Plasma Taurine Concentrations in Normal Dogs and in Dogs With Heart Disease

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Plasma taurine concentrations were determined in 76 dogs with dilated cardiomyopathy (DCM), 28 dogs with acquired valvular disease (AVD), and 47 normal (control) dogs. The data were collected at 2 referral centers, The Animal Medical Center, New York, NY (AMC), and the University of California, Davis (UCD), and the studies were conducted independently. Different anticoagulants (sodium citrate at AMC and lithium heparin at UCD) were used to collect the plasma samples. Paired analysis of samples showed a significant difference in plasma taurine concentrations, depending on the anticoagulant used. Consequently, results from each clinic were analyzed separately. Plasma taurine concentrations were significantly higher in dogs with AVD (median, 133 nmol/mL; range, 25 to 229 nmol/mL) than in control dogs (median, 63 nmol/mL; range 44 to 224 nmol/mL) and dogs with DCM (median, 72 nmol/mL; range, 1 to 247 nmol/mL) at AMC ($P < .001$). The number of dogs with AVD at UCD was too small to draw meaningful conclusions. At UCD, the median plasma taurine concentration was 98 nmol/mL (range, 28–169 nmol/mL) in dogs with AVD, 75 nmol/mL (range, 0.1–184 nmol/mL) in dogs with DCM, and 88 nmol/mL (range 52–180 nmol/mL) in control dogs. There were no significant differences in plasma taurine concentrations between dogs with DCM and the control dogs at either hospital. Congestive heart failure and administration of cardiac medication had no significant effect on plasma taurine concentrations. Plasma taurine concentration was low (<25 nmol/mL) in 17% (13/76) of the dogs with DCM. Seven of the 13 dogs with low plasma taurine concentrations were Cocker Spaniels or Golden Retrievers. It was concluded that most dogs with DCM do not have low plasma taurine concentrations. However, certain breeds or individual dogs may have low plasma taurine concentrations in association with DCM. Whether this association is causal or not is unknown. The significance of the high plasma taurine concentrations in dogs with AVD is also unknown.

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Taurine (2-aminoethane sulfonic acid) is the most abundant free amino acid in the mammalian heart, composing more than 40% of the free amino acid pool in the normal dog's heart and more than 60% of the free amino acid pool in the heart of dogs with experimentally induced right ventricular hypertrophy and heart failure.[1] Its biochemical roles are not well defined and may vary in different tissues.[2] Investigators have shown multiple cardiac effects for taurine, including positive and negative inotropic,[3] antiarrhythmic,[4] arrhythmogenic[5] properties; enhanced sarcolemmal calcium binding and transport[6,7]; carbohydrate metabolism alterations[8]; and osmotic regulation.[9] The high myocardial taurine concentration is maintained by active transport.[10,11] Increases in myocardial taurine concentration have been reported in humans with congestive heart failure,[12,13] in rats with isoproterenol-induced cardiac hypertrophy,[14] and in dogs and rabbits with experimentally produced congestive heart failure.[1,15,16]

Low plasma taurine concentration has been associated with reversible myocardial failure in cats.[17,18] Subsequent to this finding, taurine was added to many commercial cat foods, leading to a marked reduction in the prevalence of feline dilated cardiomyopathy (DCM).[19,20] Experimentally, taurine-depleted diets resulted in reduced left ventricular systolic function, with secondary eccentric hypertrophy in 30% of cats studied.[21,22] The possibility that taurine deficiency might be associated with heart disease in species other than the cat was suggested by a report correlating DCM and low plasma taurine concentrations in foxes.[23]

Because the above studies showed significant associations between taurine concentrations and cardiac function in cats and foxes with DCM, we initiated a study to evaluate plasma taurine concentrations in dogs with DCM or acquired (degenerative) valvular disease (AVD), and compared plasma taurine concentrations in these groups to those in a group of clinically normal dogs.

Materials and Methods

This report is a combination of 2 independent studies initiated at The Animal Medical Center (AMC) in New York and the School of Veterinary Medicine, University of California, Davis (UCD). The study at AMC was designed to evaluate plasma taurine concentrations in clinically normal dogs, dogs with DCM, and dogs with AVD. The study at UCD was designed to compare plasma taurine concentrations in dogs with DCM to those in clinically normal dogs. A small number of dogs with AVD were also evaluated at UCD.

Normal Dogs

Forty-seven dogs comprised the normal reference population. Dogs were classified as clinically normal on the basis of lack of historical signs of cardiovascular disease and normal results of physical examination and thoracic auscultation. Twenty-seven were male and 20 were female. Ages ranged from 1 to 16 years (median, 6 years), and breeds included mixed breeds (n = 15), Saint Bernard (n = 5), Poodle (n = 5), Greyhound (n = 4), Beagle (n = 3), German Shepherd Dog (n = 2), Labrador Retriever (n = 20), miniature Schnauzer (n = 2), Rottweiler (n = 2), and 1 each Basenji, Basset Hound, Chow Chow, Collie, Malamute, Queensland Shepherd, Dachshund, and Chesapeake Bay Retriever. Forty-one were client-owned dogs brought to the hospital for routine examination, vaccinations, or noncardiac disorders; 18 dogs were examined at AMC

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and 23 at UCD. Six additional random source laboratory dogs from a medical school in New York City examined at AMC and found to be normal on physical examination and at necropsy were also used as controls.

Diets for the normal dogs included a large variety of commercial dog foods. A specific diet history for each dog was not included in the study analysis, because taurine is not considered an essential amino acid in this species.[24-26]

Dogs With Heart Disease

Between 1987 and 1990, plasma taurine concentrations were measured in 104 dogs (50 at AMC, 54 at UCD) with naturally occurring heart disease. Dogs were selected from the population of dogs seen for cardiac complaints at both hospitals. Only dogs with DCM (n = 76) or AVD (n = 28) were selected for study. The median ages of dogs with DCM and AVD were 8 (range, 0.5 to 14 years) and 11 (range, 5 to 16 years) years, respectively. Diagnoses were made on the basis of history, physical examination, echocardiography, electrocardiography, and radiography. Not all these diagnostic tests were performed on every dog. Primary diagnostic criteria for DCM were increased end-diastolic diameter, increased end-systolic diameter, shortening fraction less than 20%, and E-point to septal separation greater than 7 mm on echocardiography. Primary diagnostic criteria for AVD were holosystolic or pansystolic left apical murmur on auscultation, increased end-diastolic diameter with a normal-to-increased shortening fraction, left atrial enlargement, thickened mitral valve, and an E-point to septal separation <7 mm on echocardiography.

To determine whether presence or absence of heart failure or administration of cardiac medication rather than the disease affected plasma taurine concentrations, dogs were classified as either having clinical evidence of congestive heart failure or not, and as having received cardiac drugs or not. Clinical evidence of congestive heart failure was defined as presence of pulmonary edema or pleural effusion on thoracic radiography, or presence of ascites on physical examination.

Sample Collection and Taurine Analysis

Blood was drawn by jugular or cephalic venipuncture into plastic syringes containing sodium citrate (AMC; Sigma Chemical Co, St Louis, MO) or lithium heparin (UCD; Sigma Chemical Co). If not immediately placed in a centrifuge for separation of plasma, the tube containing the blood was placed in ice and centrifuged within 1 hour. After centrifugation, the plasma was immediately separated, collected into plastic vials, and stored at −30 to −80°C until analyzed. All taurine assays were performed at UCD. Samples collected at AMC were shipped on dry ice to UCD by overnight courier. Plasma proteins were precipitated with 6% sulfosalicylic acid, and taurine concentration was determined using a Beckman 121M amino acid analyzer (Beckman Industries, Palo Alto, CA). The results were reported as nanomoles of taurine per milliliter of plasma.

To determine whether the different anticoagulants used at AMC and UCD significantly affected the assay, blood samples were obtained from 13 clinically normal dogs at UCD. The samples were aliquoted into 2 tubes, 1 containing sodium citrate (Sigma Chemical Co) and 1 containing sodium heparin (Sigma Chemical Co), and analyzed for plasma taurine concentrations. Dogs used for this aspect of the study were a subset of the normal population selected from UCD.

Statistical Analysis

A paired *t*-test[27] was used to determine whether the anticoagulant used significantly affected the taurine concentration measured in plasma samples derived from a single venipuncture.

In all dogs, plasma taurine concentrations were compared among categories (normal, DCM, and AVD) using a Kruskal-Wallis test with multiple range comparisons.[28] In the dogs with heart disease, plasma taurine concentrations were compared among disease groups, between patients with and without congestive heart failure, and between patients receiving cardiac medications and those not receiving cardiovascular drugs at the time of sample collection. Of the dogs with heart disease, a Mann-Whitney rank sum test[29] was used to test for differences in plasma taurine concentrations between Doberman Pinschers and all other breeds, between dogs receiving cardiac medications and dogs not receiving cardiac medications, and between dogs with and without signs of congestive heart failure. Graphical analysis and simple least-squares linear regression was performed to test whether age could explain differences in taurine concentration in dogs with AVD at AMC.[28] Differences were considered significant when the probability of a type I error was <.05.

Results

Paired analysis of the samples (*t*-test[27]) showed that the anticoagulant used did significantly affect taurine concentrations ($P < .01$). Plasma taurine concentrations were higher in 11 of 13 samples when heparin was used as the anticoagulant (heparin mean = 80.2 nmol/mL, SD = 15.8 nmol/mL; citrate mean = 67.6 nmol/mL, SD = 13.1 nmol/mL; mean difference = 12.5 nmol/mL, SD = 16.7 nmol/mL, range = −24 to 42 nmol/mL, n = 13). Because of this, results from the 2 clinics were analyzed separately.

All dogs in this study had plasma taurine concentrations less than 250 nmol/mL (Fig 1), except for 1 dog (UCD) with AVD that had plasma taurine concentrations of 550 nmol/mL, was considered an outlier, and was thus excluded from the remainder of the analysis. A significant difference in

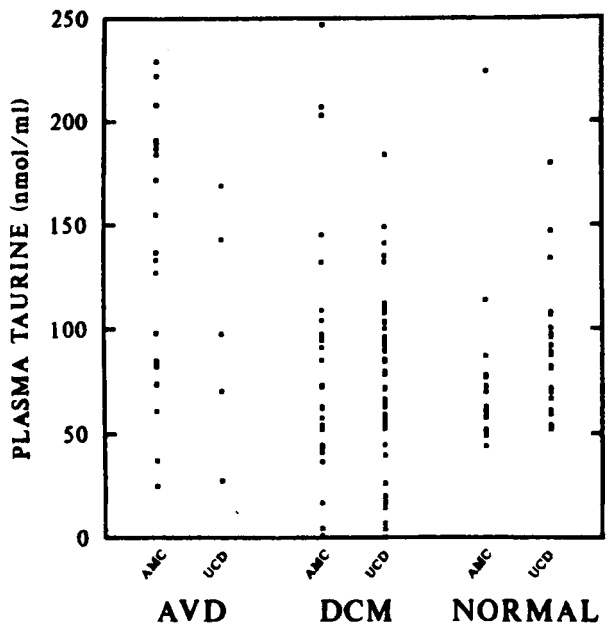

Fig 1. Plasma taurine concentrations in normal (control) dogs and dogs with AVD and DCM at the AMC and the UCD. Each point represents an individual dog.

plasma taurine concentrations between disease groups was found in the dogs at AMC (Fig 2). Plasma taurine concentrations in dogs with AVD were significantly higher (median, 133 nmol/mL; range, 25 to 229 nmol/mL, n = 21) than those in dogs with DCM (median, 72 nmol/mL; range, 1 to 247 nmol/mL, n = 22) or those in control dogs (median, 63 nmol/mL; range, 44 to 224 nmol/mL, n = 21) ($P < .001$).

No difference in plasma taurine concentrations between disease groups was detected at UCD ($P = .09$); however, the number of dogs with AVD was small (n = 5). Dogs with AVD tended to be older than dogs with DCM and control dogs; graphical analysis and simple least-squares linear regression[28] showed that regressing plasma taurine concentrations on age did not help explain the differences in taurine concentration observed at AMC (slope = −1.8 nmol/mL/y, $R^2 = .03$). Although the range of plasma taurine concentrations in dogs with DCM was broader than in control dogs, plasma taurine concentrations in dogs with DCM were not significantly different ($P = .07$) from those in control dogs at either clinic (Fig 1). Of the dogs with heart disease, and within each disease category, there were no significant differences ($P = .11$) in plasma taurine concentrations between dogs with objective clinical evidence of congestive heart failure (n = 47) and dogs without evidence of congestive heart failure (n = 57) at either AMC or UCD. Nor was there a significant difference (0.15) in plasma taurine concentrations between dogs receiving cardiac drugs (n = 70) and those not receiving drugs (n = 34).

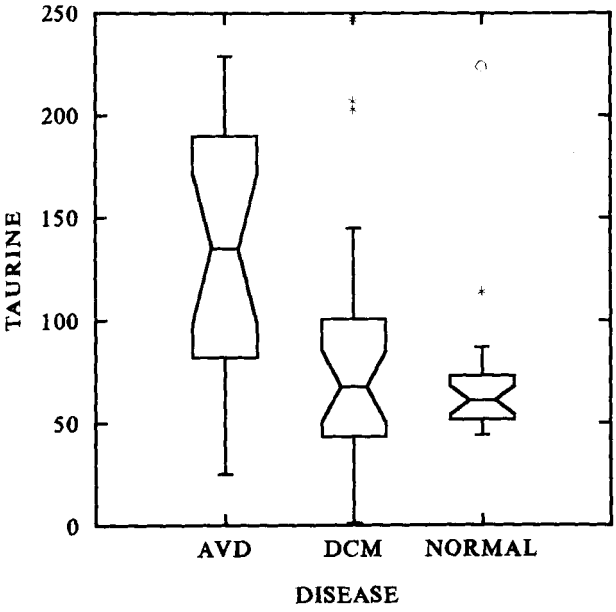

Fig 2. Box plots of plasma taurine concentrations in dogs at the AMC grouped by disease. The box encloses the middle 50% of the data. The center line of the box is the median. The hour glass shaped portion of the box inscribes the 95% confidence level around the median. The "whiskers" denote the range unless there are outliers, in which case the whiskers extend 1.5 times the range of the box above the box. *Data point beyond the range of the whiskers less than 3 times the range of the box above the upper extent of the box. ○ Data point lying greater than 3 times the range of the box above the upper extent of the body. Points denoted by * and ○ should be interpreted as "outliers."

Although plasma taurine concentrations were higher in Doberman Pinschers than in all other breeds with DCM combined (median = 89 nmol/mL, range = 20–184 nmol/mL, n = 17 and median = 66 nmol/mL, range = 0 to 149 nmol/mL, n = 31, respectively) at UCD, the difference was not statistically significant. Within the DCM cohort (Fig 2) at AMC, Doberman Pinschers had statistically significant higher plasma taurine concentrations (median = 95 nmol/mL, range = 42 to 247 nmol/mL, n = 17) than all other breeds (median = 43 nmol/mL, range = 1 to 203 nmol/mL, n = 10) (Fig 3) ($P = .015$).

Among the control dogs at AMC and UCD, plasma taurine concentrations were (judging from normal probability plots[29]) normally distributed. One AMC control dog had much higher (220 nmol/mL) plasma taurine concentrations than the next highest AMC control dog (114 nmol/mL). Excluding this 1 dog, the mean ± 1 SD plasma taurine concentrations of the UCD and AMC control dogs were 91 ± 30 nmol/mL and 64 ± 16 nmol/mL, respectively. The lowest plasma taurine concentrations in control dogs were 44 nmol/mL (AMC) and 52 nmol/mL (UCD). On the basis of these observations and an approximation of the mean ± 2 SD, a value of less than 25 nmol/mL was chosen as the lower limit of normalcy for plasma taurine concentrations in dogs at AMC and UCD.

Of the 151 dogs in the study, 14 dogs (9 from UCD and 5 from AMC) had plasma taurine concentrations less than 25 nmol/mL. All but one of these dogs had DCM. Therefore, 13 of 76 (17%) of the dogs with DCM had plasma taurine concentrations less than 25 nmol/mL. Only 1 of 33 Doberman Pinschers (3%) with dilated cardiomyopathy had plasma taurine concentrations less than 25 nmol/mL. Conversely, 4 of 6 Golden Retrievers and 3 of 3 Cocker Spaniels, all with DCM, had a plasma taurine concentration less than 25 nmol/mL.

Discussion

Thus far, the etiology of DCM in the vast majority of dogs is unknown. Consequently, it is important to identify any potential cause for this disease. An association between low-plasma taurine concentrations and DCM has been reported in cats[17] and foxes.[23] Development of myocardial failure in some cats fed taurine-depleted diets[21,22] and the reversibility of myocardial failure in taurine-deficient cats with DCM after taurine supplementation[17,18,22] add credence to the hypothesis that measurably low plasma taurine concentrations precede the development of myocardial failure in this species. This association prompted the present investigation in dogs with cardiac disease. Most cats with DCM have plasma taurine concentrations less than 25 nmol/mL.[17,22] Consequently, and as a result of the data obtained in clinically normal control dogs, a similar value was chosen as the lower limit of normalcy for use in this study in dogs.

No significant differences in mean plasma taurine concentrations were detected between control dogs and those

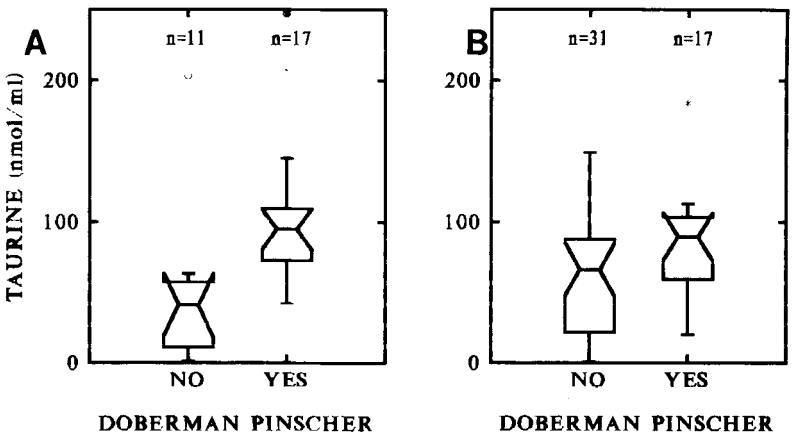

Fig 3. Box plots of plasma taurine concentrations in Doberman Pinschers and non–Doberman Pinschers with DCM. (A) AMC; (B) UCD.

with DCM at either hospital. Therefore, low plasma taurine concentrations are not a characteristic feature of dogs with DCM. The only potentially important finding in regard to plasma taurine concentrations in dogs with DCM is that in 2 breeds, Cocker Spaniels and Golden Retrievers, the plasma taurine concentrations were low in a high percentage of dogs, although the number of dogs evaluated was too small to draw meaningful conclusions. There were no Cocker Spaniels or Golden Retrievers among the control dogs or dogs with AVD. Although the sample sizes were small, the data support examining the possible association between low plasma taurine concentrations and DCM in Cocker Spaniels and Golden Retrievers. A multicenter study evaluating this association in Cocker Spaniels is currently underway.

Identifying low plasma taurine concentrations in some Cocker Spaniels and Golden Retrievers with DCM does not establish cause and effect in these breeds. This conclusion awaits data on plasma taurine concentrations from specific breeds with DCM, taurine-deficient dogs with DCM supplemented with taurine, and experimental reproduction of myocardial failure in taurine-depleted dogs.

The cause of the low plasma taurine concentrations reported in some dogs with DCM in this study is unknown. Hypothetical causes include impaired ability to absorb taurine (eg, gastrointestinal bacterial overgrowth and membrane transport defect), abnormal enterohepatic circulation of taurine-conjugated bile acids, inability to substitute glycine for taurine in conjugating bile acids, and enhanced urinary excretion of taurine. In cats the state of commercial dietary processing may affect the extent of taurine degradation in the gut, with cooked diets associated with a greater degree of degradation than uncooked diets.[30] The importance of gut microflora in determining the taurine status has been shown in cats.[31]

Of the dogs evaluated at AMC, plasma taurine concentrations were highest in dogs with AVD. Assessment of this association could not be made at UCD because of the small number of dogs with AVD evaluated. The importance of high plasma taurine concentrations in dogs with acquired valvular disease is unknown. One possible explanation is that the high plasma taurine concentrations may be part of a mechanism to provide the stressed myocardium a larger pool of taurine for active transport across the sarcolemma. The liver is a major source of taurine synthesis for export into the plasma.[32] One might therefore expect a higher L-cystine-sulfinate carboxylase (EC 4.1.1.29) activity in dogs with AVD compared with control dogs if this hypothesis is valid. Alternatively, the higher plasma taurine concentrations in dogs with AVD may be a direct result of feeding behavior of owners of dogs with AVD (generally small breeds) versus owners of dogs with DCM (generally large breeds), or it may be an artifact secondary to enhanced release of taurine from platelets or other blood elements during more difficult venipuncture in small dogs with AVD. Although enhanced sympathetic tone due to heart failure[11,13] and/or associated myocardial stress is thought to increase myocardial taurine influx,[1,15] serum taurine concentration is not high in rabbits with experimentally induced heart failure.[33] It is also unlikely that the higher plasma taurine concentrations in dogs with AVD resulted from leakage from intracellular stores secondary to metabolic abnormalities associated with heart failure, because the dogs with DCM and heart failure did not have a similar increase in plasma taurine concentrations. In cats with dilated cardiomyopathy, there is no relationship between presence or absence of congestive heart failure and plasma taurine concentrations, so it was not surprising to find no relationship in dogs either.[17]

Different anticoagulants were used at the 2 clinics in this study because the studies were initiated independently. That the anticoagulant used made a difference is not a new finding.[34-36] Despite the difference in anticoagulant and the minor differences in the design of these 2 studies, similar conclusions can be drawn from the population of dogs at each clinic.

Diet history and time of last feeding before sample collection was not included in the study analysis. These were not included because of the large varieties of commercial foods fed, possible inaccuracies or incompleteness of diet histories, and variations in gastric emptying between individuals. We do not think that the commercial foods fed to the dogs in this study had an important effect on plasma taurine concentrations. Diet does affect plasma taurine concentrations

in cats;[17] however, taurine is an essential amino acid in cats but it is nonessential in dogs.[24-26] Plasma taurine concentrations in cats are extremely labile because even in the face of dietary taurine restriction, cats exclusively conjugate bile acids with taurine, whereas dogs can use either taurine or glycine.[26,37] Enterohepatic circulation is efficient in the dog, and little synthesis of taurine is required to replace fecal loss.[37]

Most dry dog foods are cereal- and soybean-based, and contain little or no taurine.[38,39] Canned meat diets do contain more taurine, and the difference in plasma taurine concentrations in dogs with AVD (generally smaller dogs) versus those with DCM (generally larger breed dogs) may partially be explained on the basis of economics. It is possible that because larger dogs consume more food and canned foods cost more than dry foods, small rather than large dogs are more likely to be fed canned diets.

The relationship between the time food was last consumed and blood sampled in our study dogs was variable and usually not recorded. The time between the last meal and the time of blood sampling may be important in cats, which rely on exogenous taurine intake.[24,25,40] Fasting for 48 hours has no significant effect on plasma or myocardial taurine concentration in rats, another species in which taurine is not an essential amino acid.[41]

We conclude that plasma taurine concentrations may be increased in dogs with AVD and that most dogs with DCM do not have taurine deficiency. However, there may be certain breeds or individual dogs that have low plasma taurine concentrations in association with DCM. Whether this is a consistent finding in certain breeds, whether or not the association is causal, and whether or not DCM in dogs with low plasma taurine concentrations respond to taurine supplementation remains to be determined.

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