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COMMENTARY

TAURINE AND CARDIAC PHYSIOLOGY

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This review will be concerned principally with a discussion of taurine and its influence on skeletal and cardiac muscle physiology, its relationship to cardiac pathology and its potential importance in the pharmacology of the heart. An exhaustive review of the literature pertaining to taurine has not been attempted. Instead our intention is to provide an overview of the current understanding of taurine metabolism and its proposed physiological functions and to indicate the directions currently being followed by investigators in this field.

Taurine, 2-aminoethanesulfonic acid (H_2NCH_2-CH_2SO_3H), is a sulfonic acid analogue of β-alanine. It is found in all animal species as a free amino acid, but occurs to only a limited extent in plants, primarily in lower forms [1]. The single clearly defined function of taurine in animals is the formation of bile salts in certain mammalian species which serve as emulsifying agents in the gut and thus facilitate lipid digestion [2].

Taurine was first identified as a component of ox bile [3], hence the name. In mammals, taurine is present in all tissues of the body with skeletal muscle accounting for 75 per cent of the body stores [4]. In addition to skeletal muscle, the heart, brain and spleen also contain high concentrations of taurine [1]. As much as 50 per cent of the free amino acid content of the dog [5] and rat [6, 7] heart consists of taurine. The taurine content of skeletal muscle, heart and brain of a few representative species in μmoles/g wet weight is as follows (taken from Jacobsen and Smith [1]; Huxtable and Bressler [8, 9] and unpublished data from this laboratory):

Skeletal muscle: man, 5; rabbit, 5; rat, 14; guinea pig, 9; cat, 4.5
Heart: man, 5.6; rabbit, 11; rat, 28; guinea pig, 12; dog, 16
Brain: man, 5; rabbit, 2; rat, 3; guinea pig, 2; cat, 2; dog, 2
Liver: man, 1.8; rabbit, 0.5; rat, 5

The taurine content of the liver approximates that of other tissues of the body. Even though large amounts of free taurine have long been known to exist in the skeletal muscle, heart and brain, a distinct role for this compound in the physiology of these, or any other tissue, has yet to be described. It has only been in recent years that any concerted effort has been expended in an attempt to understand the influence of taurine on the physiology and metabolism of excitable tissues.

Marine invertebrates also possess large concentrations of taurine in nerve and muscle tissue [10]. In a number of species, taurine, in conjunction with other amino acids, is believed to aid in the maintenance of the intracellular ionic balance and in the regulation of intracellular osmotic pressure. Tissues of marine animals have been found to possess concentrations of taurine as much as three times greater than the concentrations found in tissues of mammals [1, 10]. The ionic composition of muscle of both marine and terrestrial animals is similar. This has suggested to some that an optimal intracellular ionic environment required for proper muscle function has been adopted universally [10]. Due to the nature of their habitat, marine species necessarily require a means of regulating ionic balances different from that of non-marine organisms. Many have adapted to the use of amino acids as osmoregulatory agents. Taurine appears to be more widely utilized for this purpose than other amino acids based on its generally greater abundance in many marine organisms.

Recent investigations suggest a physiological role for taurine in the maintenance of excitatory activity in muscle and nervous tissue of mammals. The high concentration of taurine in brain [1, 11, 12] and its reported ability to alter nervous system functions [13–17] has led to speculation that taurine may act as an inhibitory neurotransmitter [13, 16]. More recent studies demonstrating effects on behavioral activity in mice [18] and axonal membrane physiology [19, 20] also point to a neuroaffector role for taurine. A recent review by Barbeau *et al.* [21] discusses the neuropharmacology of taurine. The ability of taurine to modify electrophysiological parameters of skeletal muscle [20, 22, 23] and cardiac muscle [24–28], as well as ion permeabilities of skeletal [22] and cardiac muscle [27, 29, 30], is interpreted as evidence that taurine may be an important physiological regulator in muscle tissue as well.

CARDIAC AND SKELETAL MUSCLE PHYSIOLOGY

Interest in the study of taurine and its physiological actions has been stimulated in recent years by the observations that cardiac taurine levels are elevated in states of cardiac pathology [8, 9] and urinary taurine excretion is elevated in muscular dystrophic conditions [31, 32].

Evidence is accumulating which implicates intracellular taurine with the regulatory processes responsible for controlling ion fluxes into and out of excitable tissues such as muscle and nerve. Read and Welty [24] first suggested that taurine might influence cardiac activity by affecting ion movement. Their conclusions were based on the mitigating actions of taur-

ine toward epinephrine- or digoxin-induced arrhythmias. These same investigators [25, 26] later reported that taurine reversed the loss of K^+ from dog heart evoked by epinephrine. Strophanthin-K elicits a positive inotropic response in the isolated, perfused, guinea pig auricle without affecting the heart rate [27]. Taurine potentiates this response while having no demonstrable action in the absence of glycoside. Taurine was also shown to be effective in reversing abnormal ECGs of dog and guinea pig heart brought on by perfusion with either strophanthin-K of K^+-free medium [28]. In fibrillating hearts perfused with K^+-free medium, the addition of K^+ (2.8 mM) and taurine (8 mM), but not K^+ alone, eliminated the fibrillation. The effects of taurine on ECG parameters in the presence of strophanthin-K and low potassium are evidence for a protective action by taurine on the heart through regulation of cell permeability to potassium. It is interesting to note that homotaurine, 3-aminopropanesulfonic acid ($H_2NCH_2CH_2CH_2SO_3H$), exhibited no tendency to alter cardiac activity [27].

The nature of the inotropic response of the heart to ouabain has been demonstrated to be a species-dependent phenomenon [29]. Perfusion of isolated guinea pig or rat heart with ouabain (1.7 mM) in the presence of taurine (8 mM) increased the contractile response in the former, but decreased it in the latter. Contractility of hearts of both species is reduced when perfused with low calcium medium ($Ca^{2+} = 0.14$ mM). Addition of taurine stimulated the guinea pig heart to contract with near normal strength, but further suppressed contractility of the rat heart. The response to ouabain perfusion in low Ca^{2+} medium was qualitatively similar to the effects of taurine in both species. When perfused together the actions of taurine and ouabain were additive. Taurine also manifests a protective action on the contractility of the guinea pig heart perfused with a Ca^{2+}-free medium [30]. Contractile force was greater and maintained for a longer period of time in the presence of taurine. Kinetic analysis of Ca^{2+} washout from the perfused heart identified three compartments of exchangeable Ca^{2+}, one being identified as the vascular space and a second representing the intracellular Ca^{2+} pool. A third was characterized by a constant exchange rate and presumably represents Ca^{2+} located in the sarcoplasmic reticulum. Taurine reduced the rate of Ca^{2+} efflux from the rapidly exchangeable pools and increased the total calcium content of each compartment.

Recent reports have demonstrated an effect by taurine on calcium metabolism in subcellular components. It stimulates Ca^{2+} uptake and (Ca^{2+}–Mg^{2+})-ATPase activity of sarcoplasmic reticulum (SR) isolated from rat skeletal muscle [22] at the same time total Ca^{2+} bound to SR is increased. Incorporation of taurine in the medium during isolation increased the yield of SR. Homotaurine also enhanced uptake of Ca^{2+} and (Ca^{2+}–Mg^{2+})-ATPase activity. In a study utilizing rat liver mitochondria as a model system, taurine was reported to alter the rate of uptake of Ca^{2+} and total Ca^{2+} bound by the organelles [33]. Calcium-activated respiration was inhibited by taurine and by isethionic acid, 2-hydroxyethanesulfonic acid ($HOCH_2CH_2SO_3H$). Isethionic acid also increased Ca^{2+} uptake and binding by the mitochondria. This latter observation is of interest in view of the suggestion by Read and Welty [24] that a metabolite of taurine such as isethionic acid may have been responsible for the changes observed in ECGs of dogs pretreated with taurine. These findings must be considered whenever a mechanism for taurine effects on ion permeabilities of membranes is discussed. A detailed study of the influence of taurine on ion translocation in mitochondria may provide insight into its actions on other membrane systems.

Excitation-contraction coupling in neuromuscular preparations appears to be influenced by taurine [23]. Hyperpolarization of the resting potential of frog skeletal muscle (11.4 per cent more negative than control) and rat skeletal muscle (3.5 per cent more negative than control) was observed in the presence of taurine. Furthermore, isolated muscle of rats pretreated with taurine for 14 days prior to testing exhibited an 11 per cent reduction in action-potential duration, an increase of 23 per cent in input resistance, an increase of 11 per cent in depolarization rate and an increase in repolarization rate of 19 per cent. No changes in overshoot or threshold potentials were observed. Miniature end-plate potential (MEPP) frequency was higher in isolated frog muscle, but not in rat muscle, incubated in the presence of taurine. Muscle from taurine-loaded rats did exhibit an increase in MEPP frequency, however. The distribution of the amplitudes of MEPPs was shifted to slightly higher values in superfused frog and taurine-loaded rat muscle, but not in superfused rat muscle. The investigators interpreted their data as demonstrating a substantial postsynaptic action by taurine, indicated by the alteration of parameters describing the action potentials of the neuromuscular preparation, but only a limited presynaptic action, as indicated by the small changes in MEPP frequency and amplitude distribution. It was concluded that these effects demonstrate a membrane-stabilizing action of taurine by virtue of modifications in cell membrane permeability to ions. Furthermore, it was suggested that the ability of taurine to alter ion permeability of the cell membrane might explain the reversal of digoxin-induced arrhythmias observed by Read and Welty [24]. The resting potential, membrane resistance and action potential of the lobster axon also exhibit a sensitivity to taurine [19, 20]. The responses observed were explained on the basis of the ability of taurine to alter the permeability of the cell membrane to ions in a manner similar to that of muscle.

Thus far, taurine has been demonstrated to stabilize abnormal ECGs caused by cardiac glycosides [24, 25, 27, 28], to reverse the negative inotropic effects of perfusion with low Ca^{2+} medium [27, 30] and to restore the epinephrine- and digoxin-induced loss of K^+ from the heart [25]. It also alters membrane permeabilities to Ca^{2+} [22, 23] and K^+ [19, 20, 25]. Criticism has recently been made of the interpretations placed on the purported mitigating actions of taurine on drug-induced abnormal ECGs [34]. Only detailed study of the degree to which differences in species, drugs and experimental procedure might contribute to variations in the nature of the observed effects of taurine on cardiac physiology can resolve the questions which have been raised. Even

with these questions much evidence now exists for a direct action by taurine on the control of ion fluxes in the heart, skeletal muscle and nervous tissue. Its effects on the lobster axon are of interest in view of the suggestions that taurine may be an inhibitory neurotransmitter [13, 16]. To what extent the effects on Ca^{2+} transport are interrelated with K^+, Na^+ and Cl^- transport and the electrophysiology of the heart is unknown.

CARDIAC PATHOPHYSIOLOGY AND TAURINE

The taurine content of the heart is elevated in various states of natural and experimentally induced cardiac pathophysiology. Spontaneously hypertensive rats have a greater concentration of taurine in the heart than does heart tissue of animals of the parent strain [9]. The hypertrophied hearts, but not skeletal muscle or brain, of stress-induced hypertensive rats have greater concentrations of taurine than do hearts of unstressed controls [9]. Cardiac hypertrophy resulting from isoproterenol administration is also accompanied by an elevation of taurine [35, 36].

In dogs [5], the precipitation of congestive heart failure by pulmonary artery stenosis causes a dramatic increase in taurine concentration (μmoles/g dry weight) in the right ventricle: experimental, 126 ± 10 (mean $\pm$ S.E.M.); controls, 32.8 ± 3.4 ($P < 0.01$). Taurine content of the left ventricle was unchanged: experimental, 34.4 ± 4.6; control, 32.7 ± 3.6. With the exception of methionine and valine, which were also elevated in the right ventricle of dogs in the experimental group, no significant changes in other amino acids were observed in this study. Plasma levels of all the amino acids remained unchanged. Since taurine is not incorporated into protein, these data imply that taurine transport or synthesis in the failing heart has been modified. In humans, the left ventricle of patients who had died of congestive heart failure was found to contain much greater concentrations (μmoles/g wet weight) of taurine, 11.7 ± 1.5 (mean $\pm$ S.E.M.), than left ventricular tissue of persons having died of causes unrelated to cardiac dysfunction, 5.6 ± 0.5 ($P < 0.001$) [8]. No difference was observed in aortic tissue from the same patients, 1.6 ± 0.1 vs 2.1 ± 0.4 in patients dying of heart failure. It was also reported that patients with a history of hypertension had increased taurine in the left ventricle, normotensives, 4.84 ± 0.51 vs 8.14 ± 1.08 for hypertensives ($P < 0.01$).

To speculate on a cause–effect relationship between cardiac pathology and elevated taurine levels in the heart would be premature. However, in view of the apparent effects of taurine on ion permeabilities of cell membranes of excitable tissues and its mitigating actions on drug-induced aberrations in electrophysiological parameters of the heart, the possibility exists that the changes in cardiac taurine may reflect an attempt by the system to re-establish homeostasis in the stressed organ. The final word on this subject must await a definitive demonstration of the ability of taurine to affect cardiac physiology through changes in mechanisms which control transmembrane ion movement, exchange of ions between intracellular pools, localization of intracellular ion pools or by direct influence on the contractile apparatus itself.

BIOCHEMISTRY AND METABOLISM

Progress in describing a physiological role for taurine in the heart has been hindered by the absence of a means of manipulating endogenous cardiac taurine levels. The bulk of the taurine fed to animals is rapidly excreted unmetabolized [12]. That portion retained by the body is only slowly metabolized [12]. Attempts to alter the taurine content of the heart by fasting [4], taurine loading [12], feeding a taurine-deficient diet [12] or feeding a vitamin B-6-deficient diet [12, 37] have all proved unsuccessful.

Tissues of the rat can be placed into two groups on the basis of radioactive taurine uptake after a single injection of tracer quantities of the compound [12, 38, 39]. For most tissues the uptake and washout of label reflect the changing levels of radioactivity in the blood. Maximum uptake occurs within hours of injection followed by a rapid washout. Skeletal muscle, heart and brain, however, accumulate radioactivity at a much lower rate. The maximum amount of label in these tissues appears from 3 to 5 days after the single injection, reflecting a redistribution of label from other organs of the body. The loss of radioactivity from these tissues is correspondingly slow. On the basis of these observations, it becomes apparent why dietary manipulation is ineffective in altering cardiac taurine levels.

The biosynthesis of taurine from cysteine has been well characterized in rat liver [1]. Synthesis of taurine in cardiac tissue is poorly understood, but does not seem to occur by the same pathways operative in the liver [40, 41]. The rat [40, 41], dog [40] and cat [40] heart, and human [40] and cat liver [40] lack the enzymes necessary for converting cysteine to taurine by the same routes identified in the rat liver (Fig. 1).

In rat liver, cysteine is oxidized to cysteine sulfinic acid [42] which may then be decarboxylated [43] to hypotaurine followed by oxidation to taurine (I). Alternatively, cysteine sulfinic acid may be oxidized to cysteic acid [44], which is then decarboxylated to yield taurine (II). The decarboxylation of both cysteine sulfinic acid and cysteic acid is believed to be catalyzed by the same enzyme, L-cysteine sulfinate decarboxylase, a pyridoxal phosphate-requiring enzyme

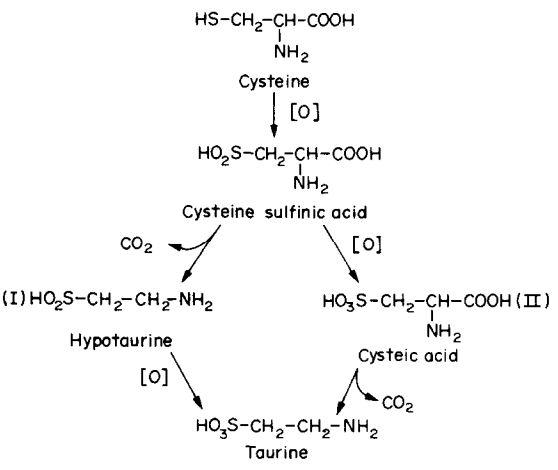

Fig. 1. Metabolism of cysteine to taurine and isethionic acid.

[40, 45, 46] which is two to eight times more active toward cysteine sulfinic acid than cysteic acid [40]. Available evidence indicates that the preferred pathway in the liver is via hypotaurine [43, 44] though the oxidation of hypotaurine to taurine is poorly understood. The soluble portion of a cell-free extract of rat liver will catalyze this latter reaction in the presence of NAD [47]. A further metabolism of taurine to isethionic acid *in vitro* has been reported to occur to a limited extent in dog heart [48, 49] and rat brain [50]. Radioactive isethionic acid has also been found in a number of organs from rats injected with radioactive taurine [51].

Cardiac taurine levels are not altered by the administration *in vivo* of potential metabolic precursors such as cysteine sulfinic acid, cysteic acid or hypotaurine [52], in marked contrast to the elevation seen in liver and other tissues under the same conditions [1, 52]. This lends support to the observations that taurine is not synthesized directly from cysteine in the heart as it is in liver and brain.

A potential alternative source of taurine in the heart is 2-mercaptoethylamine (MEA). The enzymatic conversion of MEA to taurine was first reported in equine kidney [53]. Since then, homogenates of the rat, mouse, guinea pig and beef hearts have been shown to convert MEA to hypotaurine and taurine [54]. Tissues of rat, mouse and guinea pig take up [^{35}S]-MEA from the blood [52]. A portion of the radioactivity extracted from each organ was identified as taurine [52]. The injection of [^{35}S]-cystine into rats results in the appearance of [^{35}S]-MEA and [^{35}S]-taurine in a number of tissues [52]. Over 60 per cent of the radioactivity in leg muscle, heart and lung was identified as taurine and approximately 10 per cent as MEA 20 hr after injection of [^{35}S]-cystine. These findings were offered as support for the hypothesis that taurine may be synthesized from cysteine via MEA. It was proposed that cysteine conversion to MEA was followed immediately by oxidation to taurine to explain the low ratio of MEA to taurine found in the tissues. The study was done *in vivo*; therefore, the possibility exists that cysteine was metabolized in the liver or other organs and the resultant MEA and/or taurine transported to the heart. Cystine, MEA and taurine are all taken up by heart, although the uptake of taurine is slow [4, 12]. The amount of [^{35}S]-taurine found in the heart after [^{35}S]-cystine administration *in vivo* [52] might be accounted for on the basis of taurine uptake from the blood [12] after synthesis from cysteine by an extra-cardiac source. A rigorous study of the kinetics of appearance of [^{35}S]-cysteine, [^{35}S]-MEA and [^{35}S]-taurine in the heart must be made before it can be concluded that cysteine is metabolized in cardiac tissue to MEA which then may give rise to taurine. Among the difficulties inherent in such a study is the absence of a reliable analytical method for MEA.

A "cysteine decarboxylase" activity has not been identified in heart or any other tissue which might account for the direct conversion of cysteine to MEA. An indirect means of generating MEA from cysteine would be possible by first synthesizing Coenzyme A (CoA) or pantetheine [55]. The MEA moiety of pantetheine and CoA is supplied by cysteine enzymatically linked to 4-phosphopantothenic acid by an amide bond [56] (Fig. 2). The 4-phosphopantothenylcysteine thus formed is then decraboxylated by a non-pyridoxal phosphate-dependent decarboxylase [57] to yield 4-phosphopantetheine which, in the presence of ATP, is converted to dephospho-CoA. The enzymatic hydrolysis of CoA to pantetheine and 3′,5′-dephosphoadenosine by a membrane-bound pyrophosphatase has been characterized [58]. The cleavage of pantetheine to pantothenic acid and cysteamine by pantethinase has been reported in the kidney [55]. It has been suggested that the degradation of CoA might provide substrate quantities of MEA for conversion to taurine [55]. Insufficient information is available regarding the turnover rate of CoA to allow a critical evaluation of the hypothesis that CoA or pantetheine serves as the source of MEA for taurine biosynthesis in the heart.

The biosynthesis of taurine from inorganic sulfate in chick [59] and rat liver [60] has been postulated. Incorporation of inorganic sulfate into an organosulfur compound with a carbon–sulfur covalent bond is unknown in mammalian systems. Historically, sulfate metabolism in mammals has been believed to be confined to sulfate ester formation in conjugation and detoxification reactions and to liberation from organosulfur compounds as a final step in their utilization [2, 61]. Serine has been proposed as the organic acceptor of inorganic sulfate for synthesis of taurine [62]. Sulfate is believed to be activated by formation of 3′-phosphoadenosine-5′-phosphosulfate

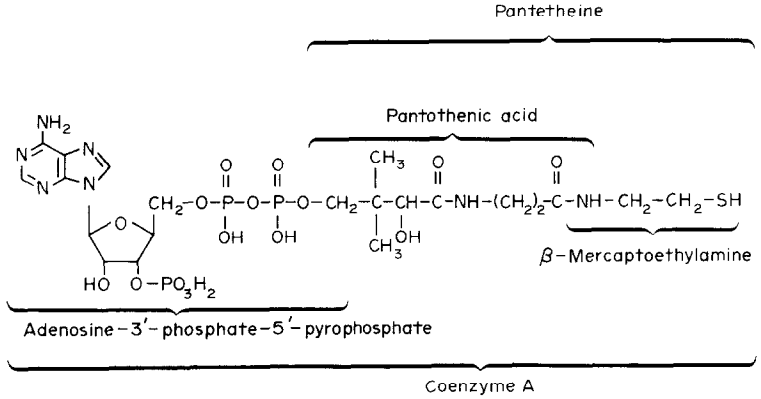

Fig. 2. Coenzyme A.

(PAPS) from which the sulfate is transferred to a dehydrated serine intermediate, e.g. α-aminoacrylic acid. The resultant sulfonic acid would then be decarboxylated to yield taurine. This mechanism is analogous to that proposed for the formation of the sulfolipid 6-sulfoquinovose in Euglena [63].

Because of the novel nature of this proposed biosynthetic pathway for mammalian systems, more rigorous criteria than that of chromatographic mobility must be utilized for the demonstration of incorporation of $[^{35}S]$-$SO_4^=$ activity into taurine. For instance, the radioactive sulfur-containing moiety in the material which co-chromatographs with taurine must be demonstrated to be non-hydrolyzable to eliminate the possibility that sulfate esters are being formed in this system. Should further investigation substantiate these preliminary observations, a unique metabolic pathway for sulfur metabolism in mammals would have been described. This could be of great importance for the understanding of taurine metabolism in tissues, such as the heart, which do not appear to possess the traditional routes for taurine synthesis from cysteine.

SUMMARY

Taurine is a ubiquitous amino acid in the animal kingdom. It is found widely throughout the body and in particularly high concentrations in excitable tissues. In spite of its prevalence, no specific physiological function has been ascribed to taurine in mammals aside from its well characterized role in bile salt formation in some species. Available evidence implies that taurine may serve a homeostatic function in excitable tissues such as nerve and muscle by stabilizing membranes in these tissues through the regulation of cell membrane permeability to ions. Taurine influences K^+, Cl^- and Ca^{2+} translocation in nerve, skeletal muscle and heart. It mitigates drug-induced abnormalities in the electrocardiograms of the heart and has been found in higher than normal amounts in states of cardiovascular pathology, i.e. congestive heart failure and hypertension in man, spontaneous and stress-induced hypertension in rats and cardiac hypertrophy in dogs and rats. Because of the lack of information concerning the metabolism of taurine by the heart and the inability of investigators to modify cardiac taurine levels *in vivo*, no cause and effect relationship can yet be proposed between altered cardiac taurine levels and naturally occurring states of cardiac pathology.

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