprotein assembly in the endoplasmic reticulum of the liver, taurine specifically decreases the assembly and secretion of lipoproteins containing the structural protein, apolipoprotein B100 (Yanagita *et al.*, 2008; Murakami *et al.*, 2010). Apolipoprotein B100 is the primary structural protein of both LDL and its precursor, VLDL. Third, taurine protects endothelial cells of vascular tissue from glucose-induced and oxidized LDL-induced toxicity, which is an early step in the development of atherosclerosis (Ulrich-Merzenich *et al.*, 2007). It has also been suggested that taurine protects endothelial cells from homocysteine-induced ER stress and apoptosis by reducing hyperhomocysteinemia (Zulli *et al.*, 2009). While oxidative stress is a primary adverse response to hyperglycemia and homocysteinemia, oxidized LDL-induced toxicity has been attributed to the accumulation of asymmetric dimethylarginine, an inhibitor of nitric oxide synthase (Tan *et al.*, 2007). Fourth, taurine suppresses platelet-derived growth factor-BB (PDGF-BB) induced vascular smooth muscle cell proliferation, which plays an important role in atherosclerosis (Yoshimura *et al.*, 2005). Taurine appears to alter the activity of a phosphatase that dephosphorylates the PDGF- β receptor, which is a potent chemoattractant and proliferative factor for vascular smooth muscle cells. However, taurine does not suppress phorbol ester-induced activation of the Raf/MEK/ERK pathway of vascular smooth muscle proliferation, leading to the suggestion that taurine's actions are specific for the PDGF- β pathway. Nonetheless, the field remains controversial. According to Terashima *et al.* (2003), taurine suppresses mesenchymal cell proliferation by inhibiting ERK activity and immediate early gene expression. Clearly, studies clarifying the effect of taurine on smooth muscle cell proliferation are warranted. Fifth, taurine diminishes the expression of LOX-1, which mediates the uptake of oxidized LDL by endothelial cells and decreases the rate of stenosis in oxidatively stressed rabbits subjected to balloon injury of the iliac artery (Gokce *et al.*, 2011). The authors also recognized the important role of taurine-mediated attenuation of oxidative stress in their findings. Finally, the possibility that taurine-mediated inhibition of atherosclerosis may involve its anti-inflam-

matory activity deserves consideration.

The epidemiological WHO-CARDIAC study showed that dietary taurine intake is correlated with reduced mortality of ischemic heart disease patients (Yamori *et al.*, 2001). In support of that study, Elvevoll *et al.* (2008) found that taurine enhances the beneficial effects of n-3 fatty acid supplementation on total cholesterol, LDL cholesterol and triglycerides. Recently, Katakawa *et al.* (2016) attributed the diminished risk of atherogenesis in humans maintained on a diet supplemented with taurine and magnesium to reductions in oxidative stress and improvement in endothelial function. These studies have revealed the importance of taurine supplementation in human health.

Ischemia-reperfusion injury: Several actions of taurine (antioxidant, modulation of $[Ca^{2+}]_i$, osmoregulation, protein phosphorylation and high energy phosphate regulation) alter the outcome of an ischemia-reperfusion insult. A discussion of the differing effects of these factors in various models of ischemia-reperfusion injury and of the importance of taurine treatment and loss during an ischemia-reperfusion insult, appeared in a recent review (Schaffer *et al.*, 2014b). Because of variable effects, it is unlikely that taurine would be adopted as an acute cardioprotective agent to diminish infarct size and minimize injury during a myocardial infarction. Rather, taurine's use may be restricted to cardiac transplantation and bypass surgery. Several investigators have reported a benefit of taurine as a component of cardioplegic solutions (Oriyanhan *et al.*, 2005) or of loading hearts with taurine prior to their use as donor hearts (Venturini *et al.*, 2009; Sahin *et al.*, 2011). Besides reducing oxidative stress and swelling, taurine loss during an ischemia-reperfusion insult leads to a decrease in $[Na^+]_i$, which not only diminishes osmotic stress but also Ca^{2+} overload (Schaffer *et al.*, 2002; Modi and Suleiman, 2004). In addition, rapid intravenous infusion of taurine before bypass surgery protects against oxidative stress and cellular necrosis (Milei *et al.*, 1992).

Myocardial arrhythmias: One of the earliest reported cardiovascular actions of taurine is its antiarrhythmic actions against a broad range of pro-arrhythmic agents (digoxin or related cardiac glycoside, epinephrine, ouabain, CsCl, hypokalemia) (Read and Welty, 1963; Chazov *et al.*, 1974). This effect is likely related to the modulation of $[K^+]_i$, $[Na^+]_i$ and $[Ca^{2+}]_i$. According to a clinical report, oral administration of taurine and L-arginine dramatically reduced cardiac arrhythmias of three subjects. Thus, under appropriate conditions, taurine is a very effective antiarrhythmic agent (Eby and Halcomb, 2006). Nonetheless, taurine is presently not used in the treatment of cardiac arrhythmias.

Role of taurine in metabolic diseases

Mitochondrial disease, MELAS: A remarkable similarity exists between the symptoms of taurine deficiency and that of the mitochondrial disease, MELAS (Schaffer *et al.*, 2013). Indeed, the characteristic symptoms of MELAS (myopathy, encephalopathy, lactic acidosis and stroke-like episodes) are also present in taurine deficiency. This is not surprising, as the pathophysiology of the two conditions is similar. MELAS is caused by specific point mutations in the region of DNA that codes for tRNA^{Leu(UUR)} (Schaffer *et al.*, 2014a). The mutations appear to alter the structure of the tRNA, preventing the conjugation of taurine with the uridine base of tRNA^{Leu(UUR)} (Kirino *et al.*, 2005). Modification of the uridine base alters the interac-

tion of the UUG codon with the AAU anticodon of tRNA^{Leu(UUR)}, thereby altering UUG decoding (Kurata *et al.*, 2003). Taurine deficiency also appears to reduce the formation of the taurine conjugate, 5-taurinomethyluridine-tRNA^{Leu(UUR)}, but the effect is related to a reduction in mitochondrial taurine content (Schaffer *et al.*, 2014a). Taurine deficiency reduces the expression of UUG-dependent proteins, with one of the most UUG-dependent mitochondria encoded protein being ND6, a subunit of complex I. Because ND6 plays a prominent role in the assembly of complex I, taurine-mediated reductions in ND6 levels lead to several features seen in MELAS, including lactic acidosis, reduced complex I activity and diminished oxygen consumption. Impaired respiratory chain function causes elevations in superoxide generation and reduced ATP generation, effects that likely play a central role in the development of the myopathy and encephalopathy of MELAS (Fig. 2). Seizures, which are another symptom of MELAS, could depend on the inhibitory neuromodulatory activity of taurine although the mitochondrial activity of taurine might also be a determinant of seizures.

Because of the direct link between taurine content and the development of MELAS, it is not surprising that patients with MELAS respond favorably to taurine therapy (Rikimaru *et al.*, 2012). In one such case study, laboratory tests revealed that a 29-year-old woman presented at the hospital with stroke-like episodes had a MELAS-like A3243G point mutation in a left biceps brachii muscle biopsy. Anticonvulsants, both phenytoin and valproate, were administered over the next 7 months but failed to halt the epileptic and stroke-like episodes. Shortly after beginning oral taurine supplementation, which increased blood taurine content about 5-fold, the epileptic and stroke-like episodes completely ceased. Also corrected by taurine therapy was lactic acidosis. In a related case study, a 21-year-old male was admitted to a hospital with right homonymous hemianopsia. He was diagnosed with A3243G-linked MELAS and lactic acidosis. Anticonvulsion therapy was used over the next several years, but the patient still experienced several stroke-like episodes, including sensory aphasia and visual impairment. After taurine supplementation, which elevated blood levels approximately 10-fold, the stroke-like episodes ceased. The same group examined the effect of taurine treatment on cytoplasmic hybrids (cybrids) harboring a 3243G-MELAS mutation; incubation of the cybrids for 4 days with medium containing 40 mM taurine partially normalized oxygen consumption and mitochondrial membrane potential, which were suppressed in the A3243G containing cybrids. Taurine treatment also attenuated the degree of oxidative stress in cybrids harboring the 3243 mutant. Thus, taurine therapy not only abolishes stroke-like episodes in MELAS patients but also restores normal mitochondrial respiratory function. These data reveal promise for the use of taurine as a therapeutic agent against MELAS.

Diabetes mellitus: Diabetes mellitus is a disease characterized by elevated blood glucose and either a decrease in plasma insulin (type 1 diabetes) or resistance to the actions of insulin (type 2 diabetes). Type 1 diabetes is an autoimmune disease that is caused by T-cell-mediated destruction of pancreatic β -cells that dramatically reduces insulin biosynthesis. Thus, the disease is characterized by hypoinsulinemia and hyperglycemia. By contrast, type 2 diabetes is a progressive disorder characterized initially by insulin resistance, in which the actions of insulin at target organs are reduced, although in

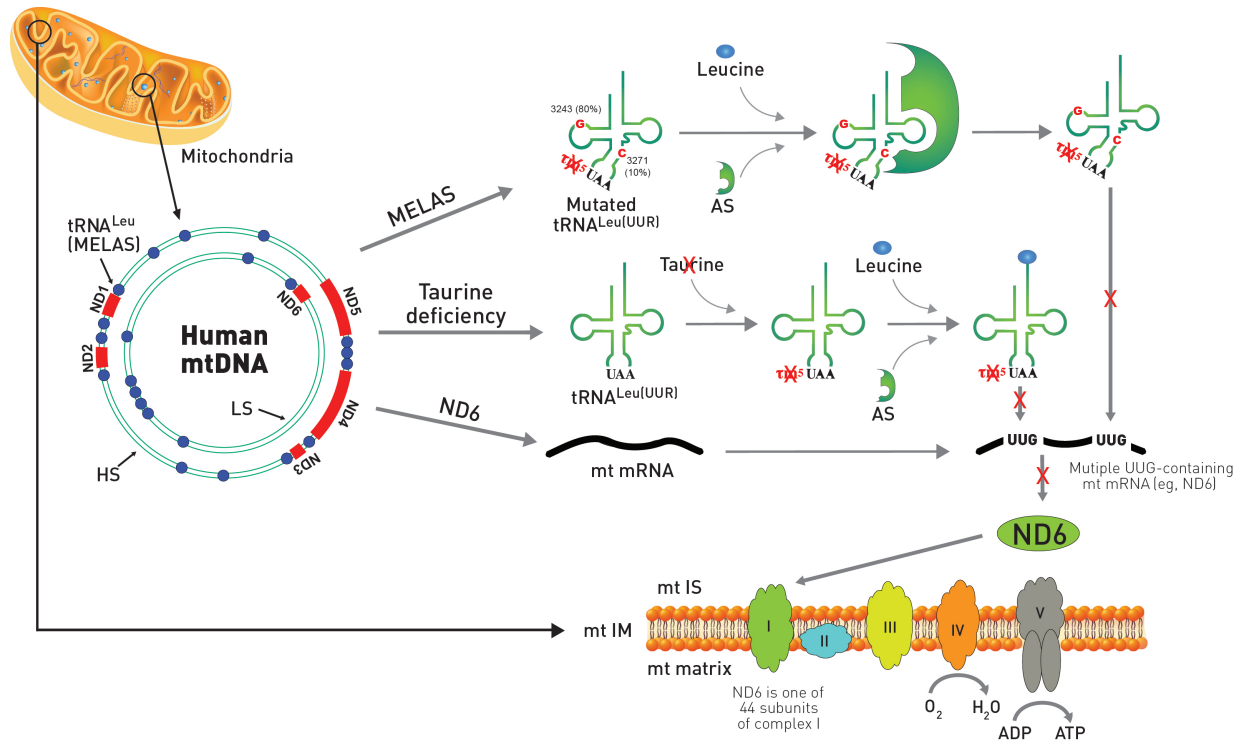


Fig. 2. Comparison of MELAS and taurine deficiency in mitochondria. The mitochondrial disease, MELAS, is caused by specific point mutations in mitochondrial DNA (mtDNA) that codes for tRNA^{Leu(UUR)}. Most of the point mutations of MELAS with 80% frequency occur at A3243G while mutations at T3271C exist with 10% frequency. In mtDNA, ND genes are shown in red color and tRNA genes are depicted as blue circles. The gene of tRNA^{Leu(UUR)} responsible for MELAS is located adjacent to ND1. The mutation in MELAS alters the structure of the tRNA^{Leu(UUR)} preventing the conjugation of taurine with the uridine base of the UAA anti-codon from forming 5-taurinomethyluridine (τ^m U), MELAS patients also show reduced aminoacylation of taurine deficient tRNA^{Leu(UUR)} by leucine catalyzed by aminoacyl-tRNA synthetase (AS). Both reduced aminoacylation of tRNA^{Leu(UUR)} by leucine and formation of the taurine conjugate of τ^m UAA-tRNA^{Leu(UUR)} prevent decoding of mitochondrial UUG-dependent proteins, including ND6, which is one of 44 protein subunits of complex I of the electron transport chain located in the mitochondria inner membrane. On the other hand, taurine deficiency has normal aminoacylation of tRNA^{Leu(UUR)} by leucine, but exhibits reduced formation of the taurine conjugate of τ^m UAA-tRNA^{Leu(UUR)}, which also prevents decoding of mitochondrial ND6 mRNA, resulting in increased superoxide generation and reduced ATP generation. MELAS: mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; ND6: NADH-ubiquinone oxidoreductase chain 6; mt IS: mitochondrial intermembrane space; mtIM: mitochondrial inner membrane; LS: light strand; HS: heavy strand.

later stages of the disease insulin secretion is also impaired. Diabetes is associated with multiple complications, including cardiovascular disease, neuropathy, nephropathy, retinopathy, foot ulcers, skin lesions and hearing impairment. Although restrictions in the degree of hyperglycemia are central to the control of these complications, several downstream factors can contribute to the severity of the complications. One of the most important of these factors is ROS. According to seminal studies by Brownlee (2005), it was proposed that glucose oxidation, which involves pyruvate metabolism by the mitochondria, produces ROS, which in turn enhances flux through several damaging pathways (advanced glycosylation end product generation, protein kinase C activation, polyol formation and hexosamine pathway stimulation) involved in the development of diabetic complications.

Two important concepts arose from the work of Brownlee (2005). First, his unifying hypothesis provided a logical link between glucose-mediated oxidative damage and several pathways implicated in diabetic complications. Moreover, it introduced the insightful idea that mitochondria-derived ROS play an important role in the development of certain diabetic complications. However, it did not take into consideration the

effect of diabetes-mediated oxidative stress on mitochondrial function itself (Higgins and Coughlan, 2014; Malik *et al.*, 2015; Coughlan *et al.*, 2016; Czajka and Malik, 2016).

The major source of ROS in most diabetic tissues is complexes I and III of the respiratory chain. Interestingly, ROS generated by complex I remain within the matrix of the mitochondria while complex III-derived ROS are distributed between the matrix and extra-mitochondrial locations. In the matrix, ROS provokes damage, as evidenced by decreased activity of the oxidant-sensitive enzyme, aconitase, increased mitochondrial DNA oxidation and if severe enough, death via apoptosis (Ricci *et al.*, 2008; Lindblom *et al.*, 2015). Although complex III-mediated ROS generation can affect targets outside of the mitochondria, the intra-mitochondrial effects appear most important in the development of diabetic complications. In leptin deficient, obese, type 2 diabetic db/db mice, elevations in mitochondrial ROS production of the heart lead to reduced ATP production, as respiratory function and energy metabolism are impaired, which in turn diminishes myocardial performance (Boudini *et al.*, 2007). Respiration and ATP generation are also defective in diabetic renal mesangial and tubular cells. Because ATP is required for reabsorption in the

proximal tubules while energy deficiency leads to renal failure, hyperglycemia-mediated mitochondrial damage and ATP deficiency appear to play a prominent roles in the development of the diabetic nephropathy (Higgins and Coughlan, 2014; Czajka and Malik, 2016; Hallan and Sharma, 2016).

Mitochondrial DNA damage, which has been detected in humans suffering from diabetes mellitus (Malik *et al.*, 2015), invariably alters the expression of mitochondria encoded proteins, leading to diminished respiratory chain activity. As a result, more ROS is produced, which triggers further mitochondrial DNA damage, ultimately leading to a vicious cycle of damage. Evidence of severe mitochondrial structural changes and dysfunction (morphology, biogenesis, respiratory chain function, fatty acid and citric acid cycle metabolism, oxidative stress, apoptosis and uncoupling activity) support a role of mitochondrial damage in the development of diabetic complications (Sivitz and Yorek, 2010; Aon *et al.*, 2015; Lindblom *et al.*, 2015; Hallan and Sharma, 2016).

Plasma and platelet taurine levels are reduced in subjects with type 1 diabetes (Franconi *et al.*, 1995). Based on 711 overweight, diabetic subjects, plasma taurine levels are related to the decline in insulin sensitivity (Zheng *et al.*, 2016). In fact, most of the major targets of diabetes (kidney, retina and neurons) undergo hyperglycemic-mediated reductions in taurine content (Schaffer *et al.*, 2009). Nonetheless, at an early age, the metabolic pattern of subjects with diabetes is very different from that of the taurine deficient mouse (Ito *et al.*, 2015b; Schaffer *et al.*, 2016). The initial defect in type 1 diabetes is insulinopenia, which reduces glucose metabolism and elevates fatty acid metabolism, while taurine deficient mice exhibit impaired respiratory chain function, increased glycolysis and decreased glucose and fatty acid oxidation (Schaffer *et al.*, 2016). Nonetheless, taurine is required for normal β -cell viability, therefore, the number of pancreatic β -cells is reduced in 12-month-old TauTKO mice (Ito *et al.*, 2015b). Moreover, the properties of the diabetic animal are altered with age, as mitochondrial oxidative injury leads to impaired respiratory chain function in the late phases of the disease. Also affecting mitochondrial function and biogenesis is diet and physical activity (Santos *et al.*, 2014). Therefore, upon aging and dietary modification, the diabetic and taurine phenotypes adopt similar features. In this regard it is interesting that Han *et al.* (2015) claim that taurine deficiency is a necessary requirement for the development of an appropriate model of diabetic nephropathy.

There is overwhelming evidence that taurine therapy reduces pathology associated with diabetes, obesity and the metabolic syndrome (Schaffer *et al.*, 2009; Ito *et al.*, 2012; Imai *et al.*, 2014; Murakami, 2015; Chen *et al.*, 2016). In many animal studies, particularly of type II diabetes, taurine treatment diminishes the degree of hypoglycemia, an effect that in turn attenuates diabetic complications (Nakaya *et al.*, 2000; Winiarska *et al.*, 2009; Das and Sil, 2012; Kim *et al.*, 2012; Chiang *et al.*, 2014; Koh *et al.*, 2014). Several mechanisms may contribute to the regulation of hyperglycemia in diabetic animals treated with taurine. First, taurine improves respiratory function and increases ATP production, effects that should improve pancreatic β -cell function and insulin secretion (Sivitz and Yorek, 2010; Schaffer *et al.*, 2016). Second, hyperglycemia and lipidemia are associated with elevations in mitochondrial ROS generation. In pancreatic β -cells, fatty acid-mediated ROS generation appears to decrease insulin

secretion, an effect attenuated by taurine treatment (Oprescu *et al.*, 2007). Third, mitochondrial dysfunction can provoke insulin resistance (Sivitz and Yorek, 2010). Haber *et al.* (2003) found that taurine treatment prevents hyperglycemia-induced insulin resistance and oxidative stress. Together, these findings indicate that taurine protects against type 2 diabetes-mediated complications, but the mechanism by which taurine diminishes the development of the complications of type 2 diabetes remain unclear, largely because it is virtually impossible to separate the mitochondrial actions of taurine from its effects on insulin secretion and action.

On the other hand, in the streptozotocin-induced model of type 1 diabetes, plasma glucose levels remain unaltered by taurine treatment while the severity of the diabetic complications are diminished. Because diabetic status in the streptozotocin model of type 1 diabetes is unaffected by taurine, one can readily establish the mechanism underlying taurine's effectiveness against the development of diabetic complications. According to several investigators, taurine-mediated reductions in the severity of type 2 diabetic complications are more closely linked to improvements in cellular stresses (ER, oxidative and inflammatory) and mitochondrial dysfunction (Schaffer *et al.*, 2009; Ito *et al.*, 2012; Imai *et al.*, 2014). Trachtman *et al.* (1995) were the first group to recognize the benefit of taurine treatment against the development of diabetic complications. They reported that male rats administered streptozotocin developed a diabetic nephropathy characterized by elevated glomerular filtration rate, glomerular hypertrophy and proteinuria and albuminuria. Administration of taurine (1% in the drinking water) reduced proteinuria by 50% and dramatically suppress glomerular hypertrophy and tubointerstitial fibrosis without affecting blood glucose. Because the amino acid also abolished the elevation in renal cortical malondialdehyde, a marker of oxidative stress, and of advanced glycol-oxidation products, a marker of advanced glycosylation end products, the protective effects of taurine were attributed to suppression of oxidative stress and advanced glycosylation. Recently, the effectiveness of taurine therapy against the development of diabetic nephropathy has been confirmed (Pandya *et al.*, 2013; Koh *et al.*, 2014). In a related study, Ikubo *et al.* (2011) found that streptozotocin-treated diabetic rats developed vascular defects that were associated with oxidative stress without a change in blood glucose. Interestingly, taurine also protects against apoptosis in cellular models of glucose toxicity (Ulrich-Merzenich *et al.*, 2007).

Obesity is a disorder characterized by insulin resistance, hyperlipidemia, hyperglycemia and inflammatory responses related to enlarged adipocytes. Taurine has been effective in decreasing body weight of obese animals and in suppressing inflammatory responses. These effects and their mechanism are not reviewed here but are covered in a complete review by Murakami (2015).

Role of taurine in inflammatory diseases: Arthritis is a term used to describe over 100 diseases, the most common being rheumatoid arthritis and osteoarthritis. The major symptoms of arthritis are joint stiffness and pain with inflammation of the joints, the tissues surrounding the joint and connective tissue. Rheumatoid arthritis is characterized by synovial inflammation and proliferation, bone erosions and thinning of articular cartilage.

The distinctive features of the acute inflammatory phase, which can last up to several days, are vascular dilation, mi-

crovascular leakage and leukocyte recruitment, the latter mediated by adhesion factors that facilitate the interaction of leukocytes with activated endothelium. Acute inflammation, which is triggered by damaged or diseased tissue, as well as irritants and pathogens, is an early phase in the repair of damage and the removal of microorganisms and harmful agents by the innate immune system. During acute inflammation, leukocytes adhere to the endothelium prior to transmigrating across the endothelium into the interstitium. Chemotactic factors and cytokines recruit the neutrophils to the site of inflammation. Activation of the leukocytes, in particular neutrophils and mononuclear phagocytes, leads to the secretion of a host of proinflammatory mediators, including microbicidal peptides, cationic microbial proteins, lytic enzymes, ROS and lysosomal granule constituents. When these proinflammatory mediators are released into phagolysosomes, they destroy engulfed microbes and other pathogens. However, when they are released into the extracellular milieu, they can cause tissue damage. In rheumatoid arthritis, activation of the inflammatory process is part of the autoimmune disorder contributing to joint deformation, erosion of bone and disruption of the cartilage-bone interface.

The content of taurine in the neutrophil is high, representing about 50% of the total free amino acid pool. The two primary functions of taurine in the neutrophil are anti-inflammatory and antioxidant actions. ROS are produced by the neutrophil as a weapon to kill pathogens, with one of those ROS being hypochlorous acid (HOCl). Myeloperoxidase-catalyzes the formation of taurine chloramine (TauCl) from taurine and HOCl. Because TauCl is a less potent oxidant than HOCl, the neutralization of HOCl represents one of the important antioxidant mechanisms of taurine. The myeloperoxidase-catalyzed reaction is also responsible for the anti-inflammatory activity of taurine, as TauCl inhibits the production of proinflammatory cytokines (Marcinkiewicz *et al.*, 1995; Park *et al.*, 1997; Barua *et al.*, 2001), attenuates elevations in nitric oxide and prostaglandin E₂ (Park *et al.*, 2000; Chorazy-Massalska *et al.*, 2004; Kim *et al.*, 2007), decreases the activity of matrix metalloproteinases and initiates leukocyte apoptosis to terminate acute inflammation (Klarmann and Shacter, 2005). For a detailed discussion of the anti-inflammatory and anti-arthritic actions of taurine please refer to the extensive review by Marcinkiewicz and Kontny (2014).

Effect of taurine on muscle

Modulation of muscle contraction: Taurine deficiency leads to impaired contractile function of both cardiac and skeletal muscle (Cuisinier *et al.*, 2000). Hamilton *et al.* (2006) found that exposure to the taurine transport inhibitor, guanidinoethanesulfonate, led to a 60% reduction in extensor digitorum longus taurine content, which was associated with a decrease in peak force contraction. More severe muscular dysfunction is seen in taurine transporter knockout mice, whose muscle taurine content is reduced by over 90%, which leads to a decline in muscle mass and muscular dysfunction (Warskulat *et al.*, 2004; Ito *et al.*, 2008; Ito *et al.*, 2014b). Also associated with severe taurine deficiency are histological changes, including disruption of the myofibrils.

There are abundant reports that taurine administration enhances exercise performance of both humans (Ishikura *et al.*, 2011; Balshaw *et al.*, 2013; Ra *et al.*, 2013, 2016) and animals (Goodman *et al.*, 1985; Dawson *et al.*, 2002; Yatabe *et al.*,

2003; Sugiura *et al.*, 2013; da Silva *et al.*, 2014). Besides improving contractile function of rodents, taurine administration was found to increase the time until exhaustion, reduce exercise-induced fatigue and diminish damage from intense exercise. When taurine is administered prior to heavy exercise, the levels of pro-inflammatory factors are reduced and exercising muscle is protected (Kato *et al.*, 2015). Also noteworthy is a trial of 36 male subjects that were administered either a branched-chain amino acid supplement, a taurine supplement, placebo or the combination of taurine and branched-chain amino acid supplements (Ra *et al.*, 2013). The least muscle damage after eccentric exercise was observed in the combination group, as muscle soreness was diminished two days after exercise and there was less lactate dehydrogenase and aldolase released into the blood. Interestingly, serum levels of 8-hydroxydeoxyguanosine, a measure of DNA oxidative damage, were also reduced in the combination group, implicating the antioxidant activity of taurine in the beneficial effects of the combination supplement. The authors suggested that taurine potentiates the beneficial effect of the branched-chain amino acid supplement. The likely candidates for the protective activity of taurine are suppression of oxidative stress and inflammation. In another study by the same laboratory, the end point of the study was arterial stiffness after eccentric exercise (Ra *et al.*, 2016). Serum malondialdehyde remained elevated for 4 days after exercise in the control placebo group while oxidative stress was decreased in the taurine treated group. There was a parallel between the increase in malondialdehyde and arterial stiffness, which led the authors to suggest that taurine-mediated reductions in oxidative stress helped attenuate the degree of arterial stiffness. For a more complete review of the role of taurine in muscle function and disorders, please refer to DeLuca *et al.* (2015).

Sarcopenia: Sarcopenia, which is the gradual loss of skeletal muscle tissue related to an imbalance between protein biosynthesis and degradation. Because sarcopenia occurs with aging and leads to physical impairment among the elderly it is a serious health problem. Interestingly, taurine deficiency is associated with a reduction in cell size (Schaffer *et al.*, 1998; Ito *et al.*, 2008). In a recent review, Scicchitano and Sica (2016) raised the possibility that taurine might counteract the adverse effects of sarcopenia. This is an interesting condition that could extend the utilization of taurine to another application.

Duchenne muscular dystrophy: Encouraging results have been reported using taurine therapy for the treatment of mdx mice, a model for Duchenne muscular dystrophy, which is a fatal muscle wasting disease characterized by oxidative stress and inflammation (Terrill *et al.*, 2016b). In humans suffering from the disease, there are no symptoms at birth, however, symptoms in the form of waddling gait and difficulty climbing steps, begin to appear at a young age. The primary cause of the disease in humans are mutations in dystrophin, a cytoskeletal protein that connects the cytoskeleton and the extracellular matrix, while in the mdx mouse model of Duchenne muscular dystrophy the mutations are replaced by inadequate expression of dystrophin.

In the disease, structural changes within the sarcolemma increase the permeability of the cell membrane and facilitate the accumulation of Ca²⁺, contributing to the development of Ca²⁺ overload in which the rate of [Ca²⁺]_i rise after depolarization is enhanced, peak [Ca²⁺]_i is increased and the relaxation

phase is prolonged (Blake *et al.*, 2002). Because the protease inhibitor, leupeptin, abolishes the exaggerated increase in $[Ca^{2+}]_i$, it has been proposed that proteases contribute to the severity of the disorder. Another factor that contributes to the development of the disorder is a lack of nNOS, which normally produces nitric oxide to ensure adequate vasodilation. Because nitric oxide levels fall in an oxidatively stressed environment, it has been proposed that oxidative stress and acute inflammation may also contribute to pathology of the disease.

Taurine has a potential to disrupt several of the steps in the development of Duchenne's muscular dystrophy, in part by restoring taurine levels that decline in the muscle disorder (Terrill *et al.*, 2015, 2016b). In fact, addition of 4% taurine to mouse chow of mdx mice after 14 days of age increases muscle taurine content, an effect correlated with reductions in inflammation (neutrophil infiltration) and mitigation of severe bouts of myocyte necrosis after exercise (Terrill *et al.*, 2016a). According to DeLuca *et al.* (2003) taurine treatment also significantly enhances forelimb strength of exercising mdx mice. This effect of taurine is largely attributed to an improvement in Ca^{2+} homeostasis, although taurine supplementation has no effect on the expression of key E-C coupling proteins (Horvath *et al.*, 2016). Creatine treatment is nearly as effective as taurine in enhancing muscle strength, indicating that delivery of more energy to the muscle prevents the decline in muscle function. In this regard, the effect of taurine on improvement in high-energy phosphate metabolism and respiratory chain function may also contribute to its beneficial actions (Schaffer *et al.*, 2016).

Myotonic dystrophy: Myotonia is a condition characterized by delayed relaxation following skeletal muscle contraction. Conte-Camerino *et al.* (1989) found that acute administration of taurine was effective in attenuating myotonic discharges by 20,25 diazacholesterol-treated rats but not by rats treated with anthracene-9-carboxylic acid. The positive effect of taurine against the 20,25 diazacholesterol model of myotonia was attributed to an improvement in flux through voltage-gated chloride channels of extensor digitorum longus myofibers. It has been suggested that the actions of anthracene-9-carboxylate preclude an effect of taurine. Taurine requires functional chloride channels, but anthracene-9-carboxylate inhibits those channels.

Several clinical trials examining the effect of chronic taurine therapy on the severity of myotonia have been evaluated. In a double-blind, single crossover study of 9 patients with dystrophia myotonica, chronic taurine therapy diminished the severity of myotonia while decreasing potassium-induced hyperexcitability (Durelli *et al.*, 1983). The possibility that taurine might also be effective against sodium channel myotonia and paramyotonia congenita has also been proposed, as taurine modulates sodium transients of the Nav1.4 channel (DeLuca *et al.*, 2015).

Taurine also increases the sensitivity of myofibrils to Ca^{2+} (Dutka *et al.*, 1985), an effect also seen in the TauTKO heart, where it has been attributed to enhanced phosphorylation of troponin (Ramila *et al.*, 2015). It is also possible that taurine affects muscular activity of the sarcoplasmic reticular Ca^{2+} pump, an effect in the heart caused by alterations in the phosphorylation state of the regulator protein, phospholamban (Ramila *et al.*, 2015).

CONCLUSION

Taurine, 2-aminoethanesulfonic acid, is an endogenous end metabolite that is distributed in various tissues at high concentration. It is a sulfur-containing amino acid synthesized from cysteine and is excreted without any further metabolism. Since the first discovery of taurine in 1827, many of its functions have been elucidated in experiments focusing on skeletal muscle, the retina and the central nervous and cardiovascular systems. The cytoprotective actions of taurine contribute to the improvement in the clinical and nutritional health of humans through various mechanisms, including antioxidation, energy production, neuromodulation, Ca^{2+} homeostasis and osmoregulation. The combination of one or more of these cytoprotective effects of taurine act to diminish the pathology and symptoms of a host of diseases ranging from those of the CNS, cardiovascular system, skeletal muscle and defective metabolism. Many CNS-related diseases, including stroke, neurodegeneration, FXS, SSDD and epilepsy, respond favorably to taurine therapy. Taurine treatment also diminishes the severity of inflammatory diseases and abnormalities of the circulatory system, such as heart failure, hypertension, atherosclerosis, ischemia-reperfusion injury, myocardial arrhythmias, diabetes mellitus and arthritis. The phenotype of taurine depletion resembles that of the mitochondrial disease, MELAS, as both conditions affect the activity of the respiratory chain. Also characteristic of the taurine transporter KO mouse is impaired skeletal muscle contraction and sarcopenia. Therefore, taurine therapy is likely to improve cardiac and skeletal muscular dysfunction in conditions, such as MELAS, diminished muscle contraction, sarcopenia, Duchenne muscular dystrophy and myotonic dystrophy. Because taurine is a naturally occurring substance that exhibits few adverse side effects and plays a fundamental role in the function of most mammalian cells, the future of taurine as an effective therapeutic agent and a nutritional supplement is seemingly bright. Although clinical evaluation of taurine has been limited to a few diseases, it has already been approved for use in congestive heart failure. Therefore, taurine is an essential nutraceutical with diverse cytoprotective and therapeutic actions.

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