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Taurine Depletion-Related Cardiomyopathy in Animals

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1. Introduction

Taurine is a nontoxic β-amino acid and a normal constituent of the human diet found in animal food sources, especially fishes and shell fishes. It is found in very high concentration in cardiac tissue, and represents approximately 60% of free amino acid pool in the mammalian heart. Mammalian cardiac taurine contents vary among the spices. Cats are known to be the species most susceptible to taurine deficiency due to poor synthetic capacity. On the other hand, rats have high amount of taurine in the heart, liver and skeletal muscle. Therefore, it may be the natural providence that cats chase rats.

While biosynthesis of taurine in heart is limited, the major determinant of myocardial taurine is uptake from plasma. The concentration in myocardium is approximately 100 times higher than that in plasma, indicating active transport process from the plasma. The biochemical aspects of its transport mechanism including changes in taurine content resulting from modification of uptake into and leakage from myocardial cells by physiological (β-adrenergic stimulation), pharmacological (guanidinoethyl sulfonate or β-alanine) and pathophysiological (congestive heart failure, ischemia, hypoxia or cardiomyopathy) interventions have been quite well documented. However, these physiological and pathophysiological roles in heart remain uncertain.

Taurine is known to possess a variety of biological actions including calcium handling, osmoregulation, anti-oxidation, bile acid conjugation and so on. In heart, some physiological or pharmacological effects have been reported, as shown in Table 1. Meanwhile, it has been discovered in 1980s that taurine deficient diet causes dilated

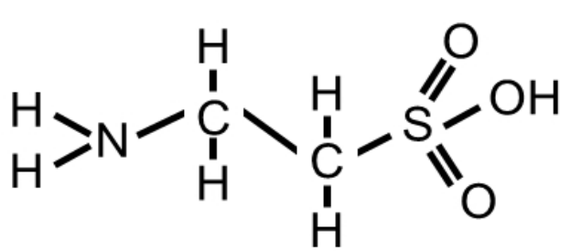


Fig. 1. Taurine (2-aminoethanesulfonic acid)

1.	Positive inotropy at low calcium concentrations
2.	Negative inotropy at high calcium concentrations
3.	Potentiation of digitalis inotropy
4.	Antagonism of negative inotropy
5.	Retardation of lesion development in calcium overload myopathy
6.	Protection against drug-induced cardiotoxicity
7.	Protection against calcium paradox- and oxygen paradox- induced myocardial injury
8.	Antiarrythmia
9.	Modulation of cardiac calcium current
10.	Antiapoptotic effect

Table 1. Action of taurine on the heart

cardiomyopathy (DCM) implicated with taurine depletion in house cats. Thereafter, taurine depletion-related cardiomyopathy has been reported in foxes and dogs. It has been reported that amount of taurine intake is widely varied among individuals in human and correlates to mortality rate caused by ischemia heart diseases in epidemiologic studies (Yamori et al., 2001, 2009), indicating taurine depletion may also occur in human. Hence, taurine depletion-induced DCM should be focused as one of the etiology of cardiomyopathy in human. In this chapter, we introduce taurine depletion-related cardiomyopathy in animals. Moreover, mechanisms underlying the pathogenesis of taurine depletion-related cardiomyopathy have been investigated, while the mechanisms remain uncertain. Studies by using β-alanine and guanidinoethane sulfonate (GES) which are the inhibitors of taurine influx into cells through taurine transporter are very useful to evaluate the molecular mechanism. Further, the genetically engineered mice knocking out taurine transporter have been recently developed. These mice also exhibited the cardiomyopathy with cardiac atrophy. We also describe recent evidences and possible mechanisms which should associate with the taurine depletion-related cardiomyopathy.

Furthermore, a lot of studies support the beneficial effect of taurine on cardiomyopathy and heart failure in animal model as well as in human. In the latter half of this chapter, we describe the pharmacological effects of taurine supplementation against heart diseases.

2. Taurine depletion-related cardiomyopathy

2.1 Cats

Taurine depletion-related DCM was firstly identified in domestic cats in 1980s. Pion et al. reported that low taurine concentration in plasma is a major causal factor of DCM in pet cats (Pion et al., 1987). They analyzed the pet cats having a diagnosis of heart failure in hospital, and found that 22 of 23 cats with echocardiographic evidence of DCM had low concentration of plasma taurine. Moreover, treatment of taurine (0.5 g administered twice daily) improved cats echocardiographically in 2-week period after treatment. At the end all cats were clinically and echocardiographically normal and were no longer receiving medication of their heart failure. In further study, the authors prospectively evaluated the long term benefits of administering taurine to cats with moderate to severe DCM (Pion et al., 1992). They compared the survival times of this prospectively evaluated population to the other population which were diagnosed as DCM before the discovery of the role of taurine deficiency in the cause of cardiomyopathy. As a result, all cats that survived more than 30 days remained clinically stable despite withdrawal of all medications except taurine. The

clinical response and 1-year survival rate of 58% in the taurine treatment group represents a marked improvement compared with a 1-year survival rate of 13% in the retrospectively evaluated population.

Further, Novotny et al. examined the intrinsic contraction-relaxation properties of left ventricle using perfused hearts isolated from cats maintained by taurine-deficient diet with or without taurine supplementation (Novotny et al., 1991). They demonstrated that coronary-perfused hearts from the taurine deficient cats did not achieve isovolumic systolic pressure and ±dP/dt max values of the magnitude generated by heart from taurine-treated cats. They also identified that the pressure-volume relation curve resulted from isovolumic heart preparations of taurine-deficient cats were shifted downward and to the right of control curves, indicating inotropic depression and increased chamber compliance or distensibility. Therefore, these data illustrate the myocardial contractile dysfunction and LV chamber dilatation in hearts from taurine-deficient cats.

Subsequent control study with cats also showed the evidence that dietary taurine deficiency induces myocardial failure (Novotny et al., 1994). Novotny et al. evaluated left ventricular function using M-mode echocardiography in cats maintained on a taurine deficient diet for 6-15 months. At 4 months from the onset of the study, plasma taurine concentration of cats fed taurine-deficient diet is 12 nmol/mL, while baseline value is 227 nmol/mL. They demonstrated that 74% of taurine-deficient cats experienced greater than 25% reductions in fraction shortening values and 91% had a greater than 25% increase in LV end-systolic short axis diameter values in response to taurine deficient diet. The average reduction of fraction shortening was 37%. Moreover, the study with colony-source cats revealed that the greatest rate of change occurred during the first four months in taurine-deficient cats. The authors concluded that while DCM was observed in some cats, decreased systolic pump function and increased LV end-systolic short axis diameter were more consistent findings.

Pion reported in 2004 that in their repeated studies, approximately 25% of all (n>100) cats depleted of taurine for more than 2 years developed overt myocardial failure (Pion, 2004). He mentioned that the other factors required for taurine developed overt myocardial failure are unknown, and that nutritional taurine deficiency combined with other causes of myocardial stress, such as congenital or acquired left ventricle overload, toxic, ischemic, nutritional, endocrine or metabolic problems, may lead to synergistic complicating effects. Furthermore, he noted that taurine deficiency in cats may be a direct result of inadequate amounts of taurine in the diet, such commercial pet food, in most cases and is thus preventable.

2.2 Foxes

Foxes are also known to have low taurine synthesis capacity. Moise et al. reported the relationship between taurine deficiency and DCM in foxes (Moise et al., 1991). They found that plasma taurine concentration in foxes from farms with a history of death caused by DCM was less than that in foxes without family history of cardiac death. Furthermore, they demonstrated that the activity of hepatic cysteinesulfinic acid decarboxylase which is a rate-limiting enzyme in taurine synthesis from cysteine was less in foxes with DCM, suggesting that inadequate cysteinesulfinic acid decarboxylase activity may contribute to susceptibility to dietary taurine deficiency. Also, the therapy with taurine supplementation for 2 months

in foxes with DCM reduced cardiac size, resolved pulmonary edema and improved systolic function, indicating DCM was reversed.

2.3 Dogs

Taurine is not an essential amino acid in dogs. Normal dogs fed diets with little or no taurine maintain plasma and whole blood taurine concentration similar to those found in normal cats. The activity of cysteinesulfinic acid decarboxylase is high in dog compared to the cat. Therefore, until recently, it was thought that taurine deficiency was not a clinical issue to consider when managing canine patients (Pion, 2004).

Soon after the identification of taurine deficiency myocardial failure in cats, Pion who firstly identified taurine depletion-related DCM in cats,, as mentioned above, began administering taurine to dogs with DCM (Kramer et al., 1995; Pion, 2004). Then he and his colleagues found that plasma taurine concentration was low in 17% of dogs with DCM studied, although there were no significant differences in the average of plasma taurine concentrations between dogs with DCM and the control dogs. They also identified that a certain breeds, such as American Cocker Spaniel and Golden Retriever, with DCM had low plasma taurine concentrations, while it was not decreased in the breeds that are more commonly afflicted with DCM. Recently, DCM associated with low taurine concentration has been reported in American Cocker Spaniel, Golden Retriever, Dalmatian, boxer, Newfoundland, Portuguese water dog, English setter, Alaskan malamute and Scottish terrier (Freeman et al., 1996; Kittleson et al., 1997; Pion et al., 1998; Fascetti et al., 2003; Alroy et al., 2005; Belanger et al., 2005). Additionally, Ko et al. reported that taurine biosynthesis rate was lower in large dogs than small dogs (Ko et al., 2007), which may be associated with the greater incidence of taurine deficiency-related cardiomyopathy in large dogs than in small dogs.

2.4 Rodents

In contrast to foxes and cats, the size of the intracellular taurine pool of most animal species remains fairly constant even with significant reductions in dietary taurine content. Despite resistance to depletion, tissue taurine levels can be decreased by treatment of these animals with a taurine transport inhibitors, such β-alanine or GES, which interfere with taurine uptake by the tissues. However, Mozaffari et al. reported that GES treatment for 3 weeks resulted in the decrease in cardiac taurine content from 77 to 34 micromoles/g dry wet weight, while it did not affect myocardial contraction as assessed by perfusion technique (Mozaffari et al., 1986). Thus, although taurine depletion model induced by β-alanine and GES is a good model to analyze the physiological role of taurine deficiency, as described below, treatment of these animals with a taurine transport inhibitor does not generally cause sufficient taurine deficiency to promote the development of severe, overt pathology.

2.5 Taurine transporter knockout mice

Therefore, a more effective means of producing taurine deficiency in rodents is the formation of taurine transporter- (TauT-) null animals. Recently, transgenic mice lacking TauT gene have been generated by us and the other group. A variety of disorders have been reported in various tissues, such as eye, kidney, heart, muscle and so on, accompanied with drastic taurine deficiency in TauTKO mice (Heller-Stilb et al., 2002; Warskulat et al., 2007).

We demonstrated that taurine influx was eliminated in the cells isolated from TauTKO mice, indicating loss of taurine transport activity in TauTKO mice (Ito et al., 2008). Tissue taurine level is severely decreased in several tissues. Especially, cardiac taurine could not be detected in TauTKO mice, and skeletal muscle taurine level is decreased by 96% in TauTKO mice compared with wild-type mice. Then, we determined the cardiac phenotype of TauTKO mice. TauTKO mice exhibited a decrease in heart weight concomitant with a lower body weight than their control littermates. According to histological analyses, it was found that the ventricular wall was thinning and the ventricle lumen was dilated in the TauTKO heart compared to their wild-type littermates (Fig. 2). Moreover, the size of cardiomyocyte was markedly decreased in the TauTKO heart, indicating cardiac atrophy in TauTKO mice. Based on echocardiographic analysis, ejection fraction was diminished in the old TauTKO mice, indicating that cardiac function was eventually compromised in the TauTKO mice. Moreover, detailed functional analysis on Langendorff perfused heart also demonstrated the age-dependent cardiac dysfunction, such as a decrease in peak positive dp/dt and an increase in negative dp/dt as well as decreased ejection fraction in TauTKO mice (unpublished data). It is well established that the expression of fetal genes, including atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and β-myosin heavy chain (β-MHC), is reactivated in heart failure (Rajabi et al., 2007). These cardiac failure markers were significantly elevated in TauTKO mice. Consistent with the cardiac function, the inductions of these genes were more significant in the old TauTKO mice. Thus, these data indicate that knockout of the TauT gene leads to an age-dependent DCM. Furthermore, in contrast to the orderly myofibrillar architecture present in wild-type cardiac muscle, electron microscopy revealed pronounced myofibrillar fragmentation, disruption of the outer mitochondrial membrane and cellular vacuolization in TauTKO hearts.

On the other hand, in another TauTKO model reported by Warskulat et al., TauTKO mice exhibited a largely normal phenotype under both control and stimulated conditions, as assessed by magnetic resonance imaging, echocardiography, and isolated heart studies (Warskulat et al., 2004). Only vasodilation was enhanced in isolated perfused TauTKO hearts during dobutamine stimulation. A possible reason for the inconsistent results between two TauTKO models is the difference of genetic background, since difference of inbred strains affects the cardiovascular phenotypes and susceptibilities against pathological stressors in mice (Barrick et al., 2007; Deschepper et al., 2004). Meanwhile, Warskulat et al. also reported that biomarker genes for heart failure, including ANP, BNP and a cardiac ankyrin repeat protein (CARP), are upregulated in TauTKO hearts, which is consistent with our TauTKO model (Warskulat et al., 2006). Furthermore, they also demonstrated that the TauTKO hearts showed a switch from α-actin 1 (skeletal muscle type, α- SKA) to α-actin 2 (smooth muscle type, α-SKA) expression. α-SMA is generally expressed in developing muscle cells, and α-SKA and α-cardiac actin (α-CAA) become upregulated and replace α-SMA during final steps of myogenesis (Tondeleir et al., 2009; Woodcock-Mitchell et al., 1988). Thus, it may be due to a reactivation of fetal gene program which is observed in pathologically hypertrophied or failing heart. Indeed, induction of smooth muscle actin has been reported in heart of DCM patients and in hypertrophied or failing heart in experimental animals. Therefore, they concluded that these hearts may be more susceptible to failure under further exogenous stresses.

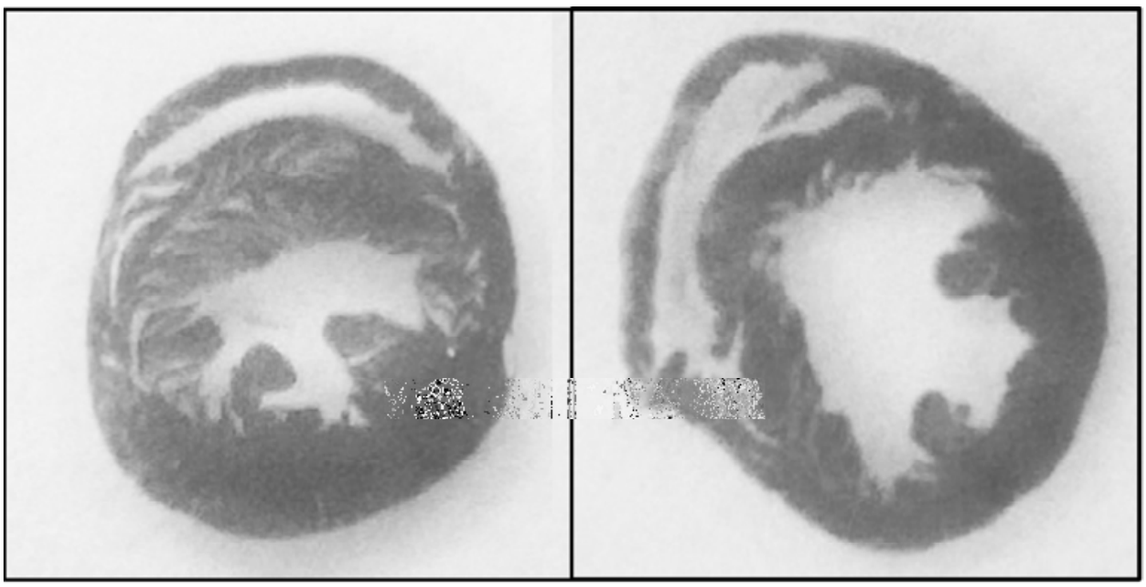


Fig. 2. Histological analysis of heart sections from WT and TauTKO mice. Heart sections were stained by hematoxylin-eosin staining method. Left: WT, Right: TauTKO. Thinning of the ventricular walls and septum and dilatation of the ventricular lumen are observed in the heart section of TauTKO mice. Ito et al. (2008)

3. Possible mechanisms for taurine depletion-related cardiomyopathy

3.1 Carbohydrate metabolism

Although the molecular mechanisms underlying the taurine depletion-related cardiomyopathy remain unclear, some potential mechanisms have been suggested.

Mozaffari et al. demonstrated that taurine depletion altered myocardial carbohydrate metabolism (Mozaffari et al., 1986). They identified that the major effect of GES treatment was stimulation in the rate of glycolysis and lactate production in rats. Furthermore, they found the activation of phosphofructokinase and a decrease in citrate in GES-treated hearts, which may relate to the activation of glycolysis. The authors concluded that taurine-depleted hearts exhibit abnormal energy metabolism and these changes may take on added importance in the stressed myocardium.

Furthermore, we reported that drug-induced taurine depletion of rat heart led to high energy phosphate metabolism due to the accumulation of free CoA, free carnitine and long-chain acylcarnitine, but a small decrease in long-chain fatty acyl-CoA (Harada et al., 1990).

Lomberdini reported the role of taurine depletion on the phosphorylation of specific protein in cardiac tissue. They demonstrated that 6-week treatment of GES in tap water increased in the phosphorylation of about 44kDa protein present in the mitochondrial fraction of the rat heart (Lombardini, 1996). Later, he identified that the 44kDa protein was pyruvate dehydrogenase which is responsible for transforming pyruvate into acetyl-CoA (Lombardini, 1998). This data suggest the role of taurine depletion in the carbohydrate metabolism through the regulation of pyruvate dehydrogenase activity. The reduction of this enzyme activity gives an explanation for the activation of lactate production in taurine-depleted hearts of GES-treated rats.

3.2 Electrophysiology and excitation-contraction coupling

Lake et al. reported the effect of GES-induced taurine depletion on electrophysiology (Lake et al., 1987). They identified an increase in the duration of ventricular action potentials in GES-treated rats and it accounted for the prolongation of QT interval by using electrocardiograms, suggesting the increased susceptibility against arrhythmias. Further, they have explored the idea that taurine deficiency may enhance vulnerability to arrhythmias in GES-treated rats operated with left coronary artery occlusion (Lake, 1992). As a result, they observed that taurine depleted animals had more and longer episodes of ventricular tachycardia and fibrillation, indicating that taurine deficient animals appear to be more susceptible to ischemia-induced arrhythmia.

Lake et al. also investigated the influence of taurine depletion to excitation-contraction coupling. They first identified that papillary muscle isolated from GES-treated rats generated tensions two third of control (Lake, 1990, 1992). Importantly, they observed small deficits in sensitivity to calcium and calcium recirculation through sarcoplasmic reticulum, but the magnitude of these change did not appear adequate to account for >40% loss in maximal calcium-activated force generation. Furthermore, Eley et al. reported that ventricular trabeculas from GES-treated rats exhibited the reductions in isometric twitch force, and demonstrated that substantial deficit in force development in taurine-depleted trabeculas was consistent with a reduced population of force generators and decreases in sarcomere proteins, but not intracellular calcium handling (Eley et al., 1994). Thus, they concluded that the inability of taurine depleted myocardium to generate the force is related to a loss of contractile proteins, which may be related to etiology of taurine depletion-related cardiomyopathy.

3.3 Osmoregulation

One of the most important biological actions of taurine is osmoregulation. In TauTKO models, compensatory induction of other organic osmolytes and osmotic stress related genes have been reported. Warskulat et al. found increases in the cytosolic concentration of various organic osmolytes, such as glutamine, alanine, glycine and glycerophosphorylcholine. Moreover, mRNA level of the system An amino acid transport protein was higher in the heart of TauTKO than of WT mice, concomitant with the increase in amino acids (Warskulat et al., 2004). Consistently, we also found increases in several genes responsive to osmotic stress, such as heat shock protein (Hsp70), amino acid transporters (Slc38a2, Slc38a4) and S100 calcium binding protein (S100A4), in TauTKO hearts (Ito et al., 2008), indicating the activation of some signal pathways responsible for regulating intracellular Osmotic balance. Thus, these data suggest that taurine depletion impairs the cellular osmotic balance, which, in turn, may activate the compensatory mechanism against osmotic stress.

Although the role of myocardial osmotic imbalance in etiology of cardiomyopathy is unknown, several possibilities are expected. First, it may be associated with ion movement in cardiac cells. When a cell is subjected to hyperosmotic stress, organic osmolytes, such as taurine, are accumulated, which minimizes the movement of water and the resulting decrease in cell volume. By contrast, hypoosmotic stress, which increases cell volume, leads to a loss of taurine and a decrease in intracellular osmolality. Although the regulatory volume change is usually transient, in the case of the cardiomyocyte of the TauTKO mouse there is a chronic decrease in cell volume. It is assumable that taurine depletion leads the

accumulation of intracellular electrolytes and results in the impairment of the cell volume regulation in cardiac muscles. It may be also associated with prolongation of the QT interval observed in GES-treated rats, as mentioned above. The role of osmoregulation in ion movement has been reviewed by Schaffer et al. (Schaffer et al., 2000).
Second, organic osmolytes have been reported to play as chemical chaperones in mammalian cells, while osmotic stress and the disturbance of ion balance also impair the membrane and protein stability (Howard et al., 2003; Yancey, 2005). Based on our electron microscopic analyses, a number of organelle collapses, such as myofibril and mitochondrial breakdowns were found in TauTKO hearts. Similarly, a decrease in contractile proteins has been observed in the heart of GES-treated rats. We assume that these findings are likely associated with the loss of macromolecular stability due to osmotic imbalance which is resulted from taurine depletion.

3.4 The role of taurine in Renin-angiotensin-aldosterone system

Renin-angiotensin-aldosterone system (RAAS) plays a crucial role in the development of heart failure through the cardiac remodelling, as well as an increase in body fluid and impairment of vascular function. We previously demonstrated that taurine treatment suppressed angiotensin II-induced hypertrophic responses, including an increase in surface cell area and an induction in hypertrophic marker genes, in the cultured cardiac myocyte (Azuma et al., 2000). Moreover, while angiotensin II induced apoptosis in the cultured cardiac myocyte, Schaffer et al. have demonstrated that taurine depletion by exposure to β-alanine enhanced the angiotensin-II induced apoptosis (Schaffer et al., 2003). They also demonstrated that this effect of taurine depletion was mediated by enhanced increases in Bax and c-Jun N-terminal kinase, which are proapoptotic proteins. These beneficial actions of taurine against angiotensin II may relate to taurine depletion-related cardiomyopathy. Furthermore, taurine might prevent angiotensin II-induced oxidative stress through the inhibition of NADPH oxidase. Grishko et al. has demonstrated that angiotensin II-induced cell death is associated with the ROS production through the activation of NADPH oxidase in the cultured cardiac myocyte (Grishko et al., 2003). Recently, Li et al. have reported that treatment with taurine prevented the cardiac myocyte from the apoptosis induced by phenylephrine (Li et al., 2009). They also found that taurine treatment suppressed the oxidative stress induced by phenylephrine through the inhibition of NADPH oxidase activation. Thus, it is assumable that inhibition of NADPH oxidase may be a critical pathway of the antiapoptotic effect of taurine against angiotensin II-induced cell apoptosis.
Further studies may provide key elements on the molecular mechanism of taurine depletion-related cardiomyopathy.

4. Pharmacological effects of taurine on cardiomyopathy and heart failure

4.1 Animal models

The useful effect of taurine against cardiomyopathy was firstly reported by McBroom and Welty in cardiomyopathic hamster BIO 14.6 (McBroom & Welty, 1977). They demonstrated that taurine treatment for 4 weeks decreased calcium overload in cardiomyopathic hamsters. Subsequently, Azari et al. examined the effect of taurine in controlling calcium overload and necrotic lesion severity in advanced stages of cardiomyopathy (Azari et al.,

1980). They demonstrated that oral taurine given for 1 month was effective in decreasing in cardiac calcium concentration and subsequent severity of lesion in myopathic hamsters.
Thereafter, we and others reported that taurine has protective activity against myocardial damage in experimental models caused by massive doses of isoproterenol or doxorubicin and by calcium paradox phenomenon. We demonstrated that oral administration of taurine in chick treated with toxic dose of isoproterenol suppressed the increased lipoperoxide and the decreased phospholipid (Ohta et al., 1988), suggesting that the beneficial effect of taurine may be due to inhibition of lipid peroxidation and calcium accumulation and due to protection against the deterioration of membrane phospholipids.
Furthermore, we reported the effect of taurine on doxorubicin-induced cardiotoxicity in mice (Hamaguchi et al., 1988). Taurine administration attenuated doxorubicin-induced biochemical alterations, such as the depletion of creatine phosphokinase, glutamic oxaloacetic transaminase and lactate dehydrogenase activities, in the myocardium. Moreover, taurine significantly improved the survival rate of the mice treated with doxorubicin.
Additionally, to confirm the effect of taurine against heart failure, we tested whether daily oral treatment with taurine had any effect upon the survival rate and hemodynamics in animal model for Chronic heart failure (CHF) induced artificially by aortic regurgitation (Azuma et al., 1985b; Takihara et al., 1986). Cumulative mortality rate at 8 weeks following aortic regurgitation was 10% in taurine treated rabbits compared with 53% in non-treated rabbits. On the hemodynamic study, the mean value of max dP/dt was significantly decreased in rabbit with aortic regurgitation without taurine. Taurine produced a marked increase in max dP/dt compared to non-treated animals, indicating that taurine improved the contractility in heart failure. Therefore, we concluded that taurine prevents the rapid decline of CHF and consequently prolongs the life expectancy.

4.2 Clinical studies

In 1974, Huxtable and Bresseler have reported that the left ventricular taurine content in patients who died of CHF was twice that in patients who died of other causes and had no cardiac pathology (Huxtable and Bressler, 1974). Subsequently, increased myocardial taurine content has been also reported in experimental animals with heart failure. It is still unclear whether the increase in myocardial taurine is causal factor in heart failure or whether this is secondary to factor related to the disease process, such as compensatory mechanism. Based on the concept of replacement therapy for deficiency symptom, such as hormone or vitamin, administration of taurine to patients with heart failure was not accepted around that time in Japan. However, since many evidence has been accumulated to show that taurine exerts various beneficial actions, including positive inotropic activity, and is useful to animals with cardiomyopathy, as described above, we dared to test the effect of taurine in patients with CHF. In 1982-1992, we have reported some clinical studies in which we evaluated the usefulness of taurine administration in the treatment of CHF.
Firstly, we have observed that the administration of taurine to the patient suffering from CHF alleviated their physical signs and symptoms (Azuma et al., 1982; Azuma et al., 1983). In open pilot study, the clinical efficacy of oral taurine administration was studied in 24 patients with CHF (New York Heart Association (NYHA) functional class; II-IV) as a result from various heart diseases, including congenital heart failure, acquired valvular disease, cardiomyopathy, ischemic heart diseases and hypertension heart diseases. The severity of

heart failure was scored based on the clinical signs (diastolic gallop rhythm, pulsus alternans, positive hepatojugular reflex, pulmonary crackles, neck vein distension, hilar congestion on chest x-lay film, cardiomegaly on chest x-lay film, pleural effusion, peripheral edema, ascites, decreased urinary output, tachycardia and weight gain) and symptoms (orthopnea, paroxysmal nocturnal dyspnea, dyspnea on exertion, fatigue, anorexia, nausea, vomiting, and palpitation) and on roentgenographic data. The benefit for taurine treatment in patients was estimated by the difference between their pretreatment and post-treatment scores. In 19 of 24 patients taurine administration for 4 weeks improved the severity of CHF. Moreover, 13 of 15 patients who were designated as NYHA class III or IV before receiving taurine were designated as NYHA class II after they completed the study.

Subsequently, we conducted another clinical study to elucidate whether oral administration of taurine to conventional management could improve the systolic time intervals in 14 patients with CHF by a placebo-controlled, double blind, crossover method (Azuma et al., 1985a; Azuma et al., 1985b). As well as prior clinical study, the effect of taurine was observed in improvement of the NYHA class, pulmonary crackles and chest-film abnormality, and was superior to placebo. Importantly, pre-ejection period index was reduced after 4 weeks of treatment with taurine, indicating the improvement of left ventricular function. Thus, these studies have confirmed the clinical usefulness of taurine in CHF.

Furthermore, in an attempt to further clarify the effect of taurine on CHF and to define its clinical position as the therapeutic agent for heart failure, we conducted a double-blind comparative study using coenzyme Q10 as a control agent (Azuma et al., 1989; Azuma et al., 1992). In this study a total of 158 patients from 26 hospitals were randomized, and finally 138 patients were divided three treatment groups; daily dose of taurine 3g, taurine 6g and coenzyme Q10 30mg. Taurine were given orally daily for 8 weeks and the patients continued to receive their prescribed conventional drugs. Improvements of NYHA functional classes were observed both of 3 groups. Moreover, significant improvements compared with baseline were noted in the severity of the objective signs, including hepatomegaly and edema in 3 groups. However, no significant differences were observed in the changes of NYHA class and objective signs. We also tested the effect of taurine on the left ventricular performance using echocardiography, and significant improvements were also noted in the parameters of cardiac output in the taurine 3g group; systolic volume, cardiac output, ejection fraction (EF) and mean velocity of circumferential fiber shortening (mVcf) in the taurine 6g group, whereas coenzyme Q10 possessed no such pharmacological activity. Thus, this study confirms that the therapeutic effects of taurine compare favorably to CoQ10. Moreover, only 3.8% of patients treated with 6g of taurine experienced minor problems, including slight anorexia and soft feces, indicating the safety of taurine.

These studies illustrated that taurine is an effective agent for the treatment of heart failure without any adverse effects. Nowadays, powder of taurine is clinically used for patients with CHF in Japan.

Since RAAS plays a central role in the pathology of CHF and taurine antagonizes against angiotensin II-induced cell damage in vitro studies, as described above, a systemic clinical study is necessary to evaluate the benefit of taurine against RAAS in future.

5. Conclusion

In this chapter, we reviewed 1) the taurine depletion-related cardiomyopathy in cats, foxes, dogs, and genetically engineered mice lacking taurine transporter and 2) the

pharmacological benefit of taurine in patients and experimental animal models with heart failure. In these animals, it is apparent that taurine deficient diet causes taurine depletion in plasma and heart, which in turn leads to cardiomyopathy. Urinary taurine concentration in human, which can represent the amount of taurine intake, varies by more than 10 times among individuals; therefore, taurine depletion may also occur in human. Although taurine depletion-related cardiomyopathy has not been reported so far, taurine deficiency should be considered as a potential pathogenesis of heart failure and/or cardiomyopathy. Meanwhile, whereas myocardial taurine content is increased in failing heart, taurine administration is "paradoxically" useful to patients with heart failure. Since an increment of myocardial taurine may be due to the activation of active transport of taurine, taurine supplementation might be necessary for some patients with failing heart as compensatory mechanism to maintain the cardiac function. To verify the unsolved problems, the physiological role of taurine in heart must be fully clarified.

It should be noted that the increasing rate of plasma taurine concentration after taurine administration varies widely among individuals (Brons et al., 2004). Additionally, there may be some genetic polymorphisms of taurine transporter which affects the taurine transport activity in human genome. Now it is well known that polymorphisms influence disease risk, drug efficacy and side-effect. Therefore, we suppose that the genetic polymorphisms of taurine transporter or the other molecules involved in the kinetics of taurine may contribute to the variation of plasma and tissue taurine concentrations. Thus, it will be plausible to find out the genetic polymorphisms which determine the variation of tissue taurine content and the rate of rise in plasma taurine after taurine administration, which will help us elucidate the role of taurine deficiency in the etiology of human cardiomyopathy.

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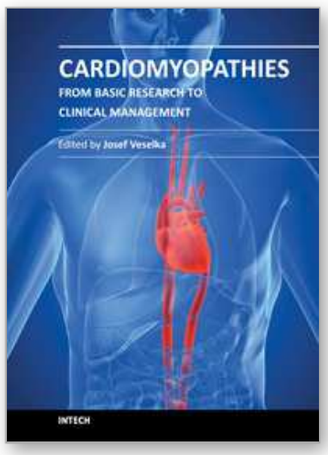
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Cardiomyopathy means "heart (cardio) muscle (myo) disease (pathy)". Currently, cardiomyopathies are defined as myocardial disorders in which the heart muscle is structurally and/or functionally abnormal in the absence of a coronary artery disease, hypertension, valvular heart disease or congenital heart disease sufficient to cause the observed myocardial abnormalities. This book provides a comprehensive, state-of-the-art review of the current knowledge of cardiomyopathies. Instead of following the classic interdisciplinary division, the entire cardiovascular system is presented as a functional unity, and the contributors explore pathophysiological mechanisms from different perspectives, including genetics, molecular biology, electrophysiology, invasive and non-invasive cardiology, imaging methods and surgery. In order to provide a balanced medical view, this book was edited by a clinical cardiologist.

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