Taurine in Human Milk: Biological Significance

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Taurine (2-aminoethanesulfonate) is a sulfur-containing β-amino acid present in many animal species but rare in most species of plants (1). Synthesized via the transulfuration pathway, taurine has long been considered a metabolically inert end-product of methionine and cysteine catabolism. In most animals, taurine synthesis is directly proportional to the specific activity of the vitamin B<sub>6</sub>-dependent enzyme, cysteinesulfmic acid decarboxylase (CSAD). The distribution of CSAD varies among species and among tissues in a particular species. For example, mice, rats, and dogs possess high CSAD activity and are obligate taurine synthesizers, whereas other species, like humans and cat, possess very low CSAD activity and synthesize limited amounts of taurine (1,2).

Unlike carboxylic-containing α-amino acids, taurine is not translationally incorporated into proteins and is not used as a source of energy. It usually occurs in millimolar concentrations as the major free amino acid in many tissues and fluids. This is especially true for the central nervous system (3), the retina (4,5), the adrenal gland, the hypophysis, and the pineal gland (6,7). In other tissues, taurine comprises one of the predominant free amino acids (1,8). Its ubiquity among a variety of animal species (1); its abundance in the free amino acid pool of most cells, tissues, and fluids (1,8); and its efficient mechanisms of cellular uptake (9), renal conservation (10), placental transfer to the fetus (11), and lactational transfer to the neonate (12) all suggest that taurine has an important physiological function and may have a fundamental nutritional role. Even though taurine has been implicated in many physiological functions, pathological conditions, and pharmacological actions, a specific role for taurine has remained elusive.

Historically, taurine was first isolated from ox bile in 1827, ergo its name (13). Since then an extensive literature has accumulated describing the pres-
ence of taurine and taurine derivatives in numerous species of animals and in lower phyla of plants (1). A renaissance of interest in the possible role for taurine in nutrition occurred a decade ago with the publication of the preliminary communication on retinal degeneration in the taurine-deficient cat (14) and in work demonstrating the failure of formula-fed preterm infants to maintain normal plasma and urine taurine concentrations (15). Unlike taurine-depleted cats, taurine-depleted infants do not demonstrate any functional impairment. Since these original observations, the conundrum has been to understand how an ostensible deficiency in humans could be apparently unassociated with any physiological impairment or pathological state, whereas the same deficiency in the cat results in profound pathological changes. This conundrum can be resolved by the concept of the conditionally essential nutrient.

**TAURINE AS A CONDITIONALLY ESSENTIAL NUTRIENT**

In studies on feeding the preterm infant, it was noted that in infants receiving various formulas, compared with those receiving pooled human milk, most plasma and urine free amino acids were increased. Taurine in contrast was present in lower concentrations in the plasma and urine of the formula-fed infants (15). These observations suggested the major source of taurine to be the diet. This hypothesis is consistent with the low specific activity of CSAD found both in immature and mature human liver (16).

The milk of many mammals contains taurine (17); however, the concentration varies among species, and the amount decreases during lactation. The milk of the dairy cow, a chronically lactating mammal, possesses very little taurine, even though the milk that the calf receives has a concentration of taurine similar to that found in human milk. These findings explain why standard bovine-milk-based formulas contain so little taurine and why the taurine concentration in plasma and urine of the formula-fed preterm infant is lower than that of the infant fed human milk. Similarly, full-term infants have a parallel response to formulas low in taurine (18,19). When these formulas are supplemented with taurine, in concentrations the same as those found in human milk, the plasma and urine concentrations of taurine in these infants are the same as those fed human milk (20,21). When adult humans are chronically fed synthetic liquid diets devoid of taurine, taurine is not present in the urine (E. Ahrens and S. Moore, personal communication). This observation is consistent with experiments demonstrating that adult humans have the ability to synthesize limited amounts of taurine (22). It would be interesting to know how far humans can expand their ability to synthesize taurine and to determine the circumstances under which such expansion occurs.

In the area of experimental nutrition, traditional studies have been con-
cerned with identifying essential nutrients, estimating their dietary requirements, and ascertaining their metabolic functions. Thus, adequate nutrition is defined as having enough or, in some instances, not too much of an essential nutrient. In recent years this definition has been modified to consider the conditionally essential nutrient (23).

A conditionally essential nutrient is usually synthesized or acquired and stored in amounts adequate to maintain health (23). Under extreme conditions, such as inherited or acquired diseases, increased metabolic demand, or decreased availability, nutrient stores are depleted, resulting in physiological changes that might result in frank pathological conditions. With respect to taurine there can be inadequate storage, as in the premature infant (15). In other instances, such as taurine-free total parenteral nutrition (E. Ahrens and S. Moore, personal communication; 24), the deficiency may be iatrogenic. Finally, in certain inherited retinopathies, altered ability to acquire sufficient amounts of taurine, combined with limited synthesis, results in irreversible retinal degeneration (25).

The first examples (14,15) of the nutrient role of taurine involved such extreme conditions. For the taurine-deficient cat, the events were the feeding of an abnormal diet plus the inability of the cat to synthesize and to conserve taurine. In the human infant, the events were premature birth, the feeding of an unnatural diet (formula) due to the inability to suckle, plus the inability to synthesize and to conserve taurine in amounts adequate to maintain body pools (15,21,26). These complex interactions allowed the identification of taurine as a conditionally essential nutrient in each case.

The effects of taurine deficiency on the retina are not limited to the cat. Retinal dysfunction and/or pathology has been identified in rodents, non-human primates, and humans. Identification of such functional impairment or structural damage has required the imposition of iatrogenic factors, i.e., the conditionally essential nutrient. In rats receiving the taurine-transport inhibitor guanidinoethanesulfonate (GES), depletion of taurine results in degeneration of photoreceptor cells (27,29). After 2 years of feeding taurine-deficient infant formulas to monkeys, there is considerable damage to the photoreceptor cone outer segments (29). In humans, abnormalities in retinal function, as measured by electroretinography, and pigment epithelium defects, as determined with fluorescein angiography, occur in the “blind-loop” syndrome (30). This syndrome results in intestinal stasis, resulting in a bacterial flora that catabolizes taurine. This catabolism produces critically low concentrations of plasma taurine, resulting in cellular deficiency and in retinal abnormalities.

Children maintained on long-term parenteral nutrition also develop low plasma taurine concentrations. No clear signs of retinal degeneration are discernible by ophthalmoscopy (24), but electroretinography and visual-evoked potentials in these individuals identify clear-cut functional impair-
ment. These retinal abnormalities can be reversed by providing taurine in the parenteral solution (24).

As discussed previously, certain inherited diseases demonstrate the conditional essentiality of a nutrient. For example, taurine transport into cultured cells from individuals with retinitis pigmentosa differ significantly from cultured cells derived from unaffected individuals (26). The mean $V_{\text{max}}$ of affected cell lines is lower than that of control cell lines, whereas the mean apparent $K_m$ for the affected cell lines is greater than that for control cell lines. With a decreased rate (or efficiency) of taurine transport ($V_{\text{max}}$) and an decreased affinity ($K_m$) to transport taurine, affected individuals cannot acquire and store adequate amounts of intracellular taurine even when plasma concentration are normal. These findings indicate that altered taurine transport may be a contributory factor in the manifestation of the retinitis pigmentosa group of disorders. The transport defect is presently unknown; it may be the taurine transporter per se or a deficiency in some component of the cell membrane that affects the transporter. The possible interactions of the nutritional availability of taurine and these alterations in transport in individuals with inherited retinal degeneration need to be investigated further, since nutritional deficiency severe enough to result in reduced plasma concentrations may be an exacerbating factor.

FUNCTIONS OF TAURINE

Taurine, along with inorganic sulfate, has for a long time been considered to be the biochemically inert end-product of the transsulfuration pathway. Certainly, taurine was not utilized for production of energy; used as a substrate or cofactor in any enzyme system; translationally incorporated into protein; or attached to lipids, nucleic acids, or polysaccharides. Even though taurine is well known for its conjugation with bile acids (31), some xenobiotics (32), and retinol (33), these reactions, which attenuate and help to eliminate toxic compounds, consume only 1% of the available taurine (32,34). Thus an important question may be, What is the function(s) for the remaining 99% of free taurine?

Several experiments have demonstrated that taurine may be a necessary and metabolically active amino acid. All of these experiments have focused on the role of taurine in protecting cellular membranes, enhancing the proliferation of cultured cells, or attenuating specific oxidants.

Six lines of evidence suggest that taurine plays an important role in the stabilization of membranes. These include

1. The original work of Hayes et al. (14), demonstrating the disruption of photoreceptor cell membranes in the taurine-deficient cat. This work was extended to include effects on the tapetum lucidum of the taurine-defi-
Taurine counteracting damage caused by external agents to the intracellular membranes of skeletal (36) and cardiac (37) muscle.

3. Taurine protecting isolated photoreceptor rod outer segments against structural damage induced by illumination and by oxidants (38).

4. Taurine protecting cultured cells against retinol-induced and ferrous sulfate-induced damage and swelling (39,40).

5. Taurine acting as an antioxidant in protecting spermatozoa (41).

6. Taurine protecting hepatic cells against damage to membranes by carbon tetrachloride (42).

In each of these cases, the membrane-protecting effect of taurine is not known. These experiments, however, do raise the possibility that the protective effects of taurine may be mediated through an ability to reduce lipid peroxidation. This could be by either interacting directly with membrane components, which could stabilize their structure, or attenuating oxidants, which could initiate peroxidative damage.

Another example demonstrating that taurine is a necessary and metabolically active molecule comes from in vitro experiments. In a cell culture system, in which taurine concentrations can be controlled, taurine enhances the proliferation of cells in a concentration-dependent manner (43). This action of taurine could result from its interacting with oxidative and peroxidative cellular products that could cause extensive cellular damage and subsequent death. This interpretation is supported by the fact that many well-known antioxidants also enhance the proliferation of cultured cells (44). Furthermore, tissues and cells that possess considerable potential for generating oxidants (i.e., the retina and neutrophils) contain high concentrations of taurine (4,5,8).

Insight into a major physiological role for taurine comes from experiments examining the phagocytic process of neutrophils (45). Neutrophils are unique in that approximately 7% of their total protein content is an enzyme called myeloperoxidase (45), and over 80% of their free amino acid pool consists of taurine (8). During phagocytosis, myeloperoxidase catalyzes the formation of hypochlorous acid (HOCI) from hydrogen peroxide and chloride anion (45–48). Hypochlorous acid is a potent oxidant; its biocidal properties are well known. It can directly oxidize a variety of biologically significant substances, such as peptides, amino acids, nucleic acids, lipids, and carbohydrates. Hypochlorous acid can also form secondary chlorinating agents, such as molecular chlorine, N-chloramides, and N-chloramines, which in turn can oxidize biologically significant molecules (49,50).

When hypochlorous acid reacts with any organic or inorganic amine, the nitrogen acquires either one or two chlorine atoms. This reaction is dependent on the concentration of hypochlorous acid and the ionic strength of the
environment. Above pH 6, the amino group acquires one chlorine atom, forming a monochloramine; below pH 6, the amino group acquires two chlorine atoms, resulting in the formation of a dichloramine.

Most N-chlorinated α-amino acids are unstable (51) and spontaneously deaminate, decarboxylate, and dechlorinate to form the respective aldehyde. This series of oxidative events can also occur on peptide linkages, resulting in the degradation of proteins; however, not all amino acids react this way to hypochlorous acid. Amino acids that possess amino groups at other carbon positions react with hypochlorous acid to form relatively stable N-chloramines (52). Taurine is a β-amino acid that can be N-chlorinated by myeloperoxidase, thus forming a stable taurine chloramine (49,50,52–54). Once formed, taurine chloramine participates in few reactions, oxidizing thioether bonds and reduced sulfhydryls (45,46). Even though taurine is still an oxidant, it reacts with fewer organic molecules than does free hypochlorous acid. Thus, taurine chloramine formation attenuates the biocidal activity of hypochlorous acid generated via enzymatic, chemical, and photochemical processes. This property of taurine may provide protection to the cells from oxidant damage and subsequent death.

The formation of taurine chloramine in various types of cells that possess phagocytic properties (51) suggests that taurine is not merely a metabolically inert end-product; rather, taurine may function in the biological system as a general detoxifier (39), eliminating excessive bile acids, removing xenobiotics, and scavenging chlorine oxidants. Taurine may thereby protect cells and tissues from self-destruction. This protective property may be reflected in the experiments examining the effect of taurine on membrane stability. Thus, deficiency of this amino acid could lead to pathological changes.

SUMMARY

The past decade of research has established taurine as a conditionally essential nutrient in humans and has given us an important insight into its role. This information provides us with a conceptual context within which to examine the physiological role of taurine in human nutrition. The next decade promises to be even more stimulating, as we elucidate the mechanism of its action as a nutrient.

REFERENCES


DISCUSSION

Dr. Ogra: Which cell line or lines did you use? Do you know whether they were predominantly B-cells or T-cells?

Dr. Gaull: The cells are not heterogeneous. They are lymphoblasts—primitive cells from the lymphoid line—and they behave mainly like B-cells but retain some characteristics of T-cells as well.

Dr. Rāiḥā: What in your opinion are the main reasons why formulas should be supplemented with taurine?

Dr. Gaull: Treating a biochemical abnormality is not sufficient in itself to make such a recommendation, but I feel that the evidence of changes in electroretinograms from patients on long-term TPN without taurine supplements, together with the evidence we have in primate models of electroretinographic and electron microscopic retinal changes, are compelling reasons to suggest that formulas should be supplemented. I do not think we can say that if we do not supplement formulas with taurine we are going to see epidemics of blindness, but I think the evidence is fairly overwhelming that you will get biochemical changes if you do not give taurine to children or adults. However, you could not really do the kind of experiments that would prove that long-term deficiency would lead to blindness in children.

Dr. Guggenbichler: Cardiomyopathy has been described in a few children with cystic fibrosis, which we have attributed to vitamin E deficiency. In light of your study, we must rethink the possible etiology of this condition. It may be a taurine-plus-vitamin E deficiency disorder.

Dr. Gaull: The largest single pool of taurine in the body is in skeletal muscle, and the myocardium is like skeletal muscle in this respect.

Dr. Guggenbichler: There is a striking decrease in taurine in children with cystic fibrosis—it fits perfectly. This may be a clinical manifestation in humans of taurine deficiency.

Dr. Hanson: Have you looked at taurine in milk of vegetarian mothers?

Dr. Gaull: No, but in the taurine-deficient cat model there is a striking decrease in taurine in the milk. You also find CNS and retinal abnormalities in the fetus, and fetal death and resorption.

Dr. Berotis: You demonstrated nicely that cells need taurine to grow in vitro, and this is important because in an isolated system you can study how the cell behaves when deficient in this nutrient alone. My question is, Have you studied the DNA content in the brains of animals that have developed in a taurine-deficient environment?

Dr. Gaull: I do not know whether there is any change in DNA content, but where there is taurine deficiency, brain development is retarded. Taurine is present in the human fetal brain in the highest concentration of all the free amino acids, and it decreases very gradually during postnatal life. In animals it has been shown that the concentration in the brain declines to adult levels by the time of weaning. When there is retardation of brain development for any reason, there is increased taurine concentration in the brain. I do not know what taurine deficiency itself does, beyond the recent information that there is a delay in cell migration.

Dr. Lucas: Could you develop in more detail what you think may be the reason for the development of the photopic electroretinographic abnormalities in taurine deficiency?

Dr. Gaull: This is not known precisely; however, we showed some time ago that taurine is rapidly transported axonally in the optic nerve of the goldfish and that this transport changes with development, so there may be a requirement for optic nerve growth. On the other hand, it is also known that taurine is concentrated by retinal
cells, especially in the photoreceptor cell layer and the retinal pigment epithelium, so where blood vessels are coming in from two directions there is concentration of taurine from both sides. This again suggests that it really is important. We have also shown that there is a decreased uptake of taurine, due either to a change in $K_m$ or $V_{max}$ or both in the same long-term lymphoid cell lines in members of families affected by retinitis pigmentosa. I am well aware that retinitis pigmentosis is a heterogeneous group of disorders, but the finding is true of all types that we have looked at. I believe that there must be a variety of changes in the retinal membranes that can be transmitted in tissue culture and are thus heritable, and which segregate according to the type of underlying defect without themselves being the primary etiology. Under such circumstances, dietary deficiency of taurine will result in more rapid onset of symptoms of the underlying disease.

_Dr. Giovannini:_ There may be a case for adding taurine to formulas for preterm babies. Do we need to do so for full-term babies as well?

_Dr. Gaull:_ I believe that taurine is a conditionally essential nutrient in humans and that you can develop functional changes when you do not have enough of it. It is perfectly safe and prudent to add taurine to a formula in the concentration present in human milk. I should say that if anything, it is rather more important in the preterm infant than the term infant.