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EDITORIAL

Clinical significance of taurine

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Introduction

The biosynthesis of the β-amino acid, taurine, from cysteine is a two-step process, involving the oxidation of the sulfhydryl group and the decarboxylation of the amino acid (Stipanuk 2004). Although taurine was considered merely an end-product of cysteine degradation for many years, the detection of damaged retina in taurine deficient cats, convinced scientists that taurine was likely a physiologically important compound. This idea was reinforced over the next decade, as taurine was identified as an essential nutrient in several species, including the cat (Hayes and Carey 1975; Knopf et al. 1978; Sturman 1986), certain dogs (Gavaghan and Kittleson 1997; Backus et al. 2003; Belanger et al. 2005), the fox (Moise et al. 1991), some monkeys (Hayes et al. 1980; Stephan et al. 1981; Imaki et al. 1987) and more recently the anteater (Nofs et al. 2013). Among the defects associated with taurine deficiency have been retinal and tapetum degeneration (Hayes and Carey 1975; Sturman 1986), cardiac dysfunction (Pion et al. 1987, 1992; Novotny et al. 1991), immune deficiency (Schuller-Levis et al. 1990), muscle atrophy (Ito et al. 2008), premature aging (Ito et al. 2013a) and impaired reproduction (Hayes et al. 1980; Sturman 1986).

The identification of taurine as an essential nutrient in some species and a semi-essential nutrient in man prompted the search for new physiological functions of the amino acid. Several of those newly discovered functions have been tied to taurine conjugation. One reaction involves the detoxification of hypochlorous acid by taurine resulting in the formation of taurine chloramine, a product that has the added benefit of possessing anti-inflammatory activity (Schuller-Levis and Park 2003; Marcinkiewicz and Kontny 2013; Kim and Cha 2014). Taurine also forms a conjugate (5-taurinomethyluridine) with the wobble position uridine of $tRNA^{Leu(UUR)}$, a reaction that enhances the interaction between the modified uridine and guanine (Kirino et al. 2005; Kurata et al. 2008; Schaffer et al. 2013). Biochemically, this enhances the binding of the UUG codon to the taurine-modified AAU anticodon of $tRNA^{Leu(UUR)}$, facilitating UUG decoding. When the formation of 5-taurinomethyluridine-$tRNA^{Leu(UUR)}$ is abolished, the biosynthesis of certain mitochondria encoded proteins dramatically declines, respiratory function falls, ATP generation decreases and the generation of oxidants by the respiratory chain increases (Jong et al. 2012; Schaffer et al. 2013). Another important function of taurine is the detoxification of xenobiotics and the neutralization of toxic aldehydes (Miyazaki and Matsuzaki 2013). Because taurine is found at a very high concentration within most cells (mM range) it is not surprising that it also serves as a key organic osmolyte (Lang et al. 1998; Huang et al. 2006). In the central nervous system, taurine specifically functions as a neuromodulator, interacting and altering the actions of the $GABA_A$ receptor and the glycine receptor (Menzie et al. 2013).

The recognition that taurine is an essential nutrient in cats and certain monkeys initially raised questions about the nutritional status of taurine in humans, who generally consume large amounts of taurine in their diet but possess a limited capacity to synthesize taurine. However, unlike taurine-dependent species, such as the cat, humans lose

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relatively small amounts of taurine in the feces as taurine conjugated bile acids. Indeed, as taurine levels decline in humans, the liver has the capability of substituting glycine for taurine in bile acid conjugation. Thus, in the absence of an undiscovered polymorphism involving taurine mishandling, taurine is considered a conditionally essential nutrient in humans (Gaull 1986).

Nonetheless, taurine plays an important role in human pathology. Based on extensive animal and human studies (Azuma et al. 1983, 1985; Ito et al. 2013b), taurine was approved as a therapeutic agent in the treatment of heart failure in Japan. Among taurine's actions that appear beneficial to patients suffering from congestive heart failure is attenuation of oxidative stress and calcium overload. Yet, in accordance with the recent focus on angiotensin II and β-adrenergic receptor antagonists in the treatment of congestive heart failure, it is likely that the most important action of taurine is attenuation of neurohumoral-mediated development of cellular hypertrophy and progression of overt heart failure (Ito et al. 2013b).

The antioxidant, anti-inflammatory and metabolic actions of taurine appear central to its attenuation of diabetic symptoms (Murakami et al. 2013). However, several investigators have also shown that taurine treatment diminishes the degree of hyperglycemia in both types 1 and 2 diabetic animals by improving insulin secretion and sensitivity (Lampson et al. 1983; Cherif et al. 1996; Wu et al. 2010). There is also evidence that taurine might reduce the severity of diabetic complications, although other investigators question those findings (Hansen 2001; Ito et al. 2012; Murakami et al. 2013). Hence, additional studies examining the therapeutic benefit (if any) of taurine in the treatment of diabetes and the metabolic syndrome are warranted.

Based on the wide multi-center, cross-sectional World Health Organization investigation known as the CARDIAC study, an inverse relationship exists between cardiovascular mortality and dietary taurine intake, as monitored by urinary taurine levels (Yamori et al. 2001, 2009). The rationale for the study is that taurine exerts opposite actions on events that influence atherosclerosis, such as hypercholesterolemia, inflammation and oxidative stress (Murakami et al. 2010a, b, 2013). Taurine also regulates platelet function, with the propensity to undergo aggregation significantly elevated by taurine deficiency (Hayes et al. 1989). Together, these findings support the view that taurine reduces the risk of stroke and myocardial infarction, an idea that warrants further study.

Taurine also protects the ischemic-reperfused heart against injury (Schaffer et al. 2013). Contributing to this action is attenuation of both excessive oxidant production and calcium overload, activation of cytoprotective pathways and improvement in mitochondrial function. Only a few studies have examined the effect of taurine as a therapeutic agent. Milei et al. (1992) found that rapid infusion of 5 g of taurine before bypass surgery provided protection against reperfusion injury. Moreover, taurine treatment was found to diminish damage to arrested hearts during cold isotonic storage prior to transplant (Sahin et al. 2011; Oriyanhan et al. 2005). The field awaits further evaluation of taurine's effect.

Epidemiological studies have shown that increased taurine intake is associated with diminished risk of hypertension (Yamori et al. 2010). This observation is consistent with animal studies showing taurine-mediated reductions in blood pressure of spontaneously hypertensive rats (Nara et al. 1978), attenuation of norepinephrine-mediated vasoconstriction by taurine (Nishida and Satoh 2009) and elevation in blood pressure in taurine deficiency (Mozaffari et al. 2006). Underlying these actions of taurine are attenuation of sympathetic and renin-angiotensin system overactivity, acceleration in renal fluid and sodium excretion and in some instances the elevation in serum nitric oxide content (Roysommuti and Wyss 2013). Perinatal taurine supplementation also diminishes hypertension in adult spontaneously hypertensive rats although it does not lower blood pressure in normal adult Sprague–Dawley rats. Furthermore, perinatal taurine imbalance has long-term developmental consequences, including alterations in renal function, autonomic nervous system regulation and renin-angiotensin activity (Roysommuti et al. 2009).

Taurine exerts multiple effects on the kidney, including modulation in renal blood flow, glomerular filtration, osmoregulation, ion reabsorption/secretion and composition of the urine (Chesney et al. 2011; Han and Chesney 2012). Taurine exposure generally is renoprotective, decreasing both cellular damage and proteinuria following exposure to a host of nephrotoxic agents (Han and Chesney 2012). These animal studies provide the rationale for suggesting that taurine might benefit patients suffering from acute kidney injury, cisplatin toxicity, renal stones, diabetes, hypertension, ischemic injury and renal transplantation (Han and Chesney 2012). However, the use of taurine as a therapeutic agent against renal dysfunction remains in its infancy.

Upon reduction in dietary taurine, most species rely heavily on hepatic biosynthesis for their source of the β-amino acid. Although the liver is a major provider of taurine for nonhepatic organs, hepatic taurine serves one major function, protecting the hepatocyte from a host of toxins that undergo cytochrome P450 2E1-mediated oxidation (Miyazaki and Matsuzaki 2013). Accordingly, taurine depletion is associated with severe hepatic damage resulting from apoptosis, fibrosis, neoplastic lesions and mitochondrial dysfunction (Warksulat et al. 2006). The cytoprotective actions of taurine appear to be primarily

related to its antioxidant and osmoregulatory properties, although taurine also modulates adipokine expression. One potential therapeutic use of taurine is the treatment non-alcoholic steatohepatitis (Miyazaki and Matsuzaki 2013).

The major physiological functions of taurine in the central nervous system include neuromodulation, osmoregulation, alteration of cation homeostasis, attenuation of oxidant production, suppression of inflammation and protection of the neuron (Menzie et al. 2013). In vitro studies have demonstrated that taurine treatment diminishes excitotoxicity mediated by amyloid peptides, which are hallmarks of Alzheimer's disease. Although there are no clinical studies examining the effect of taurine therapy on Alzheimer patients, there is abundant evidence that taurine suppresses several events initiated by amyloid peptide-mediated excitotoxicity, including Ca^{2+} overload, oxidative stress, mitochondrial dysfunction and apoptosis (Wu et al. 2009).

Parkinson's disease is associated with the loss of dopaminergic neurons that project from substantia nigra to the striatum. Taurine serves as a neuromodulator in the nigrostriatal system, regulating both dopamine release and neuronal activity. It has been proposed that taurine might benefit patients suffering from Parkinson's disease by inhibiting GABAergic substantia nigra cells and attenuating oxidative stress and apoptosis (Menzie et al. 2013).

A characteristic feature of Huntington's disease is a mutation in the huntintin gene, causing the formation of polyglutamine repeats that prevent the degradation of huntingtin protein by the ubiquitin–proteasome system. Although there are no ongoing clinical trials examining the effect of taurine treatment on Hungtinton's disease, it is relevant that taurine increases striatal GABA levels and diminishes mitochondrial oxidative stress, effects thought important in reducing locomotor hypoactivity in an animal model of Huntington's disease. However, taurine inhibits endoplasmic reticular stress, which contributes to the toxicity of the polyglutamate repeats (Menzie et al. 2013).

Aging is associated with cognitive deficits that can result in severe dementia and impaired learning. At the biochemical level, aging is associated with Ca^{2+} mishandling and diminished GABAergic system activity, events that are influenced by taurine (El Idrissi et al. 2013). El Idrissi et al. (2013) found that the expression of the $GABA_A$ receptor in the hippocampus is downregulated by taurine supplementation while the expression of cortical somatostatin-positive neurons is upregulated. Because these actions of taurine feeding are opposite the changes induced by aging, it is not surprising that taurine treatment improves cognitive function of the aging animal.

The myeloperoxidase-catalyzed reaction between taurine and hypochlorous acid leading to taurine chloramine formation plays a key role in the pathogenesis of inflammation (Marcinkiewicz and Kontny 2013; Kim and Cha 2014). Not only is taurine chloramine a less potent cytotoxin than hypochlorous acid, but taurine chloramines suppresses the activity of phagocytic cells and inhibits LPS-mediated secretion of pro-inflammatory cytokines by joint-associated adipose tissue (Kontny et al. 2000; Marcinkiewicz et al. 2006; Marcinkiewicz and Kontny 2013; Kim and Cha 2014). The anti-inflammatory activity of taurine chloramine has also been observed in animal models of collagen-induced arthritis (Marcinkiewicz and Kontny 2013; Kim and Cha 2014). Thus, the studies by Marcinkiewicz and Kontny (2013) support the view that taurine chloramine might at least partially alleviate some symptoms of rheumatoid arthritis.

The covalent reaction of taurine with the wobble position uridine of $tRNA^{Leu(UUR)}$ plays a fundamental role in maintaining normal respiratory chain function, ensuring adequate ATP generation and preventing excessive mitochondrial superoxide production (Schaffer et al. 2013). These fundamental biochemical events are defective in the mitochondrial disease, mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS), which is caused by one of several $tRNA^{Leu(UUR)}$ mutations. One of the major biochemical abnormalities of the $tRNA^{Leu(UUR)}$ mutations is decreased formation of 5-taurinomethyluridine in the wobble position of $tRNA^{Leu(UUR)}$ (Kirino et al. 2005; Kurata et al. 2008). Because taurine conjugation enhances the interaction of the UUG codon with the taurine-modified AAU anticodon of $tRNA^{Leu(UUR)}$, the synthesis of mitochondria encoded proteins, such as ND6, is highly dependent upon the 5-taurinomethyluridine modification (Jong et al. 2012). Hence, taurine deficiency and MELAS are both associated with complex I deficiency (Santa 2010; Jong et al. 2012). Because taurine deficiency and MELAS lead to a defect in taurine conjugation, it is possible that taurine therapy might partially restore 5-taurinomethyluridine-$tRNA^{Leu(UUR)}$ levels, thereby benefiting patients suffering from MELAS.

Conflict of interest The authors declare that they have no conflict of interest.

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