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INVITED REVIEW

The effect of taurine on chronic heart failure: actions of taurine against catecholamine and angiotensin II

Takashi Ito · Stephen Schaffer · Junichi Azuma

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Abstract Taurine, a ubiquitous endogenous sulfur-containing amino acid, possesses numerous pharmacological and physiological actions, including antioxidant activity, modulation of calcium homeostasis and antiapoptotic effects. There is mounting evidence supporting the utility of taurine as a pharmacological agent against heart disease, including chronic heart failure (CHF). In the past decade, angiotensin II blockade and β-adrenergic inhibition have served as the mainstay in the treatment of CHF. Both groups of pharmaceutical agents decrease mortality and improve the quality of life, a testament to the critical role of the sympathetic nervous system and the renin–angiotensin system in the development of CHF. Taurine has also attracted attention because it has beneficial actions in CHF, in part by its demonstrated inhibition of the harmful actions of the neurohumoral factors. In this review, we summarize the beneficial actions of taurine in CHF, focusing on its antagonism of the catecholamines and angiotensin II.

Keywords Chronic heart failure · Angiotensin II · Catecholamine · Taurine

Introduction

Taurine (2-aminoethanesulfonic acid) is a ubiquitous free amino acid found in millimolar concentrations in most mammalian tissues. The cardiac taurine concentration is about 20 mM, which is about 100 times higher than its plasma concentration. The major sources of taurine in the body are hepatic biosynthesis from cysteine, and dietary intake, with seafood being especially rich in the amino acid (Pasantes-Morales et al. 1980; Rana and Sanders 1986; Stipanuk et al. 2009). Tissue taurine content is increased in the failing heart of patients who have died of heart failure, but is reduced during an ischemia–reperfusion insult (Crass and Lombardini 1977; Huxtable and Bressler 1974). Importantly, it has been revealed that in certain animal species, taurine depletion leads to the development of a dilated cardiomyopathy that can progress to heart failure (reviewed in Ito and Azuma 2012). In cats and fox whose capacities to synthesize taurine from cysteine are very low, maintenance on a taurine deficient diet results in severe hypotaurinemia and leads to development of a cardiomyopathy (Moise et al. 1991; Novotny et al. 1994; Pion et al. 1987). Tissue taurine deficiency induced by genetically disruption of the taurine transporter also results in the development of a cardiomyopathy in mice (Ito et al. 2008). Moreover, administration of the taurine transport inhibitor, β-alanine, leads to atrophic cardiac remodeling (Pansani et al. 2012). These observations reveal the biological importance of taurine in maintaining normal cardiac function.

Taurine therapy has proven beneficial in a number of animal models of CHF (Azuma et al. 1982, 1983, 1985). The beneficial effects of taurine treatment in heart failure have been reported in various animal models, such as cardiomyopathic hamsters (McBroom and Welty 1977), calcium paradox in rats and chicken (Kramer et al. 1981; Yamauchi-Takihara et al. 1988), rabbits with aortic regurgitation (Takihara et al. 1986), diabetic cardiomyopathy (Li et al. 2005), iron overload-induced model (Oudit

T. Ito · J. Azuma (✉)
Department of Clinical Pharmacogenomics, School of Pharmacy, Hyogo University of Health Sciences, Kobe, Hyogo, Japan
e-mail: azuma@huhs.ac.jp

S. Schaffer
Department of Pharmacology, College of Medicine, University of South Alabama, Mobile, AL, USA

et al. 2004) and tobacco smoke-induced cardiac remodeling (Denipote et al. 2011).

The pioneering work of Azuma and coworkers (Azuma et al. 1989, 1992, and reviewed in Ito and Azuma 2012) led to the approval of taurine as acceptable therapy in the treatment of heart failure in Japan. They found that daily taurine administration to patients suffering from CHF improved cardiac output and key symptoms of CHF (Table 1). Their findings were confirmed in a study using energy drink as the source of taurine (Jeejeebhoy et al. 2002). Moreover, taurine administration has been shown to improve exercise capacity of patients with CHF (Beyranvand et al. 2011). Importantly, several clinical studies have shown that administration of 3–6 g taurine/day has no adverse effect, indicating its use is clinically safe. Indeed, a toxic dosage of taurine has still not been identified (Shao and Hathcock 2008).

CHF is considered the final presentation of a number of cardiac-damaging diseases, such as coronary artery disease, alcohol toxicity, adriamycin toxicity, rheumatic fever, hypertension and myocarditis. In each of these conditions, the decrease in cardiac output activates a baroreceptor reflex, causing an elevation in plasma catecholamines. The increase in sympathetic activity leads to the constriction of the afferent arterioles of the kidney, reducing renal blood flow. As a result of reduced renal blood flow and the elevation in sympathetic activity, renin is released from the juxtaglomerular cells of the kidney. Angiotensin II (Ang II) and aldosterone levels rise, which together with elevations in sympathetic activity, results in many of the characteristic symptoms of CHF, such as tissue edema, fatigue, dyspnea, confusion and anorexia. Ang II and norepinephrine (NE) also mediate changes in the structure of the heart. Both neurohumoral agents stimulate protein synthesis leading to cardiac hypertrophy, which initially improves cardiac function. However, they also promote cardiomyocyte apoptosis and ventricular remodeling, events involved in the deterioration of the heart by triggering the transition from cardiac hypertrophic state to overt heart failure, as well as the progression of CHF (Braunwald 2008).

It is generally accepted that reactive oxygen species (ROS) which are generated by neurohumoral agents (Ang II and NE), as well as inflammation and ischemia, play important roles in deterioration of the failing heart (Nakamura et al. 1998; Nakamura et al. 2002). Ang II directly stimulates ROS production in the cytosol and the mitochondria, the latter responsible for the permeabilization of the mitochondrial membrane and the initiation of apoptosis (Ricci et al. 2008). In the cytosol, ROS derived from NADPH oxidase initiates signaling pathways that lead to cardiac hypertrophy (Sirker et al. 2007). There is also evidence that the activity of the sarcoplasmic reticular Ca^{2+} ATPase is also under the regulation of oxidative stress, an effect that leads to disturbances in both diastolic and systolic functions (Sharov et al. 2006). Excessive accumulation of calcium overload can also contribute to ROS-mediated cell death (Giordano 2005). It is also well known that the neurohumoral agents are associated with the induction of an abnormal pattern of cardiac gene expression, referred to as the "fetal gene program", which is one of the features of the failing heart (Colucci 1998; Rosenkranz 2004). In particular, the fetal contractile protein isoforms, β-myosin heavy chain (MHC) and α-skeletal actin, are upregulated, which in turn impairs contractile function and prognosis (Braunwald and Bristow 2000). Several large-scale clinical trials have shown that AngII blockade using ACE inhibitors (ACEI), AngII type 1 receptor blocker (ARB) and β-adrenoceptor blocker (β-blocker) diminishes long-term morbidity and mortality in patients with CHF (reviewed in Landmesser et al. 2009). These trials prove that excess secretion of catecholamines and AngII mediates progressive left ventricular dysfunction and structural remodeling in the failing heart.

There are several lines of evidences suggesting that taurine attenuates neurohumoral activity in CHF. While the impact of AngII on CHF is associated with, not only direct

Table 1 Clinical studies to attempt the effect of taurine treatment against CHF

Study	Method (*n*)	Intervention	Duration	Outcome
Azuma et al. (1983)	Open pilot ($n = 24$)	Taurine (3 g/day)	4 weeks	Improved the severity of CHF (clinical signs and symptoms)
Azuma et al. (1985)	Double-blind, cross over ($n = 14$)	Taurine (3 g/day) or placebo	4 weeks	Improved the severity of CHF
Azuma et al. (1989)	Double-blind, comparative ($n = 158$)	Taurine (3, 6 g/day) or CoQ10 (30 mg/day)	4.8 weeks	Improved the severity of CHF, ↑ systolic volume, cardiac output, ejection fraction (Greater than CoQ10)
Jeejeebhoy et al. (2002)	Double-blind, placebo-controlled ($n = 38$)	MyoVive (taurine (3 g/day), CoQ10, carnitine, etc.)	30–45 days	↓ Left ventricular end-diastolic volume
Beyranvand et al. (2011)	Single-blind, placebo-controlled ($n = 29$)	Taurine (1.5 g/day) or placebo	2 weeks	↑ Exercise time, distance, metabolic equivalents

cardiac actions, but also indirect actions in various tissues, the beneficial effect of taurine involves kidney, brain and immune function, as well as cardiac function. In this review, we describe the effects of taurine on the adverse responses of the heart to catecholamine and the renin/angiotensin II/aldosterone system in CHF.

Molecular mechanism involved in the beneficial actions of taurine against heart failure

Regulation of calcium handling

The mechanisms underlying the beneficial effect of taurine in CHF are likely complex. Taurine possesses several pharmacological actions in the heart, including positive inotropy or negative inotropy depending on medium calcium concentration, antiarrythmic and prosurvival. These actions may, in part, result from the interaction between taurine and ion channels (reviewed in Satoh and Sperelakis 1998; Schaffer et al. 2010). Especially, taurine normalizes calcium handling. We have previously demonstrated that taurine prevents the negative inotropic effect of low-calcium medium (Chovan et al. 1980; Sawamura et al. 1983). We further reported that taurine stimulates the inward calcium current at low [Ca]o, and inhibits it at high [Ca]o in isolated cardiomyocyte, whereas the amino acid does not influence calcium current at normal [Ca]o (Sawamura et al. 1990). It also normalizes action potential duration at both high [Ca]o and low [Ca]o (Satoh and Sperelakis 1998). Furthermore, taurine protects the heart from calcium overload-mediated damage induced by multiple types of stress, including doxorubicin, isoproterenol and the calcium paradox (Azuma et al. 1987; Kramer et al. 1981; Ohta et al. 1988; Yamauchi-Takihara et al. 1988). These observations indicate that taurine acts as a modulator of calcium homeostasis. Recent evidence suggests that calcium-dependent cell signal proteins, such as calcineurin and calmodulin-dependent kinase (CaMK), play critical roles in development of hypertrophy and in the transition from hypertrophy to heart failure (Ling et al. 2009; Ritter and Neyses 2003). Therefore, the calcium handling property of taurine may contribute to the observed attenuation of heart failure.

Reduction in oxidative stress

It is well documented that taurine treatment attenuates oxidative stress in experimental animal models of heart disease (reviewed in Schaffer et al. 2009). Several studies have demonstrated that taurine prevents malondialdehyde formation, a measure of lipid peroxidation (Hamaguchi et al. 1988; Ohta et al. 1988; Oudit et al. 2004; Raschke et al. 1995). Although low levels of ROS stimulate cell growth, including adaptive hypertrophy, high levels of ROS are pathological and lead to ventricular remodeling, fibrosis, contractile dysfunction and cell death (Takimoto and Kass 2007).

According to various reports, the antioxidant activity of taurine can be attributed to several mechanisms. First, taurine is a scavenger of hypochlorous acid, which is mainly secreted by neutrophils and is a highly toxic oxidant (Marcinkiewicz and Kontny 2012). It is well established that oxidation of LDL-cholesterol by hypochlorous acid contributes to the development of atherosclerosis (Carr et al. 2000). As described below, it has been recently reported that the stimulation in hypochlorous acid production by Ang II is linked to the development of atrial fibrosis and atrial fibrillation (Rudolph et al. 2010). Second, taurine prevents autooxidation of adrenaline to adrenochrome, an oxidant that appears to contribute to the progression of heart failure (Dhalla et al. 2010; Hanna et al. 2004). Third, taurine suppresses the severity of cellular oxidative stress. Taurine is found at very high concentration in the mitochondria, where it is involved in a posttranslational modification of two mitochondrial transfer RNAs (mt-tRNA), one specific for leucine and the other for lysine (Schaffer et al. 2013; Suzuki et al. 2002) Because taurine is found at such high concentrations in the mitochondria, it may buffer intramitochondrial pH (Hansen et al. 2010). Since taurine-conjugated mt-tRNA regulates the biosynthesis of respiratory chain subunits, it directly alters flux of electrons through the electron transport chain. Recently, it has been reported that taurine depletion by β-alanine treatment results in a decrease in complex I activity (Jong et al. 2012), an increase in oxidative stress and induction of apoptosis in cultured cardiomyocytes, indicating the importance of taurine in suppression of ROS production. Moreover, taurine inhibits NE-induced NADPH oxidase activation, resulting in a decrease in ROS production (Li et al. 2009). These antioxidant actions of taurine may contribute to the beneficial effect of the amino acid on patients suffering from CHF, particularly because oxidative stress leads to impaired contractile function, calcium mishandling, cell death and ventricular remodeling.

In addition to its direct cardiac actions, taurine exerts a variety of biological actions in a multitude of tissues, including the kidney, blood vessels, central nerves, the immune system, etc. These diverse actions may also mediate cardioprotection.

The effects of taurine against catecholamines

Catecholamine toxicity in heart

Activation of the sympathetic nervous system is one of the critical events in CHF (Braunwald 2008). Although

increased cardiac sympathetic activity initially supports contractile function, it ultimately contributes to ventricular remodeling and vascular resistance, which drive the heart into overt failure. Indeed, elevations in plasma NE concentration are correlated with increased mortality in patients with CHF. Several clinical trials have revealed that inhibition of sympathetic overactivity by treatment with β-blockers benefits patients with CHF. There are several lines of evidence supporting the view that taurine can inhibit the toxic effects of catecholamines on the cardiac myocyte. We have examined the histological and biochemical changes induced by a toxic dose of isoprenaline in chick heart and found increases in heart weight and necrotic changes in chick hearts (Ohta et al. 1986, 1988). Taurine administration was found to prevent cellular necrosis and calcium accumulation induced by isoprenaline. Moreover, isoprenaline-mediated increases in lipid peroxidation and decreases in phospholipid content were attenuated by taurine administration, indicating that the beneficial effect of taurine may relate to diminished damage related to oxidative stress and calcium overload, a concept supported by confirmative data by other investigators (Shi et al. 2002; Shiny et al. 2005). Catecholamines are known to induce cardiomyocyte apoptosis. It has been reported that taurine inhibits NE-induced apoptosis in cultured cardiomyocytes (Li et al. 2009). Taurine also prevents noradrenaline-induced nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase activation and ROS production. Li et al. (2009) also found that both taurine and an NADPH oxidase inhibitor block NE-induced activation of calpain, a calcium-dependent protease that contributes to cardiomyocyte injury and stress-induced apoptosis.

Indirect actions elicited by the auto-oxidation product, adrenochrome, may also contribute to the cardiotoxicity of the catecholamines (Dhalla et al. 2010). Adrenochrome is a highly reactive quinine compound that may cause intracellular Ca^{2+}-overload, coronary spasms, myocardial cell damage, depletion of high energy stores, and ventricular arrhythmias. Taurine prevents adrenochrome-induced apoptosis in cardiomyocytes (Li et al. 2009). Additionally, it has been demonstrated that taurine inhibits auto-oxidation of epinephrine leading to the formation of adrenochrome, likely related to the antioxidative action of taurine (Hanna et al. 2004; Oliveira et al. 2010).

Vasculature reaction to catecholamines

Patients with CHF exhibit high peripheral vascular resistance (Zelis et al. 1968). Overactivation of the sympathetic nervous system may mediate arteriolar constriction, which in turn contributes to the elevation of vascular resistance. High vascular resistance in turn causes an increase in ventricular afterload, which diminishes cardiac output. It also increases preload pressure, resulting in a rise in cardiac oxygen demand, elevating the risk of angina.

Taurine is a vasorelaxant, as reflected by its anti-hypertensive activity (reviewed in Abebe and Mozaffari 2011; Militante and Lombardini 2002). Taurine also reduces vascular tone that is elevated by NE. Several reports have demonstrated that taurine inhibits NE-induced contraction in isolated artery, including rabbit ear arteries, rat aortas, porcine coronary arteries, rat renal and mesenteric arteries (Franconi et al. 1982; Liu et al. 2009; Nishida and Satoh 2009; Niu et al. 2008; Ristori and Verdetti 1991). Thus, taurine may reduce the rise in vascular resistance induced by overactivation of the sympathetic nervous system in CHF. In contrast to NE, taurine treatment fails to influence Ang II-mediated vasculature constriction (Li et al. 1996).

Release of catecholamine from sympathetic nervous system

Patients with CHF also exhibit increased sympathetic tone, which is associated with the functional severity of CHF (Francis et al. 1984). This sympathetic overactivity causes not only myocardial toxicity but also peripheral vasoconstriction and sodium retention. Consequently, attenuation of sympathoexcitation by specific treatment is recognized useful therapy for patients with CHF. Taurine acts as an inhibitory neurotransmitter by enhancing Cl^- influx via Cl^- channel coupled receptors, including gamma-aminobutyric acid (GABA)-a receptor and glycine receptor. Therefore, it is reasonable to conclude that taurine controls neuronal excitation in CHF.

It has been demonstrated that taurine treatment suppresses high fat diet-enhanced urinary NE excretion in healthy male volunteers, supporting the view that taurine suppresses the sympathetic nervous system in humans (Mizushima et al. 1996). It has also been shown that taurine administration decreases plasma adrenaline and blood pressure in patients with borderline hypertension (Fujita et al. 1987), indicating that taurine inhibits stress-dependent adrenaline secretion from adrenal chromaffin granules. These data suggest that taurine suppresses pathological stress-induced sympathoadrenal tone.

Some of the animal studies show that taurine treatment concomitantly improves catecholamine-mediated changes and hypotension. Yamamoto et al. (1985) have reported that taurine supplementation suppresses short-term shaker stress-induced blood pressure while increasing plasma catecholamines in spontaneously hypertensive rats (SHR). In a related study, Sato et al. (1987) reported that taurine attenuates the development of the hypertension mediated by slowing of cardiac and splenic NE turnover. Cumulatively, these studies suggest that taurine can suppress sympathetic overactivity. It has also been reported that

taurine suppresses NE overflow from peripheral nerves. Hano et al. (2009) have demonstrated that addition of taurine to the perfusion buffer attenuates electrical stimulation-induced NE overflow and pressor response in isolated mesenteric artery of rat, an effect more prominent in SHRs. They have also reported that chronic treatment with taurine improves baro-reflex sensitivity in response to NE infusion, and attenuates stress-induced renal nerve activation in SHR, demonstrating that taurine suppresses both central and peripheral nervous systems. Moreover, taurine may modulate central nervous system action of Ang II, as described in more detail below.

The effects of taurine against AngII

Cardiac hypertrophy, fibrosis and apoptosis induced by AngII

AngII mediates cardiac hypertrophy, inflammation and fibrosis in the heart, which in turn leads to cardiac failure. Patients suffering from CHF produce excessive amounts of AngII. Several large-scale clinical trials have proven that ACEI and ARB improve cardiac output and life expectancy in patients suffering from CHF. They also reduce cardiac remodeling and diminish the severity of CHF.

We have previously investigated the interaction between taurine and AngII on myocardial contractile function, myocyte hypertrophy and apoptosis. Addition of AngII to the perfusion buffer increases cardiac contraction in perfused hearts, an effect blocked by treatment with high concentrations of taurine, an effect linked to changes in the activity of the Na^+/Ca^{2+} exchanger (Ballard-Croft et al. 1997; Schaffer et al. 2000a, b). Meanwhile, taurine treatment inhibits AngII-induced elevations in $[Ca^{2+}]i$, cell size and gene expression of ANP and TGF-beta of cultured cardiomyocytes (Takahashi et al. 1997; Azuma et al. 2000). These observations illustrate that taurine antagonizes the harmful effects of AngII in cardiac cells. Moreover, in cultured cardiac fibroblasts, taurine prevents AngII-enhanced cell proliferation and expression of immediate early response genes, such as c-fos and c-jun (Takahashi et al. 1997), suggesting that taurine protects against AngII-mediated cardiac fibrosis.

We have also shown that β-alanine-mediated taurine depletion accelerates AngII-induced apoptotic cell death in cardiomyocytes, an effect associated with elevations in Bax and an increase in protein kinase C activity (Schaffer et al. 1998, 2000a, b).

Renal role of taurine and AngII

AngII enhances the release of aldosterone, which acts on the kidney to promote water and salt retention. This action contributes to an increase in cardiac preload by increasing body fluid, an effect that exacerbates the condition of the failing heart by reducing contractile function and stimulating ventricular remodeling. Moreover, AngII may play a critical role in the development of renal dysfunction. Although there is no information which shows how taurine interacts with AngII in the kidney, two studies have compared the renoprotective effect of taurine with ACEIs. Cruz et al. (2000) have demonstrated that both ACEIs and taurine reduce aging-dependent increases in extracellular matrix proteins, such as collagen I, IV, and TGF-β in Fischer 344 rats. Moreover, they demonstrated that taurine inhibits TGF-β1-stimulated synthesis of ECM proteins in cultured human mesangial cells, suggesting that taurine can serve as an alternative to ACEI in preventing renal fibrosis in elderly individuals. In another paper, Mozaffari et al. (2003) compared long-term treatment with taurine, ACEI enalapril alone and the combination of taurine and enalapril on renal dysfunction in hypertensive, glucose intolerant rats. All three treatment regimens decreased urinary protein excretion and improved renal excretory function. Notably, the combination of taurine and enalapril exerted the greatest beneficial effect on glomerular filtration rate.

Central nervous system action of AngII

Central RAS is also activated in CHF. AngII excites the sympathetic nervous system via several actions, including a central action to increase sympathetic outflow, a stimulatory effect on sympathetic ganglia and adrenal medulla, and a peripheral action on sympathetic nerve endings, the latter that serves to facilitate sympathetic neurotransmission (Reid 1992; Zucker 2006).

Abe et al. (1987, 1988) have studied the effect of taurine on the central nervous system actions of AngII. They demonstrated that administration of taurine as well as GABA and the GABA agonist, muscimol, into both the cerebroventricle area and the preoptic area inhibits AngII-induced water intake, while preoptic injection of AngII stimulates water intake. However, intravenous administration of taurine fails to suppress water intake, suggesting central venous action of taurine suppresses the actions of AngII. They also demonstrated that taurine administration into the cerebroventricular area and the preoptic area prevents renin-induced water intake and blood pressure elevation. Furthermore, they found a similar effect of central taurine administration on renin action in SHR, an effect consistent with the ability of long-term oral taurine administration to suppress blood pressure (Abe et al. 1987). Taken together, these studies suggest that taurine may antagonize AngII and/or intrinsic RAS in the brain and control sympathetic nerve activity.

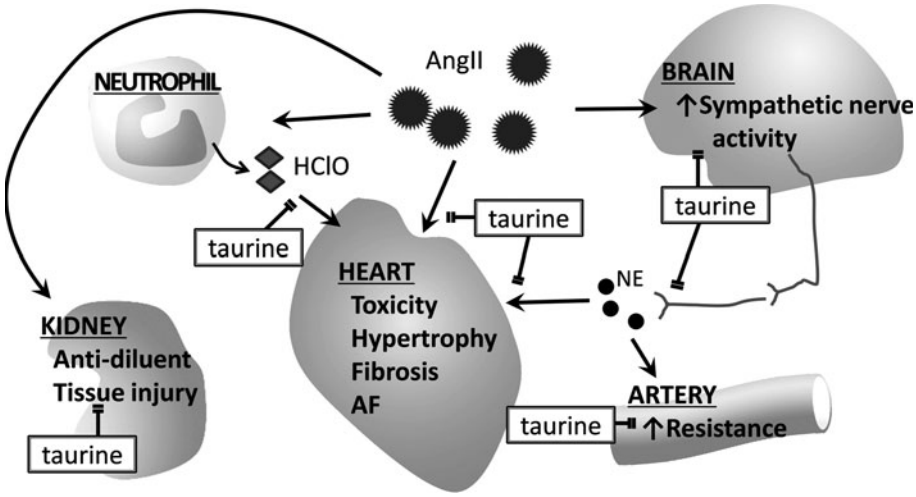

Fig. 1 Schematic representation of potential mechanisms underlying taurine-mediated antagonism of catecholamine (norepinephrine, *NE*) and angiotensin II (*AngII*) actions in CHF. Taurine may prevent (1) NE- and AngII-induced cardiotoxicity and AngII-induced hypertrophy and fibrosis, (2) enhanced arterial contraction in response to NE, (3) AngII-related overactivation of sympathetic nerves in the brain, (4) AngII-related renal dysfunction and (5) angiotensin II-promoted atrial fibrillation caused by the actions of neutrophil-derived hypochlorous acid (*HClO*)

GABA is also known to play an important role in central cardiovascular control (Patel and Zheng 2012). Blockade of the $GABA_A$ receptors in the paraventricular nucleus (PVN) increases sympathetic outflow, whereas activation of $GABA_A$ receptors reduces sympathetic activity and blood pressure (Gomes da Silva et al. 2012). It has been demonstrated that an imbalance between the inhibitory "GABAergic" and excitatory "angiotensinergic" pathways in the PVN causes excessive activation of the sympathetic nervous system in CHF (Zucker 2006). Since taurine acts as an inhibitory neurotransmitter or regulator of the GABAa receptor, taurine has the potential to antagonize AngII-induced sympathetic nerve activation in the PVN.

Scavenging role of taurine against hypochlorous acid

AngII also plays a crucial role in atrial fibrillation (AF). Some clinical studies have revealed that ACEI and ARB prevent the development of AF in patients with heart diseases, such as CHF and myocardial infarction (Healey et al. 2005). Animal experiments have demonstrated that ACEI and ARB prevent AF by attenuating heart failure-induced cardiac fibrosis and remodeling, indicating that AngII causes arrhythmogenic atrial structural remodeling (Shi et al. 2001). More recently, it has been demonstrated that myeloperoxidase (MPO), which is expressed in neutrophils and generates hypochlorous acid, a powerful oxidant, plays a key role in AngII-induced AF (Rudolph et al. 2010). AngII infusion results in the accumulation of the MPO-product, 3-chlorotyrosine. Interestingly, MPO-deficient mice treated with AngII exhibit diminished degrees of atrial fibrosis, which in turn markedly reduces the incidence of AF. Moreover, individuals with AF undergoing coronary bypass surgery exhibit higher atrial MPO and 3-chlorotyrosine content. In a related study, Tang et al. (2006) demonstrated that plasma MPO levels are increased in CHF patients compared to non-CHF patients. Therefore, MPO and hypochlorous acid appear to contribute to development of AF in CHF patients.

Taurine acts as a scavenger of hypochlorous acid (Marcinkiewicz et al. 2000; Schuller-Levis and Park 2003). Hypochlorous acid reacts with and damages macromolecules, such as protein, DNA and fatty acids. Amines, including taurine and other amino acids, can react with hypochlorous acid in the presence of MPO to form chloramines. Since taurine is abundant in the neutrophil and its chloramine form is less reactive than hypochlorous acid, taurine may suppress the toxic action of hypochlorous acid.

Zulli et al. (2009) and Zulli (2011) found that orally administered taurine prevents the formation of hypochlorous acid-mediated oxidation of LDL (OCl-LDL) in plasma of animals fed an atherogenic diet. However, taurine also lowers plasma homocysteine content, which is also a potent mediator of OCl-LDL formation. Thus, it remains to be determined if taurine directly suppresses the production of OCl-LDL by scavenging hypochlorous acid or by reducing homocysteine levels. Further studies are necessary to elucidate the direct role of taurine in AngII-induced neutrophil activation.

Conclusion

Taurine exerts several actions that diminish the progression of CHF. Figure 1 summarizes the actions of taurine that

attenuate the detrimental effects of the catecholamine and of AngII on the failing heart (Fig. 1). The actions of taurine are complex because they involve multiple organs and multiple pathways and impact the adverse effects of both the catecholamines and AngII. We anticipate that pharmacological and nutritional intervention with taurine will act synergistically with standard drug treatment to improve the outcome of patients with CHF. Clearly, further clinical trials are warranted to clarify the effect of taurine therapy on the detrimental actions of elevated neurohumoral activity on the development, progression and severity of CHF.

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References

Abe M, Shibata K, Matsuda T, Furukawa T (1987) Inhibition of hypertension and salt intake by oral taurine treatment in hypertensive rats. Hypertension 10:383–389

Abe M, Tokunaga T, Yamada K, Furukawa T (1988) Gamma-aminobutyric acid and taurine antagonize the central effects of angiotensin II and renin on the intake of water and salt, and on blood pressure in rats. Neuropharmacology 27:309–318

Abebe W, Mozaffari MS (2011) Role of taurine in the vasculature: an overview of experimental and human studies. Am J Cardiovasc Dis 1:293–311

Azuma J, Hasegawa H, Sawamura A, Awata N, Harada H, Ogura K, Kishimoto S (1982) Taurine for treatment of congestive heart failure. Int J Cardiol 2:303–304

Azuma J, Hasegawa H, Sawamura A, Awata N, Ogura K, Harada H, Yamamura Y, Kishimoto S (1983) Therapy of congestive heart failure with orally administered taurine. Clin Ther 5:398–408

Azuma J, Sawamura A, Awata N, Ohta H, Hamaguchi T, Harada H, Takihara K, Hasegawa H, Yamagami T, Ishiyama T et al (1985) Therapeutic effect of taurine in congestive heart failure: a double-blind crossover trial. Clin Cardiol 8:276–282

Azuma J, Hamaguchi T, Ohta H, Takihara K, Awata N, Sawamura A, Harada H, Tanaka Y, Kishimoto S (1987) Calcium overload-induced myocardial damage caused by isoproterenol and by adriamycin: possible role of taurine in its prevention. Adv Exp Med Biol 217:167–179

Azuma J, Katsume H, Kagisgima T, Furukawa K, Awata N, Ishiyama T, Yamagami T, Ishikawa H, Iwata H, Kishimoto S et al (1989) Clinical evaluation of taurine in congestive heart failure—a double-blind comparative study using CoQ10 as a control drug. In: Iwata H, Lombardini JB, Segawa T (eds) Taurine and the heart. Kluwer Academic Publishers, Boston, pp 75–97

Azuma J, Sawamura A, Awata N (1992) Usefulness of taurine in chronic congestive heart failure and its prospective application. Jpn Circ J 56:95–99

Azuma M, Takahashi K, Fukuda T, Ohyabu Y, Yamamoto I, Kim S, Iwao H, Schaffer SW, Azuma J (2000) Taurine attenuates hypertrophy induced by angiotensin II in cultured neonatal rat cardiac myocytes. Eur J Pharmacol 403:181–188

Ballard-Croft C, Mozaffari MS, Azuma J, Schaffer S (1997) Interaction between taurine and angiotensin II: modulation of calcium transport and myocardial contractile function. Amino Acids 13:105–114

Beyranvand MR, Khalafi MK, Roshan VD, Choobineh S, Parsa SA, Piranfar MA (2011) Effect of taurine supplementation on exercise capacity of patients with heart failure. J Cardiol 57:333–337

Braunwald E (2008) Biomarkers in heart failure. N Engl J Med 358:2148–2159

Braunwald E, Bristow MR (2000) Congestive heart failure: fifty years of progress. Circulation 102:IV14–IV23

Carr AC, McCall MR, Frei B (2000) Oxidation of LDL by myeloperoxidase and reactive nitrogen species: reaction pathways and antioxidant protection. Arterioscler Thromb Vasc Biol 20:1716–1723

Chovan JP, Kulakowski EC, Sheakowski S, Schaffer SW (1980) Calcium regulation of low-affinity taurine binding sites of cardiac sarcolemma. Mol Pharmacol 17:295–300

Colucci WS (1998) The effects of norepinephrine on myocardial biology: implications for the therapy of heart failure. Clin Cardiol 21:I20–I24

Crass MF III, Lombardini JB (1977) Loss of cardiac muscle taurine after acute left ventricular ischemia. Life Sci 21:951–958

Cruz CI, Ruiz-Torres P, del Moral RG, Rodriguez-Puyol M, Rodriguez-Puyol D (2000) Age-related progressive renal fibrosis in rats and its prevention with ACE inhibitors and taurine. Am J Physiol Renal Physiol 278:F122–F129

Denipote F, Ardisson LP, Azevedo PS, Minicucci MF, Lima-Leopoldo AP, Chiuso-Minicucci F, Polegato BF, Matsubara BB, Matsubara LS, Novelli E et al (2011) Influence of taurine on cardiac remodeling induced by tobacco smoke exposure. Cell Physiol Biochem 27:291–298

Dhalla NS, Adameova A, Kaur M (2010) Role of catecholamine oxidation in sudden cardiac death. Fundam Clin Pharmacol 24:539–546

Francis GS, Goldsmith SR, Levine TB, Olivari MT, Cohn JN (1984) The neurohumoral axis in congestive heart failure. Ann Intern Med 101:370–377

Franconi F, Giotti A, Manzini S, Martini F, Stendardi I, Zilletti L (1982) The effect of taurine on high potassium- and noradrenaline-induced contraction in rabbit ear artery. Br J Pharmacol 75:605–612

Fujita T, Ando K, Noda H, Ito Y, Sato Y (1987) Effects of increased adrenomedullary activity and taurine in young patients with borderline hypertension. Circulation 75:525–532

Giordano FJ (2005) Oxygen, oxidative stress, hypoxia, and heart failure. J Clin Invest 115:500–508

Gomes da Silva AQ, Xavier CH, Campagnole-Santos MJ, Caligiorne SM, Baltatu OC, Bader M, Santos RA, Fontes MA (2012) Cardiovascular responses evoked by activation or blockade of GABA(A) receptors in the hypothalamic PVN are attenuated in transgenic rats with low brain angiotensinogen. Brain Res 1448:101–110

Hamaguchi T, Azuma J, Awata N, Ohta H, Takihara K, Harada H, Kishimoto S, Sperelakis N (1988) Reduction of doxorubicin-induced cardiotoxicity in mice by taurine. Res Commun Chem Pathol Pharmacol 59:21–30

Hanna J, Chahine R, Aftimos G, Nader M, Mounayar A, Esseily F, Chamat S (2004) Protective effect of taurine against free radicals damage in the rat myocardium. Exp Toxicol Pathol 56:189–194

Hano T, Kasano M, Tomari H, Iwane N (2009) Taurine suppresses pressor response through the inhibition of sympathetic nerve activity and the improvement in baro-reflex sensitivity of spontaneously hypertensive rats. Adv Exp Med Biol 643:57–63

Hansen SH, Andersen ML, Cornett C, Gradinaru R, Grunnet N (2010) A role for taurine in mitochondrial function. J Biomed Sci 17(Suppl 1):S23

Healey JS, Baranchuk A, Crystal E, Morillo CA, Garfinkle M, Yusuf S, Connolly SJ (2005) Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. J Am Coll Cardiol 45:1832–1839

Huxtable R, Bressler R (1974) Taurine concentrations in congestive heart failure. Science 184:1187–1188

Ito T, Azuma J (2012) Taurine depletion-related cardiomyopathy in animals. In: Veselka J (ed) Cardiomyopathies—from basic research to clinical management. doi:10.5772/30023. ISBN 978-953-307-834-2

Ito T, Kimura Y, Uozumi Y, Takai M, Muraoka S, Matsuda T, Ueki K, Yoshiyama M, Ikawa M, Okabe M et al (2008) Taurine depletion caused by knocking out the taurine transporter gene leads to cardiomyopathy with cardiac atrophy. J Mol Cell Cardiol 44:927–937

Jeejeebhoy F, Keith M, Freeman M, Barr A, McCall M, Kurian R, Mazer D, Errett L (2002) Nutritional supplementation with MyoVive repletes essential cardiac myocyte nutrients and reduces left ventricular size in patients with left ventricular dysfunction. Am Heart J 143:1092–1100

Jong CJ, Azuma J, Schaffer S (2012) Mechanism underlying the antioxidant activity of taurine: prevention of mitochondrial oxidant production. Amino Acids 42:2223–2232

Kramer JH, Chovan JP, Schaffer SW (1981) Effect of taurine on calcium paradox and ischemic heart failure. Am J Physiol 240:H238–H246

Landmesser U, Wollert KC, Drexler H (2009) Potential novel pharmacological therapies for myocardial remodelling. Cardiovasc Res 81:519–527

Li N, Sawamura M, Nara Y, Ikeda K, Yamori Y (1996) Direct inhibitory effects of taurine on norepinephrine-induced contraction in mesenteric artery of stroke-prone spontaneously hypertensive rats. Adv Exp Med Biol 403:257–262

Li C, Cao L, Zeng Q, Liu X, Zhang Y, Dai T, Hu D, Huang K, Wang Y, Wang X et al (2005) Taurine may prevent diabetic rats from developing cardiomyopathy also by downregulating angiotensin II type2 receptor expression. Cardiovasc Drugs Ther 19:105–112

Li Y, Arnold JM, Pampillo M, Babwah AV, Peng T (2009) Taurine prevents cardiomyocyte death by inhibiting NADPH oxidase-mediated calpain activation. Free Radical Biol Med 46:51–61

Ling H, Zhang T, Pereira L, Means CK, Cheng H, Gu Y, Dalton ND, Peterson KL, Chen J, Bers D et al (2009) Requirement for Ca^{2+}/calmodulin-dependent kinase II in the transition from pressure overload-induced cardiac hypertrophy to heart failure in mice. J Clin Invest 119:1230–1240

Liu Y, Niu L, Zhang W, Cui L, Zhang X, Liang Y, Zhang M (2009) Effects of taurine on contractions of the porcine coronary artery. Pharmacol Rep 61:681–689

Marcinkiewicz J, Kontny E (2012) Taurine and inflammatory diseases. Amino acids [Epub ahead of print]

Marcinkiewicz J, Chain B, Nowak B, Grabowska A, Bryniarski K, Baran J (2000) Antimicrobial and cytotoxic activity of hypochlorous acid: interactions with taurine and nitrite. Inflamm Res 49:280–289

McBroom MJ, Welty JD (1977) Effects of taurine on heart calcium in the cardiomyopathic hamster. J Mol Cell Cardiol 9:853–858

Militante JD, Lombardini JB (2002) Treatment of hypertension with oral taurine: experimental and clinical studies. Amino Acids 23:381–393

Mizushima S, Nara Y, Sawamura M, Yamori Y (1996) Effects of oral taurine supplementation on lipids and sympathetic nerve tone. Adv Exp Med Biol 403:615–622

Moise NS, Pacioretty LM, Kallfelz FA, Stipanuk MH, King JM, Gilmour RF (1991) Dietary taurine deficiency and dilated cardiomyopathy in the fox. Am Heart J 121:541–547

Mozaffari MS, Miyata N, Schaffer SW (2003) Effects of taurine and enalapril on kidney function of the hypertensive glucose-intolerant rat. Am J Hypertens 16:673–680

Nakamura K, Fushimi K, Kouchi H, Mihara K, Miyazaki M, Ohe T, Namba M (1998) Inhibitory effects of antioxidants on neonatal rat cardiac myocyte hypertrophy induced by tumor necrosis factor-alpha and angiotensin II. Circulation 98:794–799

Nakamura K, Kusano K, Nakamura Y, Kakishita M, Ohta K, Nagase S, Yamamoto M, Miyaji K, Saito H, Morita H et al (2002) Carvedilol decreases elevated oxidative stress in human failing myocardium. Circulation 105:2867–2871

Nishida S, Satoh H (2009) Vascular modulation of rat aorta by taurine. Adv Exp Med Biol 643:37–46

Niu LG, Zhang MS, Liu Y, Xue WX, Liu DB, Zhang J, Liang YQ (2008) Vasorelaxant effect of taurine is diminished by tetraethylammonium in rat isolated arteries. Eur J Pharmacol 580:169–174

Novotny MJ, Hogan PM, Flannigan G (1994) Echocardiographic evidence for myocardial failure induced by taurine deficiency in domestic cats. Can J Vet Res-Revue Canadienne De Recherche Veterinaire 58:6–12

Ohta H, Azuma J, Onishi S, Awata N, Takihara K, Kishimoto S (1986) Protective effect of taurine against isoprenaline-induced myocardial damage. Basic Res Cardiol 81:473–481

Ohta H, Azuma J, Awata N, Hamaguchi T, Tanaka Y, Sawamura A, Kishimoto S, Sperelakis N (1988) Mechanism of the protective action of taurine against isoprenaline induced myocardial damage. Cardiovasc Res 22:407–413

Oliveira MW, Minotto JB, de Oliveira MR, Zanotto-Filho A, Behr GA, Rocha RF, Moreira JC, Klamt F (2010) Scavenging and antioxidant potential of physiological taurine concentrations against different reactive oxygen/nitrogen species. Pharmacol Rep 62:185–193

Oudit GY, Trivieri MG, Khaper N, Husain T, Wilson GJ, Liu P, Sole MJ, Backx PH (2004) Taurine supplementation reduces oxidative stress and improves cardiovascular function in an iron-overload murine model. Circulation 109:1877–1885

Pansani MC, Azevedo PS, Rafacho BP, Minicucci MF, Chiuso-Minicucci F, Zorzella-Pezavento SG, Marchini JS, Padovan GJ, Fernandes AA, Matsubara BB et al (2012) Atrophic cardiac remodeling induced by taurine deficiency in Wistar rats. PLoS ONE 7:e41439

Pasantes-Morales H, Chatagner F, Mandel P (1980) Synthesis of taurine in rat liver and brain in vivo. Neurochem Res 5:441–451

Patel KP, Zheng H (2012) Central neural control of sympathetic nerve activity in heart failure following exercise training. Am J Physiol Heart Circ Physiol 302:H527–H537

Pion PD, Kittleson MD, Rogers QR, Morris JG (1987) Myocardial failure in cats associated with low plasma taurine—a reversible cardiomyopathy. Science 237:764–768

Rana SK, Sanders TA (1986) Taurine concentrations in the diet, plasma, urine and breast milk of vegans compared with omnivores. Br J Nutr 56:17–27

Raschke P, Massoudy P, Becker BF (1995) Taurine protects the heart from neutrophil-induced reperfusion injury. Free Radic Biol Med 19:461–471

Reid IA (1992) Interactions between ANG II, sympathetic nervous system, and baroreceptor reflexes in regulation of blood pressure. Am J Physiol 262:E763–E778

Ricci C, Pastukh V, Leonard J, Turrens J, Wilson G, Schaffer D, Schaffer SW (2008) Mitochondrial DNA damage triggers mitochondrial superoxide generation and apoptosis. Am J Physiol 294:C413–C422

Ristori MT, Verdetti J (1991) Effects of taurine on rat aorta in vitro. Fundam Clin Pharmacol 5:245–258

Ritter O, Neyses L (2003) The molecular basis of myocardial hypertrophy and heart failure. Trends Mol Med 9:313–321

Rosenkranz S (2004) TGF-beta1 and angiotensin networking in cardiac remodeling. Cardiovasc Res 63:423–432

Rudolph V, Andrie RP, Rudolph TK, Friedrichs K, Klinke A, Hirsch-Hoffmann B, Schwoerer AP, Lau D, Fu X, Klingel K et al (2010) Myeloperoxidase acts as a profibrotic mediator of atrial fibrillation. Nat Med 16:470–474

Sato Y, Ando K, Fujita T (1987) Role of sympathetic nervous system in hypotensive action of taurine in DOCA-salt rats. Hypertension 9:81–87

Satoh H, Sperelakis N (1998) Review of some actions of taurine on ion channels of cardiac muscle cells and others. Gen Pharmacol 30:451–463

Sawamura A, Azuma J, Harada H, Hasegawa H, Ogura K, Sperelakis N, Kishimoto S (1983) Protection by oral pretreatment with taurine against the negative inotropic effects of low-calcium medium on isolated perfused chick heart. Cardiovasc Res 17:620–626

Sawamura A, Sada H, Azuma J, Kishimoto S, Sperelakis N (1990) Taurine modulates ion influx through cardiac Ca^{2+} channels. Cell Calcium 11:251–259

Schaffer SW, Ballard-Croft C, Takahashi K, Azuma J (1998) Effect of taurine depletion on angiotensin II-mediated modulation of myocardial function. Adv Exp Med Biol 442:145–152

Schaffer SW, Lombardini JB, Azuma J (2000a) Interaction between the actions of taurine and angiotensin II. Amino Acids 18:305–318

Schaffer S, Solodushko V, Azuma J (2000b) Taurine-deficient cardiomyopathy: role of phospholipids, calcium and osmotic stress. Adv Exp Med Biol 483:57–69

Schaffer SW, Azuma J, Mozaffari M (2009) Role of antioxidant activity of taurine in diabetes. Can J Physiol Pharmacol 87:91–99

Schaffer SW, Jong CJ, Ramila KC, Azuma J (2010) Physiological roles of taurine in heart and muscle. J Biomed Sci 17(Suppl 1):S2

Schaffer SW, Jong CJ, Warner D, Ito T, Azuma J (2013) Taurine deficiency and MELAS are closely related syndromes. Adv Exp Med Biol 776:153–165

Schuller-Levis GB, Park E (2003) Taurine: new implications for an old amino acid. FEMS Microbiol Lett 226:195–202

Shao A, Hathcock JN (2008) Risk assessment for the amino acids taurine, L-glutamine and L-arginine. Regul Toxicol Pharmacol 50:376–399

Sharov VS, Dremina ES, Galeva NA, Williams TD, Schöneich C (2006) Quantitative mapping of oxidation-sensitive cysteine residues of SERCA in vivo and in vitro by HPLC electrospray-tandem MS: selective protein modification during biological aging. Biochem J 394:605–615

Shi Y, Ducharme A, Li D, Gaspo R, Nattel S, Tardif JC (2001) Remodeling of atrial dimensions and emptying function in canine models of atrial fibrillation. Cardiovasc Res 52:217–225

Shi YR, Bu DF, Qi YF, Gao L, Jiang HF, Pang YZ, Tang CS, Du JB (2002) Dysfunction of myocardial taurine transport and effect of taurine supplement in rats with isoproterenol-induced myocardial injury. Acta Pharmacol Sin 23:910–918

Shiny KS, Kumar SH, Farvin KH, Anandan R, Devadasan K (2005) Protective effect of taurine on myocardial antioxidant status in isoprenaline-induced myocardial infarction in rats. J Pharm Pharmacol 57:1313–1317

Sirker A, Zhang M, Murdoch C, Shah AM (2007) Involvement of NADPH oxidases in cardiac remodeling and heart failure. Am J Nephrol 27:649–660

Stipanuk MH, Ueki I, Dominy JE Jr, Simmons CR, Hirschberger LL (2009) Cysteine dioxygenase: a robust system for regulation of cellular cysteine levels. Amino Acids 37:55–63

Suzuki T, Wada T, Saigo K, Watanabe K (2002) Taurine as a constituent of mitochondrial tRNAs: new insights into the functions of taurine and human mitochondrial diseases. EMBO J 21:6581–6589

Takahashi K, Azuma M, Taira K, Baba A, Yamamoto I, Schaffer SW, Azuma J (1997) Effect of taurine on angiotensin II-induced hypertrophy of neonatal rat cardiac cells. J Cardiovasc Pharmacol 30:725–730

Takihara K, Azuma J, Awata N, Ohta H, Hamaguchi T, Sawamura A, Tanaka Y, Kishimoto S, Sperelakis N (1986) Beneficial effect of taurine in rabbits with chronic congestive heart failure. Am Heart J 112:1278–1284

Takimoto E, Kass DA (2007) Role of oxidative stress in cardiac hypertrophy and remodeling. Hypertension 49:241–248

Tang WH, Brennan ML, Philip K, Tong W, Mann S, Van Lente F, Hazen SL (2006) Plasma myeloperoxidase levels in patients with chronic heart failure. Am J Cardiol 98:796–799

Yamamoto J, Akabane S, Yoshimi H, Nakai M, Ikeda M (1985) Effects of taurine on stress-evoked hemodynamic and plasma catecholamine changes in spontaneously hypertensive rats. Hypertension 7:913–922

Yamauchi-Takihara K, Azuma J, Kishimoto S, Onishi S, Sperelakis N (1988) Taurine prevention of calcium paradox-related damage in cardiac muscle. Its regulatory action on intracellular cation contents. Biochem Pharmacol 37:2651–2658

Zelis R, Mason DT, Braunwald E (1968) A comparison of the effects of vasodilator stimuli on peripheral resistance vessels in normal subjects and in patients with congestive heart failure. J Clin Invest 47:960–970

Zucker IH (2006) Novel mechanisms of sympathetic regulation in chronic heart failure. Hypertension 48:1005–1011

Zulli A (2011) Taurine in cardiovascular disease. Curr Opin Clin Nutr Metab Care 14:57–60

Zulli A, Lau E, Wijaya BP, Jin X, Sutarga K, Schwartz GD, Learmont J, Wookey PJ, Zinellu A, Carru C et al (2009) High dietary taurine reduces apoptosis and atherosclerosis in the left main coronary artery: association with reduced CCAAT/enhancer binding protein homologous protein and total plasma homocysteine but not lipidemia. Hypertension 53:1017–1022