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Taurine: A therapeutic agent in experimental kidney disease

Review Article

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Summary. Taurine is an abundant free amino acid in the plasma and cytosol. The kidney plays a pivotal role in maintaining taurine balance. Immunohistochemical studies reveal a unique localization pattern of the amino acid along the nephron. Taurine acts as an antioxidant in a variety of *in vitro* and *in vivo* systems. It prevents lipid peroxidation of glomerular mesangial cells and renal tubular epithelial cells exposed to high glucose or hypoxic culture conditions. Dietary taurine supplementation ameliorates experimental renal disease including models of refractory nephrotic syndrome and diabetic nephropathy. The beneficial effects of taurine are mediated by its antioxidant action. It does not attenuate ischemic or nephrotoxic acute renal failure or chronic renal failure due to sub-total ablation of kidney mass. Additional work is required to fully explain the scope and mechanism of action of taurine as a renoprotective agent in experimental kidney disease. Clinical trials are warranted to determine the usefulness of this amino acid as an adjunctive treatment of progressive glomerular disease and diabetic nephropathy.

Keywords: Taurine – Antioxidant – Lipid peroxidation – Puromycin aminonucleoside nephropathy – Focal segmental glomerulosclerosis – Diabetic nephropathy – Hypertension

Introduction

Taurine (2-aminoethanesulfonic acid) is a ubiquitous amino acid in the cells of nearly all body organs. It is present as a free molecule and is not incorporated into structural protein (Chesney, 1985; Huxtable, 1992; Sturman, 1993). The cytosolic concentration of taurine is 1–5 mM depending on the particular type of tissue (Chesney, 1985). The transmembrane gradient between the plasma

and cell can exceed 100, a difference that is maintained by an epithelial Na^+-Cl^- coupled transporter (Huxtable, 1992).

Taurine is normally an abundant nutrient in the diet and it is readily absorbed from the gastrointestinal tract (Jacobsen et al., 1968). It is also synthesized from the metabolic precursor, cysteine, via the enzyme, cysteinesulfinic acid decarboxylase (Jacobsen et al., 1968). Although the hepatic biosynthetic capacity for taurine is limited in humans, the effects of dietary taurine deficiency are ameliorated by decreased conjugation of bile acids with taurine and a greater proportion of bile conjugation with glycine (Sturman, 1993). Therefore, taurine is considered a conditionally essential amino acid and serum and tissue levels of the amino acid can be compromised in newborn infants and patients receiving parenteral alimentation with taurine-free solutions for prolonged periods (Gaull, 1989; Zelikovic et al., 1990). Under most conditions, the adequacy of total body taurine balance is determine by the difference between dietary intake and urinary excretion of the amino acid (Chesney, 1985).

The kidney plays a crucial role in regulating body stores of taurine. It possesses the electrogenic Na^+-Cl^- coupled co-transporter in the proximal tubule brush border membrane (Zelikovic et al., 1989). This membrane protein carries out secondary active transport of taurine and other β-amino acids into the cytosol, taking advantage of the sodium gradient generated by the Na^+-K^+ ATPase pump that is present in the basolateral membrane. The activity of this carrier, the V_{max} of the transporter, is directly modulated by nutritional availability of taurine. When there is excessive taurine in the diet, reabsorption is suppressed; in contrast, under conditions of taurine deficiency, the activity of the transporter is upregulated (Chesney et al., 1985). Relative deficiency of this transporter accounts for the amino aciduria and hypertaurinuria observed in newborn infants (Chesney et al., 1986).

Taurine serves many functions including bile acid conjugation, modulation of neurotransmission, stabilization of the retinal membrane and osmoregulation (Chesney, 1985). The accumulation of taurine as a compatible organic osmolyte in cerebral and renal cells under conditions of hyperosmolality is accomplished to preserve cell volume (Trachtman et al., 1988, 1990; Nakanishi et al., 1991). Increased cytosolic taurine content minimizes changes in intracellular ionic strength and perturbations in protein structure and function. These cells enhance the activity of the Na^+-Cl^- coupled co-transporter in response to increases in ambient osmolality. This adaptation has been demonstrated in cerebral cells during chronic hypernatremia and hyperglycemia and in kidney cells during antidiuresis. Cultured MDCK (Madin-Darby canine kidney) cells, analogues of the distal tubule, display osmotically-regulated taurine uptake across the basolateral membrane (Jones et al., 1990; Uchida et al., 1991; Jones et al., 1995). These aspects of taurine handling by the kidney, including response to dietary changes and osmolal disturbances, have been well summarized in a recent report (Jones et al., 1993).

This review will summarize recent experimental findings that document a beneficial effect of taurine as a therapeutic agent to attenuate renal disease.

The bulk of the data will be based upon the antioxidant capacity of this amino acid. The ability of taurine to ameliorate kidney disease independently of its function as an endogenous antioxidant agent will also be presented.

Taurine and oxidant injury

There is considerable information gathered from *in vitro* reaction systems that taurine is an ineffective antioxidant that is unable to inactivate or scavenge common oxidant species such as the hydroxyl or superoxide radical. It is much less potent than hypotaurine and other sulfur-containing molecules at disrupting the initiation or propagation of oxidation processes (Arouma et al., 1988; Tadolini et al., 1995).

Despite the disappointing results that have been collected in chemical studies, there is abundant evidence that taurine functions as an antioxidant in a variety of *in vivo* biological systems. Taurine reacts with HOCl, a potent oxidizing agent generated by activated neutrophils, to form the less toxic product, taurine chloramine (Thomas et al., 1985; Cantin, 1994). This reaction retards damage to ocular surfaces exposed to HOCl (Nakamori et al., 1993). Taurine protects cultured lymphoblastoid cells against iron-ascorbate or retinol-induced oxidant damage and enhances cell viability (Pasantes-Morales et al., 1984; Pasantes-Morales et al., 1985). Taurine supplementation protects the lung from oxidant-induced damage following exposure to ozone or nitrogen dioxide (Banks et al., 1990; Gordon et al., 1986). In the case of ozone, the pulmonary injury is caused by increased expression of inducible nitric oxide synthase in lung macrophages and increased nitric oxide production. Taurine, via the formation of taurine chloramine, inhibits inducible nitric oxide synthase (iNOS) and prevents lung damage (Cantin, 1994; Schuller-Levis et al., 1994). Taurine alone or in combination with niacin reduces pulmonary fibrosis following intratracheal installation of the oxidants, amiodarone (Wang et al., 1992a) or bleomycin (Wang et al., 1992b). Finally, taurine attenuates adriamycin-induced cardiotoxicity in perfused chick hearts by decreasing myocardial lipid peroxidation (Hamaguchi et al., 1989).

Oxidant injury and the kidney

Reactive oxygen molecules are involved in progressive organ damage in several experimental models of kidney disease. In ischemic acute renal failure caused by bilateral renal artery clamping, intra-renal infusion of free radical scavengers such as catalase and superoxide dismutase lessens the reperfusion injury following restoration of renal blood flow (Paller et al., 1984). The hydroxyl radical contributes to the nephrotoxicity of the aminoglycoside antibiotic, gentamicin (Walker et al., 1988).

In chronic renal failure induced by 5/6 nephrectomy, tubular hypermetabolism and increased generation of oxygen free radicals have been implicated in the progressive tubulointerstitial fibrosis and loss of kidney function

(Trachtman et al., 1992a). Maneuvers that reduce iron accumulation within the remnant kidney decrease oxidant stress and preserve renal integrity following ablation of the bulk of the renal mass (Nankivell et al., 1994).

Oxygen free radicals are implicated in the pathogenesis of the glomerulopathies induced by puromycin aminonucleoside and adriamycin. Administration of allopurinol, catalase and the iron chelating agent, desferrioxamine, reduces the severity of acute phase puromycin aminonucleoside-induced injury (Diamond et al., 1986; Thakur et al., 1988). Provision of tungsten, an inhibitor of renal xanthine oxidase/xanthine dehydrogenase, alleviates adriamycin nephropathy (Ginveri et al., 1990). Administration of vitamin E reduces proteinuria, maintains tissue levels of sulfhydryl proteins and lessens structural injury in nephrotoxic serum nephritis (Endreffy et al., 1991). In diabetic nephropathy, hyperglycemia directly promotes lipid peroxidation of cell membranes and causes renal cell injury (Baynes, 1991). Glycosylation of proteins initiates a series of autoxidative chemical reactions resulting in the accumulation of advanced glycosylation end products (AGEs) in the kidney. These compounds contribute to the development of diabetic nephropathy (Baynes, 1991).

Taurine as a renal antioxidant: In vitro studies

Most of the evidence that taurine is an antioxidant in cultured renal cells is derived from work examining the direct effects of hypoxia or nephrotoxic agents. Addition of taurine (0.1–1.0mM) to renal transplant preservative solutions prolonged the survival and enhanced the viability of LLC-PK_1 cell monolayers that were exposed to hypoxic conditions followed by reoxygenation (Wingenfeld et al., 1994). The protective effect was more apparent with the University of Wisconsin compared to the Euro-Collins perfusion solution. In contrast, Heyman et al. (1992) and Baines et al. (1990) failed to demonstrate any protective effect of adding taurine to the perfusion solution on the extent of medullary tubule damage in the isolated perfused rat kidney preparation. However, glycine was able to reduce the degree of morphologic injury to medullary tubules. Similarly, glycine but not taurine attenuated lethal renal cell injury, assayed by LDH and K^+ release, in response to increases in cytosolic calcium in the two cultured tubular epithelial cell lines, MDCK and LLC-PK_1 (Weinberg et al., 1991a,b).

Exposure of cultured glomerular mesangial cells to high glucose concentration (28mM) increases lipid peroxidation assessed by malondialdehyde or conjugated diene content (Trachtman et al., 1993a). An elevated ambient glucose also inhibits mesangial cell proliferation (Trachtman et al., 1994). Addition of taurine (500μM) to the ambient medium prevented these changes (Trachtman et al., 1993a, 1994). The protection against high glucose-induced oxidant injury was reproduced by the addition of vitamin E, consistent with a direct antioxidant effect of the amino acid (Trachtman, 1994).

In order to assess the role of activated polymorphonuclear leukocytes and oxidants in mediating glomerular injury, isolated rat glomeruli were exposed

to a variety of reactive oxygen species and free radical scavengers. Glomerular damage was assessed by measuring the permeability to albumin following imposition of an oncotic gradient. Hydrogen peroxide (0.1M) together with myeloperoxidase (2.5U/ml) and activated leukocytes enhanced glomerular damage; these changes were reversed by the addition of taurine (50mM) (Li et al., 1994). These findings support a role for the reaction of taurine with halide-myeloperoxidase products in preventing injury to the glomerular capillary barrier.

Taurine as a renal antioxidant: In vivo studies

Localization of taurine within the kidney

A prerequisite for understanding the potential function of taurine as a renal antioxidant is clarification of the distribution of the amino acid within the different structural components of the nephron. In the 1980's, a technique was developed for making antibodies to amino acids by conjugating them with glutaraldehyde to proteins such as bovine serum albumin or polylysine (Storm-Mathisen et al., 1983). This advance enabled the localization of amino acids to be determined in a variety of tissues. Using highly specific polyclonal antibodies to taurine that were preabsorbed with structurally similar amino acids, several investigators have examined the localization of taurine within the kidney. Trachtman et al. (1993b) incubated normal rat kidney tissue with an antibody raised to a taurine-glutaraldehyde-BSA conjugate and visualized the amino acid by the biotin-avidin-peroxidase-diaminobenzidine method. They found that the staining intensity for taurine was most pronounced in medullary tubules with minimal secondary staining in proximal tubules and the glomeruli. These findings were independently confirmed by two other groups of investigators. Amiry-Moghaddam et al. (1994) used peroxidase-antiperoxidase and immunogold staining procedures to demonstrate localization of taurine primarily in collecting duct cells, proximal convoluted and straight tubules and thin descending limbs of Henle. Finally, Ma et al. (1994) utilized an immunoperoxidase method to verify that taurine reactivity was most prominent in glomeruli and the collecting tubules. The heterogeneous staining pattern of taurine within renal cells under conditions of stable dietary intake and urinary osmolality argues in favor of a specific role for this amino acid in the preservation of renal structure and function under normal conditions and in disease states.

Acute and chronic renal failure

In rats with acute renal failure induced by bilateral nephrectomy, there is a rise in the plasma taurine concentration; in addition, hepatic taurine content is increased while in skeletal muscle, heart, and brain tissue, the amino acid level is unchanged (Michalk et al., 1983). There are no comparable data about the effect of acute renal failure on plasma or tissue levels of taurine.

In rats with chronic renal failure, the plasma taurine concentration and cerebral content of the amino acid are elevated (Michalk et al., 1983). Patients with chronic renal failure manifest a similar increase in plasma taurine concentration. This change has been documented early in the course of this disease, prior to the onset of protein malnutrition (Ceballos et al., 1990). In patients on hemodialysis, the elevated plasma taurine concentration was normalized by the dialysis treatment (Jung et al., 1991). However, under these circumstances, there was evidence of disparate taurine levels in circulating blood cells. Thus, while taurine concentration was elevated in erythrocytes and normal in granulocytes and lymphocytes, it was lower than normal in platelets (Jung et al., 1991). Skeletal muscle taurine content is diminished compared to normal in patients with chronic renal failure (Bergstrom et al., 1989). The observation that the taurine level in muscle remains low up to 3 months post-renal transplantation is additional evidence in support of body taurine depletion in this condition (Perfumo et al., 1994).

Despite the abundant evidence that reactive oxygen molecules contribute to acute and chronic renal failure, we have failed to demonstrate any beneficial effect of taurine under these circumstances. Thus, in rats with bilateral renal ischemia for 30–60 minutes, pre-treatment with a 1% taurine solution for 2 weeks did not reduce the peak serum creatinine concentration observed after 24 hours or hasten recovery of renal function (Trachtman, unpublished observation). In addition, this regimen failed to ameliorate the severity of gentamicin nephrotoxicity induced by injection of the aminoglycoside antibiotic (100 mg/kg/day) for 7 days (Trachtman, unpublished observation). Finally, this dietary treatment had no discernible impact on mortality or the long term renal outcome in rats subjected to 5/6 nephrectomy and observed for 8–10 months (Trachtman et al., 1986).

Nephrotic syndrome

Puromycin aminonucleoside (PAN) is an epithelial cell toxin and administration of a single dose of this agent to experimental animals causes a lesion that resembles minimal change nephrotic syndrome (Diamond et al., 1986). Venkatesan et al. (1993, 1994) examined rats given PAN, 100 mg/kg intraperitoneally, and reported that provision of taurine, in a daily dose of 500 mg for 10 days, reduced total proteinuria, albuminuria and urinary excretion of N-acetyl-β-D-glucosaminidase by nearly 50%. This treatment also ameliorated the hyperlipidemia observed in these animals. The effects of taurine were associated with restoration of renal content of glutathione, total thiols, ascorbic acid and vitamin E towards the levels observed in normal rats.

These same investigators have studied the effect of taurine on the nephropathy induced by another epithelial cell toxin, adriamycin. Once again, treatment with taurine reduced the severity of proteinuria and the hyperlipidemia observed in this nephrotic condition (Venkatesan, under review).

Injection of serial doses of PAN produces a renal lesion that is similar to the clinical entity, focal segmental glomerulosclerosis (Grond et al., 1984).

Using this model, we evaluated the effect of dietary taurine supplementation provided as 1% taurine-containing drinking water. This regimen resulted in stabilization of renal function and less severe glomerulosclerosis and tubulointerstitial fibrosis. The beneficial effects of taurine were attributed to its antioxidant properties because provision of the amino acid was associated with decreased renal cortical malondialdehyde content and decreased peak intensity of an oxidizing metallo-protein complex in EPR spectra (Trachtman et al., 1992b). The protective effect of taurine was associated with increased intensity of the immunohistochemical staining for taurine in medullary tubules (Trachtman et al., 1993b).

Diabetic nephropathy

Taurine depletion has been noted in nerve tissue isolated from rats with streptozocin (STZ)-induced diabetes for 21 days (Stevens et al., 1993). In 39 patients with insulin-dependent diabetes mellitus, plasma and platelet taurine levels were reduced compared to normal subjects; both values were normalized by taurine supplementation (1.5 g/day) for 90 days (Franconi et al., 1995).

In rats with STZ-diabetes, Goodman and Shihabi studied the effect of giving taurine as 0.1% drinking water for 8 weeks (Goodman et al., 1990). Although there was no change in the severity of hyperglycemia or glycosuria, the hypertriglyceridemia and hypercholesterolemia seen in the untreated diabetic animals was reduced by taurine treatment. The duration of the study was not sufficient to elucidate the effect of this maneuver on renal function and structure.

We recently reported the effects of long-term dietary taurine supplementation (1% drinking water) for 1 year to rats with STZ-diabetes (Trachtman et al., 1995). This treatment did not ameliorate hyperglycemia. However, from 6 months on, there was a 50% reduction in proteinuria and albuminuria. Although the total kidney and estimated single nephron glomerular filtration rate remained elevated in taurine-treated rats, there was a reversal of glomerular hypertrophy and prevention of glomerulosclerosis and tubulointerstitial fibrosis. These changes occurred in association with reduced serum free iron concentration and lowered renal cortical malondialdehyde content. Finally, taurine supplementation reduced the content of pentosidine and total fluorescence, advanced glycosylation end products, in collagen extracted from rat skin. These changes were paralleled by increased immunohistochemical staining intensity for taurine in glomeruli and medullary tubules (Trachtman et al., 1993b). In contrast to the beneficial effects of taurine on the course of experimental diabetic nephropathy, administration of a diet that was moderately enriched in vitamin E exacerbated the renal lesion in the diabetic rats (Trachtman et al., 1995). The effect of taurine on the course of diabetic nephropathy has not been examined in humans.

In closing this section on the *in vivo* effects of taurine on experimental renal disease, it is important to emphasize the difference between the mechanism of action of this amino acid and other protective maneuvers such as dietary protein restriction and administration of angiotensin converting en-

zyme inhibitors. There is much evidence that the later procedures act primarily by normalizing the intraglomerular hemodynamic profile observed in chronic renal failure, i.e., reducing efferent arteriolar tone and lowering the glomerular capillary pressure (Brenner and Anderson, 1992). In contrast, the beneficial effect of taurine on experimental renal disease is seen without any alteration in glomerular filtration rate and presumably no change in single nephron hemodynamics. The antioxidant capacity of taurine, evidenced by reduced renal malondialdehyde content, may ameliorate kidney disease by preventing altered renal cell growth and matrix deposition in response to oxygen free radical-induced injury. This is accord with the notion that glomerular hypertrophy, tubular hypermetabolism, and tubulointerstitial injury are pivotal processes in the progression of renal disease (Klahr et al., 1988; Culpepper et al., 1992; Johnson, 1994).

Hypertension

In the SHR strain of rats that are genetically predisposed to develop hypertension, we have shown that administration of taurine as 1% drinking water for 16 weeks caused a significant reduction in blood pressure that was maximal (20%) after 12 weeks. The antihypertensive effect of taurine was associated with a two-fold rise in plasma norepinephrine levels in the treated animals (Trachtman et al., 1989). The beneficial effect of taurine on blood pressure was also observed in the stroke-prone SHR strain (Nara et al., 1978). In another genetic model of hypertension, taurine (3% drinking water) administration for 4 weeks prevents hypertension in the Dahl-sensitive strain by amplifying renal kallikrein expression (Ideishi et al., 1994).

Another widely studied model of experimental hypertension is that induced by a unilateral nephrectomy, administration of deoxycorticosterone acetate (DOCA), and provision of 1% NaCl drinking water. In these animals, there is augmented cardiac and hypothalamic noradrenergic activity (Fujita et al., 1986). Administration of 1% taurine drinking water to these animals prevents the development of DOCA-salt hypertension and restored cardiac norepinephrine turnover to normal (Fujita et al., 1988). The vasodepressor effect of taurine was associated with increased β-endorphin-like immunoreactive material in the hypothalamus, a change that may reduce central stimuli to increase blood pressure (Fujita et al., 1988).

There is a paucity of clinical data about the effect of taurine on blood pressure in hypertensive individuals. In young patients with borderline hypertension and increased adrenomedullary activity, administration of taurine (6 g for 7 days) lowered blood pressure by 9/4 mm Hg and reduced plasma epinephrine levels by 23% (Fujita et al., 1987).

Challenges for the future

There is much additional work that is needed to gain a better understanding of the role of taurine in the modulation of renal disease. The mechanism of

action of this amino acid requires further clarification. The contribution of taurine acting as an organic osmolyte and the impact of possible changes in the cytosolic content of molecules such as myo-inositol should be addressed in the development of diabetic nephropathy. The interaction of taurine with various intracellular signalling systems and peptide growth factors should be addressed because these are likely to contribute to the biological effects of the amino acid. It is conceivable that the beneficial effect of taurine, acting as a antioxidant, is based upon its ability to regulate inducible or endothelial nitric oxide synthase, alter nitric oxide synthesis, or inhibit the accumulation of oxidant NO products. Alternatively, taurine may act in combination with NF-$\varkappa$B, an oxidant sensitive transcription factor, or directly modulate oxidant-sensitive transcription of extracellular matrix genes by virtue of its capacity to alter redox sensitive promoter regions. Finally, like vitamin E, taurine may inhibit activation of protein kinase C and reduce synthesis of extracellular matrix proteins (Kunisaki, 1994). This mechanism may be especially important in the pathogenesis of diabetic nephropathy. All of these effects are amenable to direct study using a combination of *in vitro* and *in vivo* systems.

The optimal taurine dosage needed to achieve a renoprotective effect and the timing of initiation of amino acid supplementation should be investigated in the relevant disease models. It is necessary to ascertain which particular diseases states that are characterized by oxidant-mediated injury are amenable to modification by taurine treatment. The features that define responsiveness to taurine need to be determined. For example, it is unclear why taurine is ineffective in aminoglycoside nephrotoxicity or acute ischemic renal failure while it exerts a beneficial effect in puromycin aminonucleoside nephropathy or diabetic kidney disease. Differences between chronic *versus* acute disease states may be critical in defining the efficacy of taurine treatment. Finally, consideration should be given to the performance of clinical trials to ascertain whether taurine supplementation can attenuate the severity of refractory nephrotic syndrome or delay the progression of incipient diabetic nephropathy.

Conclusion

Over the past 10 years, a great deal of data has been accumulated indicating that taurine exerts beneficial effects on renal function and structure in a wide variety of disease states. The bulk of the evidence suggests that taurine is acting as an antioxidant under these circumstances to attenuate renal cell injury. Additional work is required to clarify the specific conditions that determine whether taurine is an agent with therapeutic potential (diabetic nephropathy *versus* 5/6 nephrectomy). Moreover, it is clear that taurine does not cure renal disease. Instead, it appears to act in a non-specific manner to retard progressive loss of kidney function. Because its mechanism of action is distinct from other maneuvers such as dietary protein restriction or angiotensin converting enzyme inhibitors, it may act synergistically with these

therapeutic modalities to attenuate progressive renal damage. However, based on the existing data, it would seem prudent to consider clinical trials to ascertain whether taurine is effective as an adjunctive treatment to ameliorate kidney injury in a wide variety of renal diseases.

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