

# Therapeutic Applications of Taurine

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## Abstract

Taurine is a conditionally-essential amino acid which is not utilized in protein synthesis, but rather is found free or in simple peptides. Taurine has been shown to be essential in certain aspects of mammalian development, and *in vitro* studies in various species have demonstrated that low levels of taurine are associated with various pathological lesions, including cardiomyopathy, retinal degeneration, and growth retardation, especially if deficiency occurs during development. Metabolic actions of taurine include: bile acid conjugation, detoxification, membrane stabilization, osmoregulation, and modulation of cellular calcium levels. Clinically, taurine has been used with varying degrees of success in the treatment of a wide variety of conditions, including: cardiovascular diseases, hypercholesterolemia, epilepsy and other seizure disorders, macular degeneration, Alzheimer's disease, hepatic disorders, alcoholism, and cystic fibrosis.

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## Introduction

Taurine (2-aminoethanesulfonic acid, see Figure 1) is a conditionally-essential amino acid which is not utilized in protein synthesis, but rather is found free or in simple peptides. First discovered as a component of ox bile in 1827, it was not until 1975 that the significance of taurine in human nutrition was identified, when it was discovered that formula-fed, pre-term infants were not able to sustain normal plasma or urinary taurine levels.<sup>1</sup> Signs of taurine deficiency have also been detected in children on long-term, total parenteral nutrition,<sup>2</sup> and in patients with "blind-loop" syndrome.<sup>3</sup> *In vivo* studies in various species have shown taurine to be essential in certain aspects of mammalian development, and have demonstrated that low levels of taurine are associated with various pathological lesions, including cardiomyopathy, retinal degeneration, and growth retardation, especially if deficiency occurs during development.<sup>4</sup>

Derived from methionine and cysteine metabolism, taurine is known to play an important role in numerous physiological functions. While conjugation of bile acids is perhaps its best-known function, this accounts for only a small proportion of the total body pool of taurine in humans. Other metabolic actions of taurine include: detoxification, membrane stabilization, osmoregulation, and modulation of cellular calcium levels. Clinically, taurine has been used in the treatment of a wide variety of conditions, including: cardiovascular diseases, epilepsy and other seizure disorders, macular degeneration, Alzheimer's disease, hepatic disorders, and cystic fibrosis. An analog of taurine, acamprosate, has been used as a treatment for alcoholism.

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## Biochemistry and Metabolism

Although frequently referred to as an amino acid, it should be noted that the taurine molecule contains a sulfonic acid group, rather than the carboxylic acid moiety found in other amino acids. Unlike true amino acids, taurine is not incorporated into proteins, and is one of the most abundant free amino acids in many tissues, including skeletal and cardiac muscle, and the brain.<sup>5</sup>

In the body, taurine is synthesized from the essential amino acid methionine and its related non-essential amino acid cysteine (see Figure 2). There are three known pathways for the synthesis of taurine from cysteine. All three pathways require pyridoxal-5'-phosphate (P5P), the active coenzyme form of vitamin B6, as a cofactor. A vitamin B6 deficiency has been shown to impair taurine synthesis.<sup>6</sup>

The activity of cysteine sulfinic acid decarboxylase (CSAD), the enzyme which converts both cysteine sulfinic acid into hypotaurine, and cysteic acid into taurine, is thought to reflect the capacity for taurine synthesis.<sup>7</sup> Compared to other mammals, humans have relatively low CSAD activity, and therefore possibly lower capacity for taurine synthesis.<sup>8</sup> Much of the published research on taurine has involved studies done on cats, which do not synthesize taurine, but must consume it in their diet.<sup>5</sup> Therefore, since humans have the capacity to synthesize at least some taurine, it is unclear to what extent feline studies can be extrapolated to humans.

## Cardiovascular Effects

Taurine comprises over 50 percent of the total free amino acid pool of the heart.<sup>9</sup> It has a positive inotropic action on cardiac tissue,<sup>10</sup> and has been shown in some studies to lower blood pressure.<sup>11,12</sup> In part, the cardiac

effects of taurine are probably due to its ability to protect the heart from the adverse effects of either excessive or inadequate calcium ion ( $\text{Ca}^{2+}$ ) levels.<sup>13</sup> The consequence of  $\text{Ca}^{2+}$  excess is the accumulation of intracellular calcium, ultimately leading to cellular death. Taurine may both directly and indirectly help regulate intracellular  $\text{Ca}^{2+}$  ion levels by modulating the activity of the voltage-dependent  $\text{Ca}^{2+}$  channels, and by regulation of  $\text{Na}^+$  channels. Taurine also acts on many other ion channels and transporters. Therefore, its action can be quite non-specific.<sup>14</sup> When an adequate amount of taurine is present, calcium-induced myocardial damage is significantly reduced, perhaps by interaction between taurine and membrane proteins.<sup>15</sup> At least one study has

suggested taurine's ability to function as a membrane stabilizer is related to its capacity to prevent suppression of membrane-bound NaK ATPase.<sup>16</sup>

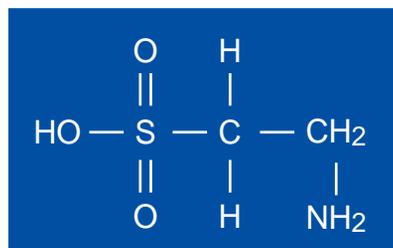
Other research demonstrates taurine can protect the heart from neutrophil-induced reperfusion injury and oxidative stress. Because the respiratory burst activity of neutro-

phils is also significantly reduced in the presence of taurine, perhaps taurine's protective effect is mediated by its antioxidative properties.<sup>17</sup>

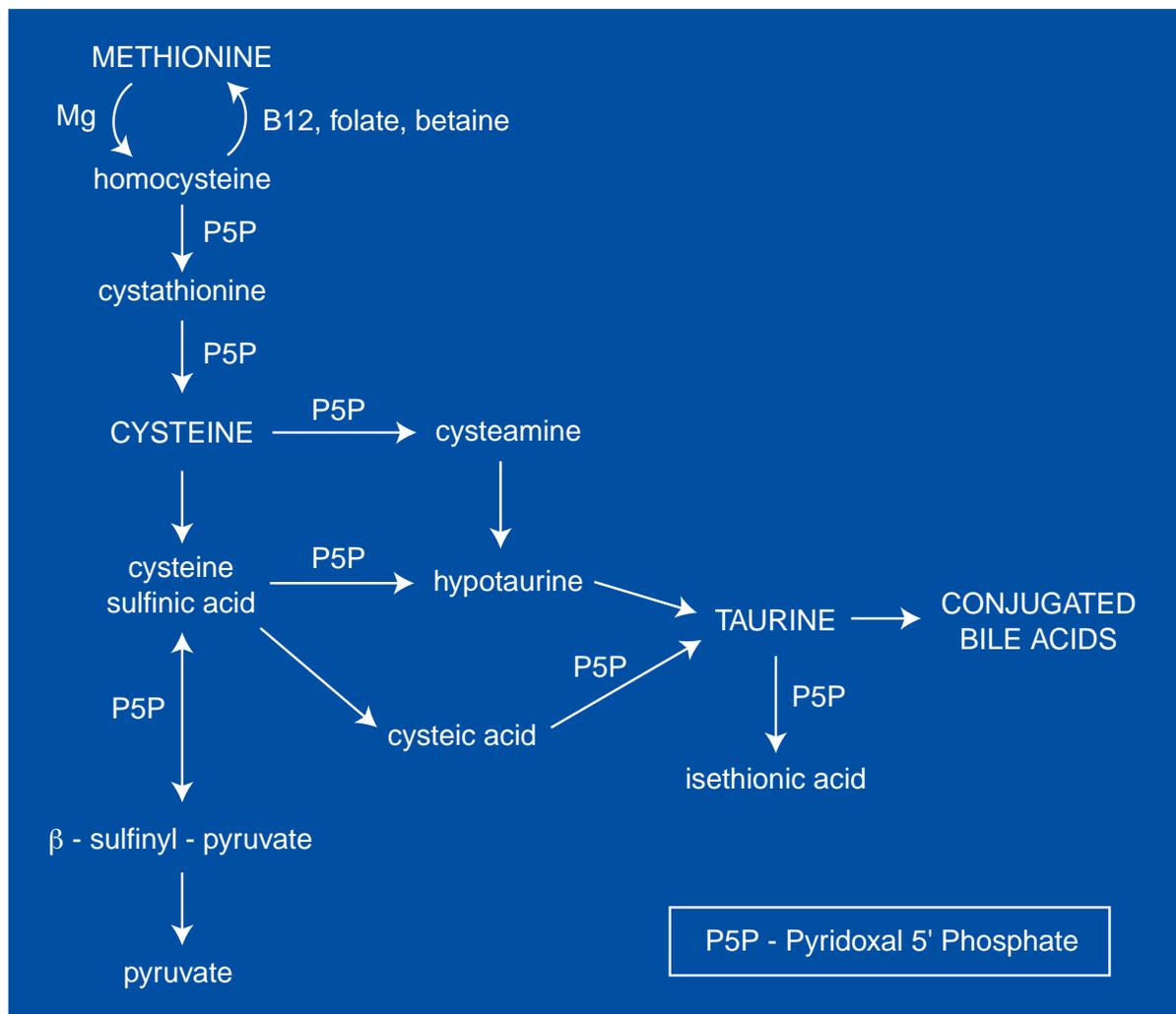
Azuma and associates have observed that taurine alleviates physical signs and symptoms of congestive heart failure (CHF).<sup>18-20</sup> Chazov et al were able to demonstrate that taurine could reverse EKG abnormalities such as S-T segment changes, T-wave inversions, and extra systoles in animals with chemically-induced arrhythmias.<sup>21</sup>

A double-blind, placebo-controlled crossover study suggested, "taurine is an effective agent for the treatment of heart failure without any adverse effects."<sup>22</sup> Fourteen

**Figure 1.** Structure of Taurine



**Figure 2.** Synthesis of Taurine



patients (9 men and 5 women) with CHF were evaluated initially and baseline data were obtained. Patients were assigned a “heart-failure score” based on the degree of dyspnea, pulmonary sounds, signs of right-heart failure, and chest film abnormalities. All patients were continued on digitalis with diuretics and/or vasodilators throughout the study period. Patients received 6 grams per day in divided doses of either taurine or placebo for four weeks, followed by a 2-week “wash-out” period. Prior to the cross-over period, baseline data were obtained for the following study period, in which patients received placebo or taurine, whichever was not taken during the first study period. Heart-failure scores fell from  $5.8 \pm 0.7$  before taurine administration to  $3.7$

$\pm 0.5$  after taurine ( $p < 0.001$ ); the score did not change significantly during the placebo period. A “favorable response was observed in 79 percent (11/14 patients) during the taurine-treated period and in 21 percent (3/14 patients) during the placebo-treated period; 4 patients worsened during the placebo period, whereas none did during the taurine period ( $p$  less than 0.05).”<sup>22</sup>

Research has also been conducted in animals to determine whether oral taurine increased survivability in CHF which resulted from surgically-induced aortic regurgitation. Albino rabbits received either taurine (100 mg/kg) or placebo after surgical damage to the aortic cusps, which produced aortic regurgitation. “Cumulative mortality at 8

weeks of non-treated rabbits following aortic regurgitation was 52% (12/23 animals) compared with 11% (1/9 animals) in taurine-treated group (p less than 0.05)... Taurine prevented the rapid progress of congestive heart failure induced artificially by aortic regurgitation, and consequently prolonged the life expectancy.”<sup>23</sup>

### **Bile Acid Conjugation and Cholesterol Excretion**

The liver forms a 2-4 gram bile acid pool that has approximately ten enterohepatic cycles per day, with the terminal ileum serving as the main absorption site for the enterohepatic recycling of approximately 80 percent of these acids. Bile acids function as a detergent for emulsification and absorption of lipids and fat-soluble vitamins. Critical to this function of bile are the bile salts which, because of their lipophilic and hydrophilic components, can lower surface tension and form micelles. Two major bile acids are derived from hepatic cholesterol metabolism: cholic acid and chenodeoxycholic acid. From these primary bile acids, intestinal bacteria form the secondary bile acids deoxycholic acid and lithocholic acid, respectively. For these bile acids to be solubilized at physiological pH, it is essential they be conjugated through peptide linkages with either glycine or taurine; these amino acid conjugates are referred to as bile salts.

Taurine conjugation of bile acids has a significant effect on the solubility of cholesterol, increasing its excretion, and administration of taurine has been shown to reduce serum cholesterol levels in human subjects. In a single-blind, placebo-controlled study, 22 healthy male volunteers, aged 18-29 years, were randomly placed in one of two groups and fed a high fat/high cholesterol diet, designed to raise serum cholesterol levels, for three weeks. The experimental group received 6 grams of taurine daily. At the end of the test

period, the control group had significantly higher total cholesterol and LDL-cholesterol levels than the group receiving taurine.<sup>24</sup>

### **Cystic Fibrosis**

Most cystic fibrosis (CF) patients suffer from nutrient malabsorption, where much of the insult is in the ileum. Since the terminal ileum serves as the main absorption site for the enterohepatic recycling of approximately 80 percent of bile acids, they are malabsorbed as well. Taurine supplementation has been shown to decrease the severity of steatorrhea associated with many CF cases.<sup>25,26</sup> In one double-blind crossover study, 13 CF children with steatorrhea of at least 13 grams per day were treated with a taurine dose of 30 mg/kg/day. The study continued for two consecutive 4-month durations and involved both placebo and treatment periods. Ninety-two percent of the CF children showed decreased fecal fatty acid and sterol excretion while taking taurine.<sup>25</sup> In CF patients with a high degree of steatorrhea, bile acid absorption was increased with taurine supplementation, suggesting a possible role for taurine in treating malabsorption.<sup>26</sup>

### **Detoxification**

Due to its ability to neutralize hypochlorous acid, a potent oxidizing substance, taurine is able to attenuate DNA damage caused by aromatic amine compounds *in vitro*.<sup>27</sup> Because of taurine's unique structure, containing a sulfonic acid moiety rather than carboxylic acid, it does not form an aldehyde from hypochlorous acid, forming instead a relatively stable chloroamine compound. Hence, taurine is an antioxidant that specifically mediates the chloride ion and hypochlorous acid concentration, and protects the body from potentially toxic effects of aldehyde release.

Taurine has also been reported to protect against carbon tetrachloride-induced toxicity.<sup>28-31</sup> In rats exposed to carbon

tetrachloride (CCl<sub>4</sub>), hepatic taurine content decreased significantly 12 and 24 hours after CCl<sub>4</sub> administration. However, oral administration of taurine to CCl<sub>4</sub>-exposed rats was able to protect these animals from hepatic taurine depletion, suggesting that hepatic taurine may play a critical role in the protection of hepatocytes against hepatotoxins such as CCl<sub>4</sub>.<sup>28</sup>

Exposure to bacterial endotoxins has been suggested as one factor which can augment the magnitude of individual responses to xenobiotics.<sup>32</sup> Circulating endotoxins of intestinal origin have been found to create a positive feedback on endotoxin translocation from the gut, stimulating increases in serum endotoxin levels. In experimental animals, taurine was found to significantly inhibit intestinal translocation and to protect the animals from endotoxemic injury.<sup>33</sup> Therefore, it is possible taurine might be able to modify factors underlying susceptibility to toxic chemicals.

## Hepatic Disorders

Two groups of patients with acute hepatitis, all with serum bilirubin levels above 3 mg/dl, were studied in a double-blind, randomized protocol. Subjects in the treatment group received 4 grams of taurine three times daily. Bilirubin, total bile acids, and biliary glycine:taurine ratio all decreased significantly in the taurine group within one week as compared to controls.<sup>34</sup>

## Alcoholism

Twenty-two patients undergoing treatment for alcohol withdrawal were given 1 gram of taurine three times per day orally for seven days. When compared to retrospective controls, significantly fewer of the taurine-treated patients had psychotic episodes (14% vs. 45%,  $p < 0.05$ ). The number of psychotic cases after admission who had also been psychotic before admission was

1/16 for the taurine group and 11/17 for the controls ( $p < 0.001$ ).<sup>35</sup>

Recently, acamprosate, a synthetic taurine analog, has been shown to be clinically useful in the treatment of alcohol dependence.<sup>36-41</sup> Currently available only in Europe, acamprosate (calcium acetylhomotaurinate) has a chemical structure similar to that of gamma-aminobutyric acid, and is thought to act via several mechanisms affecting multiple neurotransmitter systems, and by modulation of calcium ion fluxes. About 50 percent of alcoholic patients relapse within three months of treatment. In a pooled analysis of data from 11 randomized, placebo-controlled trials involving a total of 3,338 patients with alcohol dependence, those treated with acamprosate showed higher abstinence rates and durations of abstinence during 6- to 12-month post-treatment follow-up periods, when compared to those receiving placebo.<sup>36</sup>

In a two-year, randomized, double-blind, placebo-controlled study, 272 patients initially were given short-term detoxification treatment, and then received routine counseling and either acamprosate or placebo for 48 weeks, after which they were followed for another 48 weeks without medication. Subjects who received acamprosate showed a significantly higher continuous abstinence rate at the end of the treatment period compared to those who were assigned to the placebo group (43% vs 21%,  $p = .005$ ), and they had a significantly longer mean abstinence duration of 224 vs 163 days, or 62 percent vs 45 percent days abstinent ( $p < .001$ ). However, there was no difference in psychiatric symptoms. At the end of a further 48 weeks without receiving study medication, 39 percent and 17 percent of the acamprosate- and placebo-treated patients, respectively, had remained abstinent ( $p = .003$ ).<sup>37</sup>

Two *in vitro* studies have been published comparing the effects of acamprosate and calcium acetyltaurinate on ionic membrane transfer.<sup>40,41</sup> Ethanol has been

shown to reduce ionic transfer through alterations in the cationic paracellular pathway, the coupling between two adjacent epithelial cells, the monovalent cation pump, and the antiport system. In both of these studies, the results indicate two closely related compounds have different effects on ionic membrane transfer. Therefore, caution should be used in extrapolating the effects of acamprosate to taurine or other taurine analogs.

### Ocular Disorders

The retina contains one of the highest concentrations of taurine in the body. In cats, when the retina has been depleted to about one-half its normal taurine content, changes in the photoreceptor cells begin to appear, and further depletion can result in permanent retinal degeneration.<sup>42</sup> In some respects, the retinal degeneration seen in the human disease retinitis pigmentosa (RP) is similar to that observed in taurine-deficient cats. However, studies of plasma and platelet taurine levels in patients with RP have yielded very inconsistent results.<sup>43-45</sup> A clinical trial of taurine (1-2 g/day) for one year in patients with RP did not result in any laboratory or clinical evidence of improvement, although some subjective benefits were reported.<sup>46</sup>

### Epilepsy

Although several clinical trials involving taurine supplementation in epileptic patients have been reported, most have major methodological flaws.<sup>47</sup> Depending on the criteria used, the degree of success reported in various trials using taurine in the treatment of epilepsy has been between 16 and 90 percent.<sup>48-56</sup> In these trials, dosages ranged from 375 to 8,000 mg/day. The precise role of taurine in synaptic transmission is uncertain, and its antiepileptic action, confirmed in several models of experimental epilepsy and in short-term clinical studies, does not seem to possess major clinical relevance since trials

with a longer follow-up period have generally produced less satisfactory results. Taurine's limited diffusibility across the blood-brain barrier may be the main factor restricting the antiepileptic effect of this compound.

### Alzheimer's Disease

Levels of the neurotransmitter acetylcholine have been described as abnormally low in patients with Alzheimer's disease. These insufficient levels are presumed to be related to the memory loss which characterizes the condition, and treatment of Alzheimer's disease based on this premise has been proposed.<sup>57</sup> Taurine administered to experimental animals has been able to increase the level of acetylcholine in the brain,<sup>58</sup> and researchers have demonstrated that decreased concentrations of taurine are present in the cerebral spinal fluid of patients with advanced symptoms of Alzheimer's disease when compared to age-matched controls.<sup>59</sup> To date, no clinical trials on the use of taurine for the treatment of Alzheimer's disease have been reported in the medical literature.

### Diabetes

Both plasma and platelet taurine levels have been found to be depressed in insulin-dependent diabetic patients; however, these levels were raised to normal with oral taurine supplementation. In addition, the amount of arachidonic acid needed to induce platelet aggregation was lower in these patients than in healthy subjects. Taurine supplementation reversed this effect as well, reducing platelet aggregation. *In vitro* experiments demonstrated that taurine reduced platelet aggregation in diabetic patients in a dose-dependent manner, while having no effect on the aggregation of platelets from healthy subjects.

### Conclusion

Although it is readily apparent that taurine is important in conjugating bile acids to

form water-soluble bile salts, only a fraction of available taurine is used for this function. Taurine is also involved in a number of other crucially important processes, including calcium ion flux, membrane stabilization, and detoxification. Some areas of investigation into the clinical uses of taurine have revealed significant applications for this amino acid: congestive heart failure, cystic fibrosis, toxic exposure, and hepatic disorders. Other conditions such as epilepsy and diabetes will require further research before a clear rationale for the use of taurine can be developed.

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