Taurine: An Overview of Its Role in Preventive Medicine

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Taurine (2-aminoethanesulfonic acid), well known for its role in bile salt synthesis, is also involved in a number of crucial physiological processes including modulation of calcium flux and neuronal excitability, osmoregulation, detoxification, and membrane stabilization. With the exception of cow’s milk, taurine is widely distributed in foods from many animal, but not plant, sources. Although taurine is synthesized from sulfur-containing amino acids, concern has been expressed about the adequacy of endogenous sources, especially in neonates. Accordingly, proprietary milk formulas are now supplemented with taurine. Retinal dysfunction occurs in taurine-deficient animals. A milder form of this condition has been observed in children on long-term total parenteral nutrition. Preliminary evidence suggests a possible role for taurine administration in congestive heart disease, acute hepatitis, cystic fibrosis, and myotonia. Further studies are required before taurine can be routinely advocated for use in these and other disorders. Recent discoveries concerning taurine’s role in cellular proliferation and membrane protection underscore its physiological significance. In this context, taurine’s interaction with other nutrients, biochemicals, and xenobiotics warrants extensive exploration. As a conditionally essential nutrient, taurine has several important preventive medical applications.

INTRODUCTION

Taurine (2-aminoethanesulfonic acid) has been known to science for over one and a half centuries since its discovery in ox bile (130). Long considered the practically inert end-product of sulfur amino acid metabolism, a resurgence of biological, biochemical, and medical interest in taurine was prompted by two reports published in 1975. Hayes et al. (53) claimed that taurine is an essential nutrient for cats, deficiency of which causes blindness. Râlha et al. (103) reported that formula-fed preterm infants were unable to maintain normal plasma and urinary taurine levels, although no functional impairment was demonstrated at that time. Subsequently, retinal signs of taurine deficiency were detected in children maintained on long-term total parenteral nutrition (46) and in patients with the “blind-loop syndrome” (117). As a consequence of these and other studies, taurine is now characterized as a conditionally essential nutrient (28).

Besides its well-known function in bile salt synthesis (56) taurine is involved in a broad spectrum of metabolic processes including osmoregulation (128), cellular proliferation (45), modulation of calcium flux (115), stimulation of glycolysis and glycogenesis (74), modulation of neuronal excitability (20), detoxification (39), and membrane stabilization (98). Its apparent participation in crucial physiological processes appears to have potentially valuable preventive medical applications.

A number of comprehensive reviews (25, 52, 54, 57, 65, 91, 121, 146) and, since 1976, several monographs and symposia proceedings encompassing all aspects of taurine are available (13, 58, 62, 75, 90, 112). Since its discovery, taurine has been
the subject of over 2,600 publications (101). The purpose of this article is to highlight that portion of the constellation of knowledge of taurine relevant to preventive medical practice. Accordingly, emphasis will be given to studies pertinent to or involving humans. The rich body of information concerning experimental animal studies can be explored by reference to the publications cited above.

**TAURINE BIOCHEMISTRY**

Taurine is a colorless, water-soluble compound with a molecular weight of approximately 125. As a free amino acid without dissociable side groups, taurine exists as a zwitterion, even at physiological pH. Taurine differs from other amino acids in that a sulfonic acid group replaces the carboxylic acid and its amino group is located on the second rather than the first carbon. Its sulfonic acid function exhibits greater acidity than the carboxylic acid function of related compounds such as β-alanine and its amino group is also more acidic than that of comparable amino acids (146).

Taurine is derived from methionine, an essential amino acid, and cysteine, a nonessential amino acid. Cysteine sulfenic acid is decarboxylated to hypotaurine which is subsequently oxidized to taurine (52, 91). There is a general consensus that cysteine sulfenic acid decarboxylase (CSAD) activity reflects tissue taurine synthetic capacity (52). Based on CSAD activity, humans have poor hepatic taurine synthesis compared with rats (144).

CSAD and other enzymes along the *trans*-sulfuration pathway from methionine require pyridoxal phosphate as coenzyme. As anticipated, vitamin B₆ deficiency impairs taurine biosynthesis (118) and animal studies indicate that reduced intake of total protein (135) or of methionine (42) also depresses taurine formation. Dietary content of methyl donors which spare methionine may also influence taurine biosynthesis (116).

**TAURINE DISTRIBUTION AND FUNCTION**

The total taurine body pool is between 12 and 18 g (100–150 mmol) of which 15–66 mg (50–220 μmol) is present in plasma (125). The largest taurine pool is skeletal muscle, accounting for about three-quarters of total body taurine. Daily taurine losses in urine are diet-dependent but generally range from 65 to 250 mg (0.5–2.0 mmol). An excess of dietary taurine increases tissue taurine turnover rate and increases the proportion of bile acids conjugated with taurine (125).

Taurine is the most abundant free amino acid present in skeletal and cardiac muscle while in the brain it is exceeded only by the concentration of glutamic acid (77). The highest taurine concentrations occur in pineal and pituitary glands (138) and retina (91), the pigmented epithelium of the latter being capable of concentrating taurine against a 400 to 500-fold gradient. The adrenals also have a high taurine content (87). The taurine content of rat heart is 30 μmol/g wet weight with spleen, skeletal muscle, small intestine, and lung containing about half this quantity, kidney and thymus about one-quarter, and cerebrum and spinal cord about
one-sixth (60). Rat liver contains only 2 μmol/g. Human fetal and adult livers contain 2.4 and 0.8 μmol/g, respectively (110), and term placentas, 3.5 μmol/g (100).

Platelets

Taurine levels of blood platelets are approximately 600-700 times those in plasma (3). Platelets have been scrutinized because they exhibit transport properties similar to those of brain synaptosomes. Three separate transport processes have been identified in platelets, representing high-, medium-, and low-affinity taurine uptake (88). The low-affinity mechanism is much less dependent on sodium ions than the high- and medium-affinity systems which exhibit a linear dependence on sodium ion concentrations.

Taurine uptake by platelets exceeds that of other amino acids, being threefold greater than β-alanine and L-glutamate and fivefold greater than GABA uptake (50). Platelets from patients with certain disorders exhibit reduced taurine uptake compared with normal controls. These disorders include degenerative progressive myoclonus epilepsy (4) and Down's syndrome (22). Abnormal platelet taurine concentrations have been observed in hypothyroidism (16) and migraine (34), the former being below and the latter being above normal. Patients with retinitis pigmentosa sometimes (6) but not consistently (141) have abnormal platelet taurine uptake.

Lymphoblastoid Cells

Lymphoblastoid cells are another accessible source of cells with high taurine content (146). A recent discovery of interest is that supplementation of the cell-culture medium with taurine results in a dose-dependent increased viability (45). A variety of compounds inhibit taurine uptake by cultured lymphoblastoid cells through nonspecific effects on membrane integrity. Some of these are drugs that may be capable of promoting pathological changes in tissues particularly susceptible to taurine deficiency (146).

Lymphoblastoid cells from retinitis pigmentosa patients are known to have defective taurine uptake (145).

Retina

When the cat retina has been depleted to about half of its normal taurine content, deleterious changes occur in the cone photoreceptor cells. Further depletion of taurine culminates in permanent retinal degeneration (122). Less severe but similar changes occur in monkeys raised from birth for 26 months on a taurine-deficient, proprietary human infant formula (126).

Among the putative proposed functions for taurine in the retina are regulation of osmotic pressure, regulation of calcium ion homeostasis, inhibition of phosphorylation of membrane proteins, reversal of phagocytosis inhibition, function as an inhibitory neurotransmitter, and membrane stabilization by prevention of lipid peroxidation or other antioxidant function (146).
Central Nervous System (CNS)

Taurine is found in both neuronal and glial cells but is unevenly distributed in the CNS with cerebral cortex, cerebellum, olfactory bulbs, and striatum having greater concentrations than pons, medulla, and spinal cord (91). There are also substantial intraregional differences in taurine concentration. In contrast to the taurine content of most other organs, brain taurine levels are maintained during deficiency states (123).

Taurine content of the human fetal brain is over twice that of the adult (124). Taurine is unique among brain amino acids in that its concentration gradually diminishes during postnatal development, a finding which prompted the suggestion that taurine may be associated with brain development per se, in addition to any functional role it may have in the mature brain (123).

Included among taurine’s putative functions in the brain are modulator of neuronal excitability, inhibitory neurotransmitter, maintenance of cerebellar function, modulator of hormone release, and anti-convulsant (91). Taurine reduces neuronal firing by hyperpolarizing the synaptosome membrane, an effect presumably due to increasing membrane permeability to chloride ions. It has been asserted that stabilization of the excitation threshold accounts for most of the physiological effects of taurine in excitable tissues (134). If or how taurine functions as a neurotransmitter remains uncertain (20).

There is evidence that taurine functions as an osmotic regulator in mammals in addition to phylogenetically lower forms. For example, in hyponatremic young rat brains, there was an increased content of 16 of 19 amino acids with taurine accounting for more than half of this increase (128). Taurine is believed to help maintain cell volume by virtue of its relatively inert chemical reactivity yet relatively high tissue concentration. The mechanism of taurine’s osmoregulatory function in the brain seems to involve its transfer from an intracellular sequestered osmotically inactive reserve pool to the cytoplasm, as neurons release substances upon stimulation. Taurine acts regionally, for the most part, total tissue pool changes being minimal. Change in total brain taurine content is likely to ensue only after serious alteration of brain function (134).

Glutaurine (γ-L-glutamyl-taurine), also called litoralon, is synthesized by the parathyroid gland and has been isolated from the brain (41). It appears to produce many of the physiological effects of taurine but at concentrations two or three orders of magnitude less than taurine. These effects include enhancement of the macrophage reaction, protection against X-irradiation, and potentiation of the action of vitamin A (41). Glutaurine may also function as an intracellular storage form of taurine and could partially account for the stability of the intracellular taurine pool in the brain (82).

Cardiovascular System

Taurine is the most abundant free amino acid in the heart, its concentration being fourfold that of the next one, glutamic acid (57). Among its cardiovascular actions are an antiarrhythmic effect; positive and negative inotropic actions at low and high calcium concentrations, respectively; antagonism of calcium paradox; hypotensive action and potentiation of digitalis action.
Taurine protects the heart from the detrimental effects of both calcium ion deprivation and excess. Taurine offsets calcium paradox; that is, the increased permeability of cell membranes to calcium ion, resulting in cellular damage following \( \text{Ca}^{2+} \)-free perfusion. When taurine is present during reexposure to \( \text{Ca}^{2+} \), release of creatine kinase and nucleotides is significantly reduced (73). This effect of taurine may be due to its alteration of the ion exchange properties of the membrane (57) or by interaction with membrane proteins (73).

The consequence of excess \( \text{Ca}^{2+} \) exposure is intracellular calcium accumulation, ultimately leading to necrosis. Oral taurine administration reduced cardiac \( \text{Ca}^{2+} \) levels and the number and severity of lesions in the cardiomyopathic hamster, an animal model of genetically impaired regulation of calcium entry into the heart (8). This effect of taurine is not exerted by calcium ion chelation but rather by modifying the characteristics of cardiac high-affinity \( \text{Ca}^{2+} \) binding sites (115). Taurine transport into the heart is increased by raising cellular cyclic-AMP levels such as by \( \beta \) adrenergic stimulation during chronic stress (9). Acute stress during ischemia results in reduced cardiac taurine levels (31).

Taurine content of the heart has been increased by feeding large amounts of ethanol to rats for a 4-week period (38) and during adaptation to chronic hypernatremia in mice (129).

Taurine consumption lowers serum cholesterol levels in rats but not in humans (74).

**Liver**

Bile functions as a detergent for emulsification and absorption of lipids and fat-soluble vitamins. Crucial 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, to a lesser degree, lithocholic acid, respectively. For these bile acids to be solubilized at physiological pH, it is essential that they be conjugated through peptide linkage with glycine or taurine. These amino acid conjugates are referred to as bile salts since they are completely ionized at physiological pH while the free bile acids are not. Taurine conjugates are more water soluble than glycine conjugates and will remain ionized even under the conditions of low pH present, at times, in the proximal small intestine (56).

Ionization is necessary for emulsification, to prevent precipitation and to maintain high intraluminal bile salt concentrations. About three times more taurine than glycine is conjugated with cholic acid but this varies depending upon taurine availability (57). It is noteworthy that the glycine:taurine conjugation ratio is less than 1 up to 3 weeks of life in the breast-fed infant but when dietary taurine is low, the ratio exceeds 1 by the 12th day of life (23).

Animal studies have shown that taurine conjugation of bile acids has a profound effect on secretory rate, cholesterol solubility, and lithogenicity (25, 54). Lithocholic acid induces cholestasis in experimental animals, an action that is preventable by taurine administration (35). Taurine conjugation of bile acids may also...
mitigate potential hepatotoxicity in humans (94). Bile acid conjugation has the favorable effect of restricting total bile acid pool size, thus reducing secondary bile acid pool size and the amount of toxic compounds (146).

Apart from its unique function in bile salt secretion, the liver plays a prominent, but not exclusive, role in the biotransformation of xenobiotics. The amino group of taurine can form peptide linkages with organic carboxylic acids (39). This phenomenon is highly species specific and thus extrapolation is hazardous (66).

Notwithstanding the physiological significance of taurine in bile acid conjugation and in xenobiotic interactions, these functions collectively account for only a small percentage of total taurine (55).

Kidney

The total body taurine pool size is regulated by the kidney (65). Taurine is a major urinary amino acid in humans because the capacity of the renal reabsorption system is low (25). However, reduced dietary intake of taurine is compensated for by enhanced renal taurine conservation due to increased brush border membrane transport into the renal cell. Conversely, high dietary taurine results in reduced brush border membrane taurine transport and increased urinary taurine. The kidney reabsorbs taurine conjugated bile salts efficiently (15).

Young rats exhibit impaired adaptation to dietary taurine fluctuations (26). This phenomenon is not due to differences in filtration or in transport across the brush border membrane but rather reduced permeability of the antiluminal membrane in the immature nephron, thus causing higher tissue concentrations of taurine and backflux into the urine. With maturation, there is increased taurine permeability in the antiluminal membrane, reduced tissue taurine levels, and no backflux into the urine (25). Renal adaptations to low dietary taurine may contribute to maintenance of brain taurine levels (27).

Urinary taurine excretion is increased in a number of conditions and situations including acute alcohol intake, following surgery, and in various disorders (132). For example, taurine losses in the urine of patients with Friedreich's ataxia (a recessively inherited spinocerebellar ataxia appearing in childhood and progressing to invalidism and death by middle age) are double those of age-matched controls after a 250-mg loading dose (12). It had been proposed that a defect in taurine conservation represents the primary event in this disorder but this has since been retracted (108). The Fanconi syndrome, like other disorders that cause amino aciduria, produces hypertaurinuria (114).
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age, preterm infants were unable to maintain taurine concentrations in plasma and urine equivalent to those of comparable preterm infants fed human milk (103). A subsequent study of amino acid concentrations in plasma and urine of appropriate for age, low birth weight infants disclosed that while most amino acids either rose or remained the same in infants receiving taurine-deficient formulas compared with those fed pooled human milk, urine and plasma taurine concentrations were lower after 1 and 4 weeks, respectively, in the infants fed taurine-deficient formulas (44). These findings have since been extended to include full-term infants (104). These results provide additional support for the hypothesis that a dietary source of taurine is necessary during the neonatal period in human infants.

The taurine content of both human and cow milk is high early in lactation. However, marketed cow’s milk provides only 1/30 the amount of taurine available to the calf or 1 μmol/dl (105). Human milk contains 41 μmol/dl at less than 5 days and 34 μmol/dl at more than 5 days after birth (105).

Preterm infants fed pooled human milk or taurine-supplemented formulas remain predominantly taurine conjugators of bile acids while those consuming taurine-deficient formulas become predominantly glycine conjugators (142). Possible physiological consequences of this have been described above.

Other studies of taurine supplementation (30 μmol/dl or 45 μmol/kg/day) of a standard infant formula fed to low birth weight infants failed to demonstrate any consistent effect on growth or head circumference or on serum cholesterol, BUN, serum proteins, or blood acid–base balance (68). Also, no effect of taurine supplementation was found on intestinal fat absorption since both taurine-supplemented and nonsupplemented groups showed lower fat absorption than infants fed human milk (67). Nor were differences found in total duodenal bile salt concentration between taurine-supplemented and nonsupplemented groups: both had lower concentrations than infants fed human milk (69). Infants fed taurine-supplemented formula or human milk exhibited predominantly taurine-conjugated bile acids for the first 5 weeks of life. Beyond this period, the glycine:taurine ratio rose for infants fed the taurine-deficient formula (69). The rate of bile salt synthesis among taurine-supplemented and nonsupplemented groups did not differ from that in human milk-fed infants (143).

A study of low birth weight infants from an urban U.S. population fed formula to which supplemental taurine (25 or 45 μmol/kg/24 hr) either was or was not added generally confirmed the findings of previous studies on larger and more physiologically mature Scandinavian infants (93). The mean urinary taurine concentration in the supplemented group was, however, below that reported in previous studies and exhibited a significant decrease from the first to the fourth and last week of the study at which time the urinary taurine levels of supplemented and nonsupplemented infants did not differ. Also, plasma taurine values did not differ significantly between the two groups. Finally, the mean duodenal bile salt concentration of taurine-supplemented infants was about three times greater than that in the nonsupplemented group ($P < 0.052$, $n = 5$). Total duodenal bile salt concentration correlated positively with urinary taurine excretion. The authors interpreted these data as suggesting that conversion of cholesterol to bile acids was greater in taurine-supplemented infants and that taurine-depleted preterm
infants may require over 45 μmol/kg/day of exogenous taurine for optimal bile salt synthesis. In this as in previous studies, however, no effect of taurine supplementation was found on intestinal fat absorption. This may be attributed to infant preferences for bile salt biosynthesis at the expense of other and potentially more vulnerable body tissues or organs according to the authors (93).

Taurine does increase fat absorption in children with cystic fibrosis (32): this is discussed below.

**Parenteral Nutrition**

Many purified enteral and parenteral nutritional preparations lack taurine and are also low in cysteine content because the latter dimerizes to cystine, a highly insoluble amino acid (57). Shortly after the discovery of low plasma and urinary taurine concentrations in preterm infants who were fed taurine-deficient formulas, it was reported that this was also the case for infants fed on total parenteral nutrition (TPN) (107). More recently, it was discovered that a group of 21 children who had received long-term TPN exhibited mean plasma taurine levels less than half those of controls ($P < 0.001$) (46). Electroretinograms showing mild abnormalities were found in each of the 8 children tested but not in control subjects. Addition of taurine (1.5–2.25 g/day) to the iv solutions of 4 children resulted in restoration of plasma taurine levels to normal. Electroretinograms became normal in each of the 3 children who were tested following 12–14 weeks of taurine supplementation. Two of these children had low taurine levels 1 year after discontinuation of iv taurine. Since plasma levels of methionine and cysteine were adequate, the authors concluded that taurine deficiency was not the result of unavailability of its precursors (46).

Taurine supplementation of TPN for 10 days was ineffective in altering hepatocellular function of premature infants although their plasma taurine levels were raised (29).

Plasma taurine levels were also significantly reduced in eight adults with less than 25% intestinal absorption of the recommended caloric intake and were inversely related to the duration of parenteral nutrition. The electroretinograms of two adults with very low plasma taurine levels were, nevertheless, found to be normal (93).

Plasma and blood cell taurine concentrations of 40 adults undergoing long-term home parenteral nutrition were recently reported (139). In 21 patients whose estimated enteral caloric absorption was less than 25% of their daily requirement, taurine concentrations were significantly reduced to approximately one-third to one-half of normal control values in plasma, platelets, lymphocytes, and erythrocytes but not in granulocytes. In 19 patients whose estimated enteral caloric absorption was greater than 25% of their daily requirement, taurine levels were significantly below normal in plasma and erythrocytes (139). These workers also found significant reductions in plasma, platelet, and urine taurine concentrations in 19 children on long-term home parenteral nutrition compared to normal children (140).

Taurine was undetectable in three patients, all of whom died following massive intestinal resection for necrotizing enterocolitis (30). The authors proposed that
impaired bile acid metabolism due to taurine deficiency from TPN, by producing cholestasis, may play a role in severe hepatic dysfunction.

**Retinitis Pigmentosa (RP)**

The retinal degeneration observed in taurine-deficient cats in certain respects is similar to that occurring in patients with RP. Accordingly, it has been proposed that some forms of this heterogeneous disorder might be associated with defective taurine metabolism. Although there are several reports of normal plasma taurine in RP (6, 21), very low taurine levels have been found in some patients (133). Measurements of isolated platelets from RP patients have yielded inconsistent results. Some studies reported below normal (6) and others normal or above normal (141) platelet taurine levels. Reduced taurine uptake may be more common in the nonhereditary form of the disorder and increased taurine uptake more common in hereditary forms of RP.

It was recently found that taurine uptake by lymphoblastoid cells from RP patients differed significantly from that of controls, suggesting that defective taurine uptake could contribute to RP (145).

A clinical trial of taurine (1–2 g/day) for 1 year in 10 RP patients failed to provide any laboratory or clinical evidence of improvement although some subjective benefits were reported (106).

**Epilepsy**

A report of decreased taurine levels in focal areas of epileptic patients (136) instigated several clinical trials involving taurine administration despite a subsequent contradictory report (99). For the most part, these trials have been characterized by severe methodological flaws (40). Often, those patients least responsive to anticonvulsant medication served as subjects. The studies generally used small numbers of unselected and nonhomogenous patients and lacked strict evaluation criteria for seizure frequency and severity. Taurine dosages varied and there was inconsistent use of concurrent medication. Many of the studies lacked control groups. Consequently, it is difficult to draw firm conclusions concerning the efficacy of taurine administration in epilepsy (40, 92). Nevertheless, some of these studies are cited because some patients in all trials but one (80) appeared to benefit.

No change in seizure frequency was noted in six patients with mixed seizure disorders who were refractory to standard anticonvulsant treatment. Oral doses of taurine ranged from 375 to 8,000 mg/day (80). Depending upon the criteria used, the range of reported success in the other trials was 16–90% (5, 14, 19, 72, 81, 85, 127, 137). In some cases, however, an initial favorable clinical response did not persist despite continued taurine administration. Even where clinical improvement occurred, EEG abnormalities remained or disappeared slowly (72). In one report there was an aggravation of EEG pathology despite clinical improvement (85). In some cases, abnormal amino acid patterns were reversed (137).

Goodman et al. (47) have recommended that patients be screened prior to taurine administration to categorize them as high or low taurine excretors (low or high taurine reabsorbers, respectively). Those in the latter group may be most
responsive to taurine administration while those in the former group are believed to be least responsive. This procedure has been followed by Haines et al. (49) who discovered that low taurine excretors clustered in families with a generalized spike and wave (GSW) EEG history. Half of the individuals in these families exhibited this pattern. The percentages of patients with GSW EEG characterized by level of taurine excretion was 68% (11/17) low excretors, 50% (7/14) intermediate, and only 14% (1/7) high excretors. Patients with partial seizures had significantly ($P < 0.001$) elevated urinary taurine levels compared to those with multiple seizure types (49).

Lipophilic taurine derivatives capable of more rapid penetration of the blood–brain barrier are currently under investigation (61).

It has been proposed that phenytoin functions as an anticonvulsant by regulating taurine levels in the CNS (17). It has also been suggested that large doses of taurine may be harmful to some epileptic patients (137). A generalized amino aciduria occurred in one patient who received 2–2.5 g/day for 2 weeks.

**Cardiovascular Disease**

Taurine levels in the left ventricular myocardium of patients who had died from congestive heart failure were double the levels of those who had died of causes other than cardiac pathology (59). However, no differences in taurine concentration of aortic tissue were found. More recently it was reported that taurine was elevated in whole blood, but not plasma, in acute myocardial infarction (79) and also within 24 hr in patients undergoing cardiovascular surgery (78).

The results of a randomized, double-blind, crossover study of 58 patients with congestive heart failure led to the conclusion that taurine administration was beneficial (10). The study involved 28 males and 30 females, 38 to 89 years of age, including those who were diagnosed as having valvular heart disease, ischemic heart disease, cor pulmonale, hypertensive heart disease, congenital heart disease, and idiopathic cardiomyopathy. At entry, 30 patients were classified according to the New York Heart Association criteria as functional class III, 29 in class II, and 3 in class IV. Taurine (2 g, three times daily) or placebo was given for 4 weeks. Doses of digitalis, vasodilators and diuretics were continued during the study period. Clinical efficacy of taurine was superior to that of placebo for valvular and ischemic heart disease patients. In the taurine group, 16 of 58 patients showed improvement in functional class whereas 1 patient worsened and while on placebo, 6 of 60 patients improved and 7 worsened ($P < 0.01$).

In a subsequent study designed to determine the effect of taurine on systolic time intervals in patients with congestive heart failure, this research group studied 14 patients, 15 of whom had chronic ischemic heart disease (11). The protocol and taurine dosage were identical to that of the preceding study. A composite score of heart failure severity improved during taurine but not during placebo administration ($P < 0.001$). The preejection period of the left ventricle (PEP) ($P < 0.001$) and total electromechanical systole ($P < 0.05$) were reduced during taurine but not during placebo administration. Taurine also improved the PEP:left ventricular ejection time ratio (LVET) ($P < 0.001$). Among the ischemic heart disease patients, PEP was reduced ($P < 0.005$) and the PEP:LVET ratio improved ($P <
Urinary taurine, taurine clearance, and the urinary taurine:creatinine ratio were each significantly decreased in essential hypertension patients (71). Plasma renin activity was negatively correlated and urinary kallikrein was positively correlated with urinary taurine excretion in hypertension. When 6 g/day taurine was administered to six men and two women patients with essential hypertension for a 6-week period, systolic and diastolic blood pressure were significantly decreased but no change in plasma renin or aldosterone was found. Urinary taurine and kallikrein levels exhibited a significant increase in these subjects. This study was uncontrolled and consequently the observed decline in blood pressure may have been unrelated to taurine therapy.

When 6 g taurine/day for 7 days was given to young adult males with borderline hypertension their systolic and diastolic blood pressure decreased (P < 0.05) compared to placebo-treated controls (43). Taurine also reduced (P < 0.05) epinephrine levels to those of normotensive subjects and attenuated the increased response to intravenous glucagon. A correlation (P < 0.001) was noted between decrements in mean blood pressure and those in plasma epinephrine (43).

Hepatic Disorders

Two groups of patients with acute hepatitis, all having serum bilirubin levels above 3 mg/dl, were studied using a double-blind, randomized protocol (83). There were 31 patients given taurine (4 g, three times daily after meals) and 32 given a mannitol placebo on the same schedule. Bilirubin, total bile acids, and glycine:taurine ratio all dropped significantly within 1 week of therapy in the taurine group compared to the controls. The taurine-supplemented patients exhibited a decreased percentage of glycocholic and glycochenodeoxycholic acids with an increased percentage of taurocholic and taurochenodeoxycholic acids in the first week of therapy. Taurine administration also reduced the icteric period.

Taurine therapy may be beneficial when ursodeoxycholic acid (UDC) is administered in gallstone treatment since its taurine conjugate is more soluble and has a greater capacity to solubilize cholesterol and other nonpolar lipids than the glycine conjugate (63). When taurine was given with UDC at a dosage of 1.5 g/day, 10–40% of UDC was taurine conjugated compared to 65% when 3.5 g/day was used (18). Adult males given taurine (0.5 g, six times/day) for 2 weeks showed a significant decrease of 11% in bile acid pool size (51). The mean level of taurine conjugation was increased from 33 to 66%. Biliary saturation index, percentage distribution of primary bile acids, biliary cholesterol saturation, and phospholipid secretion rates were all unchanged.

Cystic Fibrosis

Taurine supplementation (30 mg/kg/day) had a favorable effect on fat absorption in 19 children with cystic fibrosis according to a single-blind, placebo-controlled, crossover trial during separate 6-month periods (32). On taurine supplementation, steatorrhea was reduced by 17.6 ± 9.7% (P < 0.05). In 10 patients with more severe steatorrhea, the decrease in fat loss approached 20% and a dose relation-
ship was observed \((r = 0.84; P < 0.01)\) between the extent of the fatty acid loss on placebo and the decrease of this loss on taurine. The authors maintained that use of taurine as an adjunct in cystic fibrosis therapy requires further confirmation before it can be recommended for general use (32).

Myotonic Dystrophy

A double-blind, single crossover study among nine myotonia patients of both sexes using oral taurine (100–150 mg/kg/day) for a 6-month treatment period led to significant clinical improvement (36). Electromyographic (EMG) and muscle sensitivity to intra-arterial infusion of KCl were favorably affected. EMG relaxation time after maximal voluntary effort was significantly \((P < 0.01)\) less than baseline and placebo levels.

Alcoholism

Taurine was given orally (1 g, three times/day) for 7 consecutive days to 22 patients undergoing alcohol withdrawal treatment (64). Their response was compared with that of 38 retrospective controls. Of the taurine-treated patients, 14% had a psychotic state after admission compared to 45% of the controls \((P < 0.05)\). 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 controls \((P < 0.001)\).

Uremia

Taurine in muscle was lower \((P < 0.01)\) than that in controls in a group of 7 uremic patients treated with essential amino acids and a low protein diet but not significantly different among another group of 9 uremic patients given the same low protein diet but with a different essential amino acid pattern (7). These workers also found plasma taurine levels reduced \((P < 0.05)\) in 12 uremic patients. In contrast, other studies have reported significant elevation of taurine in plasma (33).

The inconsistent findings of plasma taurine concentrations in uremia may be due to differences in the patient’s clinical condition or in the therapeutic modalities used. Methodological errors during measurement of plasma taurine concentrations may account for some discrepancies since contamination with platelets and leukocytes, containing very high levels of taurine, is possible (52).

PROTECTIVE ACTIONS OF TAURINE IN ANIMALS

As is the case with other aspects of taurine’s action (131), extrapolation to humans of taurine’s protective effects based on animal studies may not be prudent because many of these actions are highly species specific (66). Nevertheless, some results of such studies will be briefly noted to indicate the diversity of taurine’s protective effects.

Mice treated with 3% taurine in drinking water 8 days prior to and during an arteriopathic regimen, consisting of vitamin D3 and nicotine administration for 4 days, had an increased survival rate and reduced elevation of calcium in aorta and myocardium (147). The authors suggested that taurine may prevent progression of arteriosclerosis.
Hamsters pretreated for 14 days with 0.5% taurine in drinking water showed no tissue damage upon exposure to 7 or 30 ppm NO$_2$ for 24 hr in contrast to severe damage sustained by untreated controls (48). The authors suggested that taurine may also protect against lung injury by other oxidant gases.

Taurine exhibits protective actions against deleterious effects of various drugs. Taurine treatment of mice given taumustine, an antitumor agent, prevented the toxicity of this compound without interference with its activity (102). Parenteral administration of taurine partially protected chick hearts against necrotic changes induced by isoprenaline (89). In guinea pigs, taurine alleviated the effects of sulfolithocholate, a hepatotoxic agent (35). Retinoids are known to exhibit membrane destabilizing actions. The amino group of taurine reacts with the hydroxyl group of retinol resulting in retinotaurine, which is excreted in bile (120).

Taurine is also radioprotective. For example, it promoted leukocyte recovery and increased 30-day survival of irradiated mice (1).

**DISCUSSION**

Despite its discovery in 1827, the significance of taurine in preventive medicine has been largely overlooked until the middle of the last decade. Neglect of taurine by medical scientists is understandable. With the exception of cow’s milk and its products, taurine is widely distributed in foods of animal origin. Moreover, it can be synthesized from sulfur-containing amino acids by various human tissues and organs. Consequently it was assumed that either exogenous or endogenous sources would suffice to meet whatever physiological requirements exist. It has now, however, become apparent that for certain individuals of both normal and abnormal health status, taurine is, in some situations, an essential nutrient. Development of the concept of conditionally essential nutrients (28) provides the conceptual framework by means of which acceptance of taurine’s significance may be facilitated.

Taurine status is determined by equating the sum of its biosynthetic formation and dietary intake with tissue and organ requirements. Human infants are considered less susceptible to taurine deficiency than the young of other species because of their capacity to conjugate bile acids with glycine coupled with their relatively slow growth rate (52). However, taurine biosynthesis in infancy, at best, seems to be very limited (124). Accordingly, reliance upon endogenous production of taurine, particularly in preterm infants, may not be warranted. As a precautionary measure, the U.S. Food and Drug Administration in July of 1984 permitted taurine addition (ca. 50 mg/liter) to proprietary milk formulas (57).

While serving to minimize the likelihood of postnatal taurine deficiency, taurine fortification of human infant formulas has no influence on in utero effects of maternal consumption of a low-taurine diet. At particular risk, in this context, could be infants of strict vegetarian (vegan) mothers (122). It is uncertain whether any of the reported health problems of children on vegan diets (119) are related to taurine deficiency. Taurine depletion may accompany malnutrition because of its absence from foods of plant origin. The latter make up the bulk of calories consumed by undernourished populations. Moreover, animal studies suggest that taurine deficiency is exacerbated by protein deficiency (135). Dietary pyridoxine
deficiency may also compromise taurine status (118). Some authors consider that
dietary taurine supplementation would be beneficial to those on marginal diets,
especially during pregnancy (122).

In a study involving 4 omnivores and 4 vegetarians, it was found that taurine
excretion fell sharply from the ninth week of pregnancy (86). A further reduction
in taurine excretion occurred among the vegetarians from the end of pregnancy to
4 to 6 weeks of lactation, the respective values being 35 ± 5.5 and 15 ± 2.0
μmol/day (86). These workers also investigated taurine secretion in milk of 14
omnivore and 14 vegan mothers and found taurine concentrations lower (P <
0.01) in the latter. However, some vegan mothers secreted more taurine in their
milk than did omnivore mothers. The authors conclude that suppression of urin-
ary taurine excretion provides a mechanism for ensuring taurine availability for
the fetus and nursing infant (86).

In contrast to the uncertainties of neonatal taurine status, the likelihood of pre-
carious taurine nutriture for normal adults on a mixed diet is negligible. The
taurine content of a typical Western diet is believed to range between 40 and 400
mg/day (100–1000 ppm) (52). Compensatory mechanisms for dietary taurine depre-
ivation include alteration of the bile salt glycine:taurine ratio in favor of the
former, a relatively slow whole body turnover of taurine and the above-mentioned
reduction of urinary taurine excretion (25, 57).

Patients with disorders of renal reabsorption, chronic malabsorption syn-
dromes, hepatic or muscle diseases, and those with above normal taurine require-
ments may exhibit unsatisfactory taurine status (57). Serious consideration should
be given to taurine supplementation in long-term parenteral nutrition (139, 140).
Clinical implications of the recently discovered lower plasma and urinary taurine
concentrations in 12 male vegans are unknown (76). Although plasma taurine
concentrations were significantly reduced in this group to 78% of control values,
they were still higher than those in patients undergoing long-term parenteral nu-
trition (139).

Preliminary evidence suggests that taurine may be of value in the treatment of
congestive heart disease (11), acute hepatitis (83), cystic fibrosis (32), and myo-
tonic dystrophy (36). Confirmation of these reports is required before taurine can
be recommended for general use in these disorders. Taurine derivatives may
eventually be added to the anticonvulsant therapeutic armamentarium (61).

With few exceptions, animal (37, 65) and human (10) studies have demonstrated
that taurine, even in high doses, is generally free of serious side effects. In an early
and as yet unconfirmed report, it was noted that oral doses of 2 g produced intense
itching in psoriasis patients in 1 hr and this persists for about 24 hr (109). Skin
lesions increase in redness and begin to scale profusely about 18 hr after taurine
intake. The itching response may be elicited in patients in complete remission.

Adverse reactions occurred in 4 of 25 epileptic patients given 1.5 g/day, two of
whom discontinued therapy (127). Complaints included nausea, headache, dizziness,
nose-bleed, and mild gait disturbances. A generalized amino aciduria occurred
in one epileptic patient who received 2–2.5 g/day for 2 weeks (137).

According to unpublished observations, hypothermia and/or confirmed cardiac
taurine have occurred in several patients with uncompensated adrenocortical insufficiency with hyponatremia and hyperkalemia following administration of taurine (95). In one patient with hyperkalemia, a seizure followed a 0.5-g dose, even though this patient had never before seized (95).

On the basis of rat studies, it was concluded that taurine may have adverse affects on inhibitory or memory functions (111). Oral administration of 0.4% taurine to guinea pigs in drinking water for 2 weeks induced fatty changes and increased liver triglycerides fourfold (24). Because of their extreme variation in plasma triglyceride levels, guinea pigs may be atypically sensitive to fatty liver induction (24).

It is likely that taurine is involved in membrane stabilization at several levels and that this action accounts for many of its physiological effects (146). Taurine may protect membranes by detoxification of destructive compounds and/or by directly preventing alterations in membrane permeability.

Taurine concentrations are generally high in tissues which generate high levels of oxidants, e.g., neutrophils. Hypochlorous acid (HOCl) is formed by the myeloperoxidase of neutrophils and other phagocytes from hydrogen peroxide which, in turn, is a product of superoxide dismutase action. Hypochlorous acid is a potent oxidant, reacting with an array of biochemicals including amines to form unstable chlorinated α amino acids (146). The latter spontaneously degrade to form extremely toxic aldehydes. However, β amino acids such as taurine react with HOCl to form the more stable N-chloramines (146). Taurine chloramine (N-chlorotaurine) is far less reactive than HOCl and thereby serves as a cellular protective agent. The fact that taurine chloramine is produced by phagocytes, lymphoblastoid, epithelial, and other cells supports the hypothesis that taurine functions as a general detoxification mechanism which prevents oxidant-producing cells from autolysis (96-98).

Numerous aspects of taurine function and its interaction with other biochemicals, xenobiotics, and nutrients require further study (52). In normal subjects, plasma levels of taurine range from 50 to 220 μM but what constitutes marginal or even unacceptable plasma concentrations is currently unknown. This is also the case with urinary taurine which may exceed plasma concentrations by one order of magnitude, depending on dietary intake. Plasma taurine levels may be more indicative of taurine intake than tissue levels since most tissues concentrate taurine against a gradient. Urinary taurine levels are more sensitive to dietary taurine restriction than tissue levels, the respective concentrations changing in 1-2 weeks compared to 1 month.

Corroboration of taurine's effects in various clinical disorders including retinitis pigmentosa (145) and in the treatment of alcohol withdrawal (64) is required. A large-scale, long-term, carefully controlled study of taurine administration in the different subtypes of seizure disorders is mandatory before any firm conclusions can be made on its efficacy in epilepsy therapy (40). The taurine status of strict vegetarians, especially during infancy, also requires further study (122) as does the significance of low plasma taurine in cancer patients (84) and some uremia patients (7).
Also warranting further investigation is the influence of essential fatty acid availability on taurine nutritional status (52) and taurine's interaction with other nutrients including vitamins and minerals (97).

Finally, the hypoglycemic properties of taurine, known for over half a century (2) and mediated through potentiation of insulin action rather than by increase of serum insulin (74), merits additional study. Taurine is believed to exert its promoting and/or regulatory effects on insulin by interaction with the insulin receptor (74).

In several respects, taurine is analogous to carnitine, another conditionally essential nutrient (70). Both are derivatives of amino acid metabolism, are absent from foods of plant origin, and are reduced in body fluids of patients with certain chronic disorders and those on TPN. Both also share the dubious distinction of often being overlooked, as evidenced by their omission from a reference volume on medical nutrition (113).

To conclude, in view of its diverse functions including bile acid conjugation, neuroinhibition, membrane stabilization, modulation of cation flux, osmoregulation, and attenuation of toxic compounds, taurine fully warrants the increased level of attention and scrutiny it is now receiving. In its recently recognized role as a conditionally essential nutrient, taurine has several important preventive medical applications.


REFERENCES


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