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New Functions for an Old Molecule

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Taurine is the major free amino acid found in tissues of marine invertebrates, aquatic animals, and most mammals, including man (1). Its name derives from the species, *Bos taurus*, in whose bile it was isolated in 1827 (2). Taurine is an old molecule since it is present in invertebrate species, particularly sea crustacea, and since it was discovered in the gallbladder of an ox more than 160 yr ago. Taurine is a β-amino acid, with its amine group residing on the β-carbon, and it contains a sulfonic acid in place of a carboxyl group. One unique feature is that it has a more acidic acid group, pKa1 = 1.5, and a more acidic ammonium group, pKa2 = 8.4, than amino acids bearing a carboxyl group (2). Although taurine is a relatively inert end product of sulfur amino acid metabolism (3) arising from methionine and cysteine, during the past decade a number of observations have indicated several potentially important biological roles for this molecule which have clinical implications.

With the initial reports that feeding preterm infants various formulae was associated with reduced urine and plasma taurine concentrations as compared to infants fed pooled human milk (4), questions emerged concerning the role of this heretofore conceived inert metabolite. The result of these concerns is the inclusion of taurine, in concentrations approximating those in human milk, to most infant formulae manufactured in the United States. Taurine now is added to both cow's milk and soy protein-based formulae. Following taurine supplementation at 30 μM/dl, urinary and plasma taurine concentration are essentially the same as values found in human milk-fed infants (5). A higher proportion of bile acids are conjugated with taurine than with glycine (lower G/T ratio) over the initial 5 wk of life (6). Nonetheless, this supplementation does not improve fat absorption, alter bile acid kinetics (7, 8), or change infant growth velocity (7, 9).

Despite these studies failing to indicate a readily demonstrable effect of taurine supplementation, several new studies suggest an important role for taurine in mammalian and human nutrition. First, taurine is a remarkably prevalent amino acid often found in millimolar quantities in various tissues (3) (Table 1). It is prevalent in excitable tissues, in membrane-rich cells, in cells that generate oxidants, and finally where toxic substances—bile acids, oxidants, and xenobiotics—prevail (2). Taurine is the main free amino acid of granulocytes where it forms a stable compound—taurine chloramine—after reacting with hypochlorous acid (10). As indicated the taurine content of various organs ranges from 2 to 30 mM/kg and in several visceral organs taurine is found in quantities exceeding 10 mM/kg. It is particularly concentrated in two sites in the retina—the retinal pigment epithelium and the photoreceptor cell layer—at levels of 50 mM/kg (11, 12).

The loss of taurine from the retina has been shown to result in a variety of retinal abnormalities. Cats fed a taurine-deficient diet develop both retinal and tapetal lesions. The cat is particularly susceptible to taurine depletion since it has almost absent cysteine sulfinic acid decarboxylase activity, the rate-limiting enzyme for taurine biosynthesis from methionine and cysteine, and because feline species are obliged to conjugate their bile acids with taurine (1, 2). Cats fed a taurine-free casein diet develop a granularity in their retinae with photoreceptor cell degeneration, a hyperreflective white zone, and nondetectable electroretinograms (13). Taurine-depleted cats also have a disorganized retinal tapetum (14). The usual array of tapetal rods that reflect light back through the retina and enhance retinal sensitivity in dim light undergoes distortion. Presumably the night driver would not see the shiny reflection of the cat's eye in a taurine-deprived feline. New World monkeys fed taurine-deficient infant formulae develop degeneration of the cone, but not rod, photoreceptor cells (15). Retinal abnormalities can occur in humans with intestinal disorders or in rats with surgically constructed blind loops: bacterial catabolism accounts for taurine depletion (16). Finally in children receiving long-term total parenteral nutrition and who ingest a minimal amount of calories by the oral route, electroretinographic changes can be shown (17). These changes in the B-wave of the electroretinogram reverse with taurine supplementation.

Although the role of taurine in the retina is not established, Wright *et al.* (2) suggest that it probably stabilizes retinal cell membranes, blocks lipid peroxidation by locally generated or exogenous oxidants, scavenges hypochlorous acid by the formation of the more stable compound taurine chloramine in the retinal pigment cell layer, and may serve to regulate intracellular calcium content. It is of interest that taurine transport into cultured human lymphoblastoid cells can be inhibited by two drugs—chlorpromazine and chloroquine—which cause retinal damage (18). If these compounds blocked taurine transfer in the retina this could help explain the cause for retinal damage.

Studies of human lymphoblastoid cells grown in culture have also shown the importance of taurine (2, 19). Some 60% of the intracellular free amino acids within the lymphoblast is taurine. Thus, it is difficult to deplete cells of taurine, particularly in serum-containing media. Continued growth in serum-free media will result in taurine depletion and a decline in the percent of viable cells. Restoration of taurine to the medium, followed by its active, uphill accumulation, returns cell viability to control values (20). Wright *et al.* (2) speculate that taurine may serve to stabilize membranes and preserve osmoregulatory homeostasis. An iron-ascorbic acid challenge will result in cell swelling, cell lysis, and death (21). Retinol and retinoid acid also can cause cell swelling and reduce cell viability (22). Restoration of taurine

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Table 1. *Taurine content of various organs (mM/kg tissue)**

Heart	30
Lung	13
Liver	2
Muscle	15
Kidney	11
Spleen	16
Small intestine	15
Large intestine	12
Stomach	9
Thymus	11
Cerebellum	3
Pons	4
Midbrain	3
Frontal cortes	6
Spinal cord	4

* Adapted from Reference 1.

to the medium reduced volume and increased viability. These studies indicate that damage to the cell membrane results in increased ion and water entry, increased cell volume, lysis, and cell death. Thus under these oxidant stresses, taurine preserves cell volume. Hence, taurine can be seen to have a role in cell volume regulation.

Taurine also appears to have a biological role as an oxidant scavenger. In many cells, including human granulocytes, it forms a stable chloramine with hypochlorous acid which will attenuate the biocidal action of this highly unstable, but locally generated oxidants (10). Taurine may also protect against autolysis. A recent study of hamster lung epithelium shows that dietary taurine supplementation prevents nitrogen dioxide injury (23). Nitrogen dioxide is a common air pollutant found in automobile exhaust and tobacco smoke. Exposure of hamsters to this agent led to flattening of bronchiolar epithelium with loss of cilia on ciliated cells and a diminution in Clara-cell secretory granules. Pretreatment with dietary taurine resulted in the same morphological appearance as found in controls not exposed to NO_2.

Table 2 lists the proven and hypothetical physiological functions of taurine. Among these are the oldest known function, the conjugation of bile acids to form water-soluble bile salts (1, 2). Present evidence in man suggests that this taurine conjugation of bile acids has no positive effect on fat absorption in comparison to glycine-conjugated bile salts. However, in patients with cystic fibrosis, the addition of taurine to the diet increases the proportion of bile acids that are taurine conjugated and increases fat absorption (24). Moreover, taurine-treated patients experienced an increase in height and weight velocity as compared to patients not so treated. It should be noted, however, that taurine-supplementation of infants, which increased the fraction of bile salts conjugated with taurine relative to glycine, does not affect growth (7–9).

Ample evidence exists that the total body pool size of taurine is regulated by the kidney (1–3). The actual amount of taurine needed to conjugate bile acids is minimal, on the order of 5% (25). Excess dietary taurine is excreted in the urine and, in the face of a reduction in intake, urinary excretion is diminished (1–3, 9). Our laboratory has been interested in the renal handling of taurine both in the rat and in man. We have focused our attention on the renal adaptive response to varying dietary loads of sulfur amino acid intake. These studies involve the use of carefully constituted isoproteinic (20% protein by weight) soy protein-based diets to which varying amounts of methionine and taurine are added (26). Since methionine is limited in soy protein, the low-taurine diet (LTD) contains 0.2% methionine and 0.0% taurine. The normal-taurine diet (NTD) is supplemented with 0.5% methionine and the high-taurine diet (HTD) contains the same methionine level plus 3% taurine. This diet, fed for 8–14 days, influences plasma and urine taurine values, but not plasma and urine methionine and cystine values (27). Plasma taurine values are 321 ± 29 (SE) μmol/liter in NTD-fed rats and falls to 182 ± 20 μM/liter in LTD animals; taurine rises to 1195 ± 87 μmol/liter plasma in HTD. Urinary taurine excretion was 5 ± 1 μmol/mg creatinine in NTD and fell to 0.5 ± 0.1 μmol/mg creatinine in LTD ($p < 0.001$) and rose 35-fold to 174 ± 20 μmol/mg creatinine in HTD rats ($p < 0.001$). This conservation of taurine in the urine in the LTD animals and urinary hyperexcretion in the HTD animals represents the renal adaptive response. The renal proximal tubule is the major site of renal amino acid reabsorption (28). This nephron segment has a rich brush border surface which is the location of active Na^+-dependent amino acid accumulation. Our group has performed transport studies on vesicles prepared from the isolation of this brush border surface (26–28).

The time course of taurine uptake, driven by an external NaCl gradient, is indicated in Figure 1. Uptake is significantly higher in vesicles prepared from rats fed the LTD. Reduction of uptake is found in vesicles from HTD-fed rats. This difference occurs both initially (initial rate) and at the peak of the Na^+-dependent overshoot. A kinetic analysis of the Na^+-dependent portion of concentration-dependent initial rate uptake, determined at 15 s, shows a similar affinity of the taurine transporter for its substrate despite the diet ingested; but there is a higher Vmax or initial rate of transport after the LTD diet and a lower initial rate after the HTD diet (26–28).

β-Alanine, another β-amino acid which competitively inhibits taurine transport, reduces renal cortex taurine content when fed to rats in their drinking water (29). This exposure to β-alanine while ingesting one of three diets does not significantly change

Table 2. *Biological properties of taurine**

Conjugation of bile acids
Conjugation of retinoids and xenobiotics
Osmoregulation and cell volume regulation
Antioxidant—scavenges hypochlorous acid
Influences intracellular calcium movement
Neuromodulation—neuroinhibitor
Stabilizes neural and excitable tissue membranes

* Adapted from References 1–3.

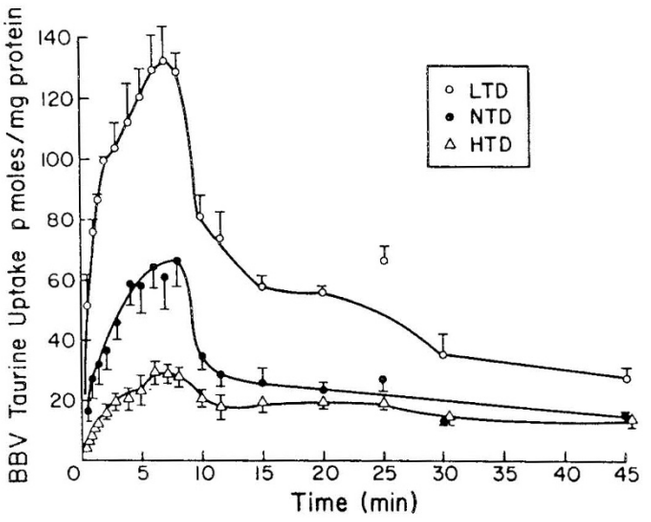

Fig. 1. The time course of ^3H-taurine uptake at 10 μM by rat renal brush border membrane vesicles. Note the difference in the uptake in relation to exposure to the low sulfur amino acid diet (LTD), the normal sulfur amino acid diet (NTD), and the high taurine diet (HTD). (Reprinted with permission from Chesney RW, et al, Kidney Int 24:588, 1983.)

plasma taurine concentrations, but does significantly increase brush border membrane vesicle uptake for each diet (Fig. 2). Also indicated in Figure 2 is that neither the type of diet ingested nor the β-alanine exposure results in changes in the concentration of taurine in brain, a site where taurine serves as an important neuromodulator (1–3).

Since the whole body taurine pool size needs to be maintained during the neonatal period when growth rate is greatest, we became interested in the nature of the renal adaptive response in lactating rap pups (30). Dams fed one of the three diets express the adaptive response to varied sulfur amino acid intake in another transporting epithelium—the mammary gland (Fig. 3). LTD-fed dams have a significantly lower and HTD-fed dams have a higher taurine content than NTD-fed dams. The renal epithelium isolated from pups exposed to each diet shows the typical adaptive response at 14 and 21 days, but not at 7 days. Also, there is an increase in the initial rate of uptake with age with uptake the lowest in 7-day-old pups and highest in adult brush border vesicles.

The uptake of taurine is Na^+ dependent and is energized by an internally directed NaCl gradient into a Na-free vesicle interior (26–30). Since cell volume regulation in marine invertebrates and certain sea-going fish is chloride-dependent, we evaluated the anionic requirement of renal taurine transport (1, 2, 31, 32). Of the various anions used in uptake studies, chloride sustained the highest level of uptake as compared to fluoride, iodide, sulfate, nitrate, thiocyanate, gluconate, and several other organic anions (31, 32). If bromide is substituted, it can sustain taurine uptake to the same degree as chloride. The use of loop diuretics, such as furosemide and bumetanide, which block Na^+-K^+-$2Cl^-$ transport across renal membranes does not impair the $NaCl^-$-driven transport of taurine. By Hill plot analysis, an hypothetical model for taurine transport across the renal proximal tubule can be constructed (Fig. 4). Taurine enters the apical or brush border side of the tubule cell coupled with at least two sodium ions and a chloride ion. Bromide can also substitute in this quarternary complex. Taurine exists at the basolateral or antiluminal side by another process; sodium is removed by the sodium pump and chloride exists by presumed Cl-HCO_3 exchange.

It is plausible that this same transport model operates in cells within the central nervous system; thus such a model may additionally contribute to the same osmoregulatory role of taurine in the brain. Taurine has other actions in the nervous system including stabilization of neural membranes, a neuroinhibitory or antiepileptic property, prevention of the paresis and cerebellar abnormalities found in kittens born of taurine-deprived queens (33), and preventing death in taurine-deficient kittens undergoing chronic hypernatremic stress (34).

The cat is unique in requiring dietary taurine, since the hepatic levels of the critical biosynthetic enzyme are extremely low (1–4). In recent studies by Trachtman *et al.* (34), taurine-deficient and taurine-sufficient kittens were exposed to 1 M NaCl for 72 h with a rise in serum Na to approximately 185 mM/liter. The outcome was that five of seven taurine-deficient animals died with a loss of brain cell water content. By contrast only one of seven taurine-sufficient cats dies and brain cell water content was maintained. These studies suggest that taurine is an impor-

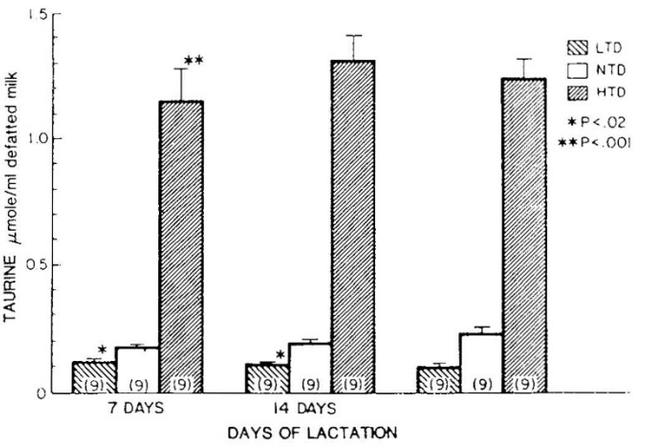

Fig. 3. Effect of diet on the taurine content of rat milk in nursing dams suckling rat pups of the ages indicated.

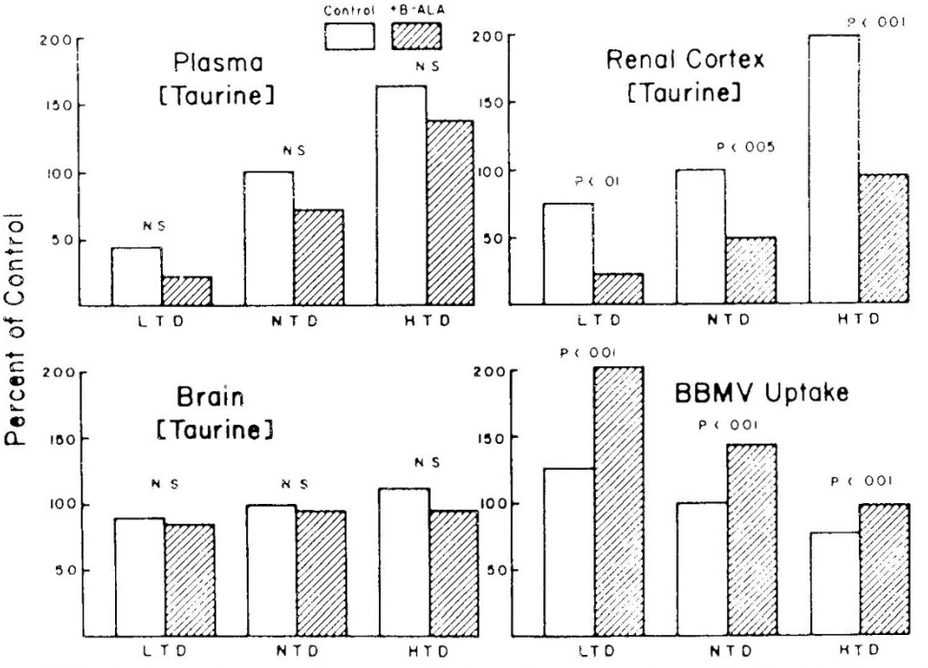

Fig. 2. Effect of diet and 3% β-alanine on plasma, renal cortex, and brain taurine concentrations and on brush border membrane vesicle uptake. (Reprinted with permission from Chesney RW, Adv Pediatr 32:1–46, 1985.)

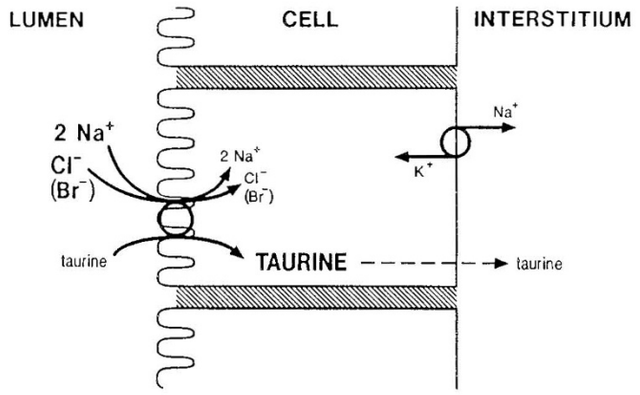

Fig. 4. An hypothetical model for taurine transport across the renal tubular epithelium in the proximal taurine.

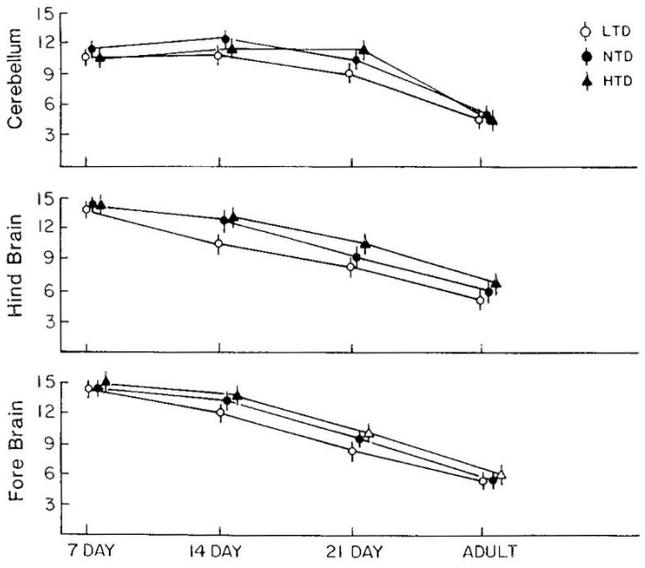

Fig. 5. Taurine content of three brain regions as influenced by age or dietary exposure (μmol/g tissue weight). *Symbols* are the same as in Figure 1.

tant idiogenic molecule that protects against cerebral edema or dessication.

In the rat not exposed to hypernatremic stress changes in diet do not influence brain taurine concentrations (35). The well-described decline in brain taurine content with age is found, but the type of diet exposure does not influence brain taurine concentrations in three brain regions (Fig. 5). We speculate that the renal adaptive response—conservation of taurine under periods of need and excreting under times of surfeit—may contribute to whole body taurine pool size. By an unknown loop, this maintenance of taurine homeostasis can contribute to the constancy of brain taurine content. If the kidney does contribute to the maintenance of brain taurine in order to preserve its neuroinhibitory and osmoregulatory properties, then the following quotation from the Talmud may have a meaning never dreamed of by its authors: "The organs of the human body were created to perform ten functions, among which is the function of the kidney to furnish the human being with thought" (36).

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