5. Taurine and the kidneys

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1.1. Introduction

The interactions between the kidney and taurine are multifaceted. Taurine contributes to several biologic processes in the kidney, and the kidney influences specific aspects of taurine homeostasis [1]. The numerous molecular and cellular regulators of taurine handling by the kidney have been recently reviewed [2]. Thus, this chapter will examine several aspects of renal function in relation to taurine and will delve into large biologic themes. In addition, the properties of taurine in the pathophysiology of kidney disease will be evaluated.

The physiochemical properties of the β-amino acid taurine are responsible for some of its biologic features. It is readily soluble in aqueous solutions and is not incorporated into protein. Thus, it can serve as an intracellular osmolyte. The taurine molecule acts as a zwitterion at physiologic pH and resides within the cell in millimolar quantities. Its accumulation within the cell requires active uphill transport from the extracellular environment, where it is found in only micromolar quantities [3]. It has the lowest pK1 and pK2 of all amino acids. Some of these properties lead to the role of conjugation of taurine with bile acids [4] and uridine in +RNA [5].

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1.2. Ion reabsorption

The active transport of taurine occurs via a sodium-dependent transporter (TauT) found in plasma membranes [6]. In addition to sodium, taurine uptake by renal epithelia requires chloride or bromide [7]. The stoichiometric model that best describes this transport is 2 Na\(^+\):1 taurine:1 Cl\(^-\) (Figure 1).

Sodium and chloride move into cells by means of an external to internal downhill Na\(^+\) gradient (a chemical gradient), followed by the sodium being pumped out of the cell by Na\(^+\)K\(^+\)-dependent ATPase, an energy-requiring step. Hence, taurine uptake occurs by a secondary active process. Taurine transport is stereospecific, inhibited by other β-amino acids and GABA (gamma-aminobutyric acid) but not by α-amino acids, and is membrane surface-specific. In a proximal tubule cell line (LLC-PK1), uptake is maximal on the apical surface; in a distal tubule cell line (MDCK), uptake occurs at the basolateral surface (Figure 2) [8]. Transcellular transport by proximal tubule cells results in reabsorption of taurine and maintenance of the total body

![Figure 1. A model illustrates the 2 Na\(^+\):1 taurine:1 Cl\(^-\) stoichiometry of taurine transport. Sodium and chloride move into cells by means of an external to internal downhill Na\(^+\) gradient (a chemical gradient), then the sodium is pumped out of the cell by Na\(^+\)K\(^+\)-dependent ATPase.](image-url)
Figure 2. Taurine transport is membrane surface-specific. In a proximal tubule cell line (LLC-PK1), uptake is maximal on the apical surface; in a distal tubule cell line (MDCK), uptake occurs at the basolateral surface.

pool, whereas distal cell transport moves taurine into the cells, where it functions as an osmolyte.

The reabsorption of taurine from glomerular ultrafiltrate involves transport across the apical membrane of proximal tubule cells by means of the TauT transporter protein, and then efflux through the basolateral membrane. Taurine efflux from renal cells is dependent on the intracellular taurine concentration and requires the presence of both $\text{Na}^+$ and $\text{Cl}^-$ in the system. It does not contribute to the renal adaptive response described below. Efflux is much slower than uptake and has a higher $K_m$. The observation that taurine egress is dependent on specific ions suggests that it is not purely passive diffusion, but probably involves a carrier-facilitated process [9].

Taurine and its transporter also interact with glucose. Taurine in the glomerular ultrafiltrate appears to blunt the rate of glucose uptake by renal tubules and can potentially lead to glucosuria. While it is tempting to assume that taurine molecules in the tubular lumen compete with glucose for sodium and hence reduce glucose uptake, the nearly 100-fold higher concentration of glucose (5.0 mM) makes this unlikely. Inhibition of the $\text{Na}^+$-independent glucose transporter 1 (GLUT1) in activated macrophages (RAW264.7 cells) by taurine chloramine is one mechanism by which inflammatory cell function can be modulated [10]. This mechanism is not well studied in kidney. Some form of allosteric competition between taurine and GLUT1 may be relevant, but GLUT1 is commonly inhibited by ascorbic acid [11] rather than by amino acids. Also, because taurine is known to enhance insulin secretion [12], it may indirectly enhance glucose entry into cells. Hence, taurine may influence the intracellular uptake as well as the transcellular movement of glucose.
1.3. Renal blood flow

Taurine has many and varied effects on renal blood flow and endothelial cell function throughout the vascular system. Sato et al. employed the deoxycorticosterone acetate (DOCA)-salt loaded rat model to study the various vasoconstrictive and vasodilatory properties of taurine [13]. Taurine status in the rat can influence renal vascular resistance [14-16], autonomic nervous system regulation of arterial blood pressure [17, 18] and the renal response to high sugar intake-induced baroreceptor reflex dysfunction [19]. Prenatal taurine exposure has long-term effects on arterial blood pressure and various renal functions in adult life, as shown in a series of models [15, 18-24].

Using the L-nitro-arginine methyl ester (L-NAME) hypertension model in the rat, Hu et al. have shown that taurine supplementation leads to increased serum levels of nitric oxide (NO) and NO synthase activity [14]. In addition, there is blunted renin-angiotensin-aldosterone axis activity and reduced elevation of cytokine and endothelin levels [14]. Taurine administration also delays the onset of hypertension in hypertension-prone Kyoto rats [17].

Under certain conditions, taurine depletion in fetal or perinatal rats results in higher blood pressure in adulthood [15, 18, 19, 24]. Because of renal immaturity and the extremely high fractional excretion of taurine in young rats, much of the taurine administered to rat pups is excreted in the urine [25]. Theoretically, this taurinuria could result in volume depletion with a chronic up-regulation of the renin-angiotensin system (RAS) [26]. Whether this leads to imprinting and overactivity of the RAS has not been studied.

Taurine has been evaluated as a renoprotective agent in various rat models [20-23], where it has been shown to preserve renal function in both healthy and diseased rats on high salt- and fat-supplemented diets. If treated with enalapril (to block the RAS) or taurine, both hypertensive and glucose-intolerant rats will demonstrate a significant reduction in urinary protein excretion. In addition, rats fed high salt or high fat diets will excrete more taurine in their urine, as do rats fed a high glucose diet. This taurinuria may be the consequence of competition for sodium-dependent transport processes, energy, or both.

1.4. Antioxidant properties

The antioxidant properties of taurine and its derivatives are well recognized [27-30]. Here, we will focus on studies relevant to the renal system.
Culturing renal mesangial cells in the presence of a high glucose concentration resulted in an increase of advanced glycosylation products, which can limit cell growth. Addition of the antioxidants taurine and vitamin E reversed growth inhibition [29].

The major mechanism of antioxidation is the reaction of taurine with hypochlorous acid (HOCl) to form taurine chloramine. In several models of glomerulopathy involving macrophage invasion there is increased intracellular activity of myeloperoxidase to yield HOCl derived from H₂O₂ present in renal tissue. These reactive oxygen species (ROS) can lead to DNA oxidation, protein nitration, and lipid peroxidation of renal cells [27, 28, 30]. Furthermore, oxidants arising from puromycin- or adriamycin-induced glomerular injury in rats are diminished following administration of 1% taurine in the drinking water [29]. Taurine has also been associated with reduction in kidney tissue oxidant levels in diabetic nephropathy [31].

1.5. Ischemia / perfusion injury

The renal ischemia/reperfusion model uses blood vessel clamping to induce antioxidant injury to renal vessels and vascular endothelium. When rat kidney undergoes 60 min of ischemia followed by 90 min reperfusion, there is a significant rise in serum creatinine and fall in renal ATP content. Prior intravenous administration of taurine at 40 mg/kg significantly reduces injury, as reflected by final serum creatinine levels in treated rats much lower than in control rats [32]. No protection in terms of ATP content was found. In a human saphenous vein model, ischemia/ reperfusion significantly reduced endothelial cell survival by increasing both apoptosis and necrosis [33]. These changes were accompanied by higher intracellular ROS and calcium ions and a reduction in endothelial nitric oxide synthase expression. Administration of taurine either prior to or following ischemia also attenuated epithelial cell damage.

The addition of taurine to University of Wisconsin (UW) kidney transplant solution was able to prevent tissue alterations during hypoxia and reoxygenation and permitted recovery of energy metabolism in LLC-PK1 cells [34]. In hepatic tissue, taurine supplementation of UW solution was even more dramatic in its effect on tissue preservation [32, 34, 35].

The main role for taurine in oxidant injury is probably the local and systemic scavenging of ROS. Taurine chloramime has been shown to serve as an oxidant reservoir, exhibiting delayed oxidant effects or acting in a distant tissue [36]. This phenomenon is particularly noteworthy in phagocytes, a source of taurine-related antioxidants [37] and prevalent in an early phase of inflammation in the glomerulus and tubules [29].
1.6. Cell cycle and apoptosis

Taurine and its transporter, the TauT protein, are important in the regulation of the cell cycle and apoptosis of kidney cells [38]. Taurine accumulates in cells via active transport by TauT, and, therefore, the quantity of transporter protein in the cell membrane determines intracellular β-amino acid concentration [1]. Cisplatin, a chemotherapeutic agent known to be nephrotoxic, reduces taurine accumulation in renal cells through a p53-dependent process in LLC-PK1 cells [38]. In human embryonic kidney cells (293 cells), cisplatin up-regulates the proto-oncogene c-Jun. These variable responses to the anti-tumor agent can be shown by reporter assay and analysis, DNA binding, and Western blots of taurine transporter protein in cells. The functional TauT gene modifies cisplatin-induced renal injury, and the transcription rate for TauT is regulated by p53 and c-Jun. The balance of such regulation determines the rate of synthesis of TauT protein, and thereby influences the uptake of taurine and the fate of renal cells.

The cell cycle-relevant pathway involving gene expression of cyclin-c and the TauT gene is cooperatively regulated by renal cells in response to hypertonicity [39] and reduced TauT promoter activity by doxorubicin-induced activation of p53. This p53 activation can be seen in human fetal kidney cells (293) and porcine proximal tubule cells (LLC-PK1), but in a cell line devoid of p53 expression, [10(1) cells], there is no repression of promoter [38]. With truncation of the TauT promoter or with mutation of the p53 binding site there is no repression of TauT activity. Activation of the WT1 (Wilms tumor 1 gene) binding site in the promoter region up-regulates TauT, as does c-Jun. Figure 3 depicts the promoter region of TauT (3a) and the details of the intracellular signaling that regulate the gene (3b). Among the binding sites in the promoter region is a taurine response element (TREE) as well as the proto-oncogenes previously mentioned [1, 2, 38].

The product of TauT expression is TauT, a transporter protein containing 12 membrane-spanning domains inserted into the apical or basolateral membranes of renal cells. The taurine transporter has been cloned from several species and tissues, including rat brain [6] and dog kidney [40]. The genes encoding TauT in various species share a high degree of homology, residing on chromosome 6 in the mouse and 3p21-25 in man [41]. The renal adaptive response to taurine availability has been demonstrated in many mammalian species, including humans [42]. The mechanisms for this adaptive response occur at the levels of transcription, translation, and post-translational modification [2]. Phosphorylation of serine 322 by protein kinase C (PKC) results in reduced transporter activity. This phosphorylation site is on the fourth intracellular loop (S4), a highly conserved motif in all mammalian species examined [6, 40].
1.7. Stress response and taurine as a renal osmolyte

Sorbitol, myo-inositol, betaine, α-glycerophosphorylcholine and taurine have been identified as major osmolytes in the renal medulla [43-45]. The taurine uptake process responds to osmolar signals under three special circumstances: 1) In fish adapting from fresh water to sea water or vice versa [42, 46, 47]; 2) In the mammalian brain under conditions of hyper- or hyponatremia [48, 49]; 3) In the unique osmolar environment of the renal medulla [43-45, 50]. Osmolar regulation results in movement of taurine into or out of the medullary cell rather than transcellular movement (reabsorption) (Figure 4).
Figure 4. The role of taurine as an osmolyte is shown by its net movement under different conditions of tonicity.

The renal medulla is the site of urinary concentration or dilution, the countercurrent multiplier mechanism, and aquaporin activity to form water channels. It can establish an osmolar gradient of 50 to 1200 mOsm in man, and even steeper gradients in rodents [51]. Osmoregulation of taurine transport occurs in cells of the loop of Henle and the medullary collecting duct. The relevant biologic process is termed “cell volume regulation” [44, 45, 52]. Several studies have demonstrated that medullary cells in culture (MDCK or M1 cells) exhibit taurine transport across the basolateral surface rather than the apical surface [44, 45, 50]. A response to hyperosmolarity is not evident in proximal cell lines [50].

Handler and Kwon have shown that cells that respond to hyperosmolar stress have a tonicity response element (TonE) that responds to a TonE binding protein (TonEBP) [44, 53]. Extracellular sucrose or raffinose leads to increased binding of TonEBP to TonE, up-regulation of the genes for osmolar transporters (sorbitol, myoinositol, etc., and including TauT), increased production of mRNA for TauT protein synthesis, export and insertion of protein into the basolateral cell membrane, and enhanced transport of taurine into the cell [44, 50]. Ito et al. have recently shown that the TonE site is located on the promoter region proximal to -124 and distal to -99 [53]. A mutant TonE was unresponsive to hypertonicity. This study also demonstrates how the TonE/TonEBP system regulates cell volume and prevents hyperosmolar stress [53] (Figure 5).

1.8. Renal regulation of taurine body pool size

Although renal regulation of ion reabsorption is a long-recognized concept in transport physiology, application of this principle to an amino acid is recent. Examined in terms of the factional excretion of taurine, a variation of 0.5% to 80% has been found [54]. From a renal physiologic viewpoint, both an increase and reduction of urinary excretion suggest an adaptive regulation of transport, as is observed for the phosphate ion. We use the term “renal adaptive response to alterations in taurine intake” to describe these observations. Adaptation of the taurine transporter system is a limited phenomenon exhibited by the kidney and the gut, and under conditions of
malnutrition [2]. When taurine depletion was induced by fasting rats overnight, urinary taurine excretion was reduced, but uptake of radiolabelled taurine by renal cortex slices and brush border membrane vesicles was enhanced [55]. Depletion of taurine body pool size by feeding rats β-alanine also enhanced the renal adaptive response in vivo and in vitro. The combination of β-alanine and fasting resulted in greater uptake by slices and vesicles. This rapid adaptive response occurs over a matter of hours, rather than the classic adaptive response, which occurs over two weeks of altered dietary intake of taurine. By use of colchicine, which disrupts microtubules within the cell, it can be shown that the rapid adaptive response involves the trafficking of preformed TauT protein into the apical membrane of the
proximal tubule after taurine restriction and movement out of the membrane into the cytoplasm as a consequence of taurine excess [56]. The classic adaptive response involves transcriptional and translational regulation that can be blocked by cycloheximide, a known inhibitor of protein synthesis [57].

From a nutritional perspective, and to optimize the synthesis of peptides and proteins, all mammals should retain amino acids. However, because taurine is a β-amino acid and is devoid of a carboxyl group, it cannot be incorporated into protein and resides freely in intracellular water.

Among other features is that taurine is not metabolized by eukaryotes and does not contribute to gluconeogenesis, but it does participate in conjugation of certain compounds (such as bile acids) [4]. It is largely inert and not a source of energy. These ideal physiochemical properties of taurine lead to a central hypothesis that taurine can be responsible for cell volume regulation, because taurine movement across the membrane surface of a cell “can evoke changes in the concentration of solutes and solvents within a cell” [52].

If taurine movement is important in the maintenance of cell volume, what regulates the transport from a dietary perspective? The transport of taurine in vivo appears to be precisely regulated by the kidney, and is mimicked in vitro in a variety of renal systems, including uptake into renal slices, renal cells in culture, isolated renal tubules, and isolated brush border membrane vesicles. It is regulated at both the level of mRNA transcription and protein synthesis [57, 58].

The renal adaptive response was first described in rats fed a low taurine diet (LTD, containing suboptimal concentration of the precursor methionine), a normal taurine diet (NTD), or a diet supplemented with 3% (high) taurine (HTD) [54]. Specific taurine transporter mRNA levels are higher in LTD-fed rats and lower in HTD-fed rats as compared to NTD-fed rats. Western blot analysis shows more taurine transporter protein in membranes from LTD-fed animals and less in those fed HTD. The transcription rate is higher in cells in culture deprived of taurine, and lower in cells exposed to excess taurine [57, 59, 60]. Exposure of cells to β-alanine, which depletes intracellular taurine, leads to enhanced uptake. Likewise, in vivo, fasted rats show higher taurine reabsorption rates and increased uptake by brush border membrane vesicles [55]. Renal brush border membrane vesicles prepared from kidneys of taurine-deprived felines, who require dietary taurine to maintain usual tissue levels, show greatly enhanced taurine uptake [61]. This evidence indicates that whatever reduces intracellular taurine content up-regulates the TauT gene and synthesis of TauT protein. Likewise, with increased taurine availability, increased dietary intake and increased intracellular taurine concentration, the
uptake of taurine by vesicles and cells is reduced and the process is down-regulated.

In an effort to clarify the signal for the up- or down-regulation, truncation analysis of the promoter region revealed that the taurine response element (TREE) resides between the c-myb and p53 binding sites (Figure 3a). Truncation proximal to this site blocks the adaptive response, as shown by reporter assay [2]. The molecule that TREE responds to is not established, but it is possible that it is the intracellular concentration of the taurine molecule per se.

Plasma taurine levels do not vary greatly with the availability of dietary taurine. Using specific antibodies, taurine can be found in the nucleus, and thus is present at the site of transcription. Addition of taurine to cell cultures that have adapted to a low taurine environment can rapidly (within 8 hr) reverse the up-regulation response [8]. Both the rapid and the slower classic adaptive responses are found in numerous mammalian species, including man, dog, pig and rodent. It is evident in herbivores, carnivores and omnivores [2]. Depending on taurine intake, the urinary fractional excretion of taurine can vary from 0.5% to 80.0% (Figure 6).

![Fractional excretion of taurine](image)

**Figure 6.** The renal adaptive response to dietary taurine intake demonstrated by several mammalian species conserves the total taurine body pool by reabsorbing or excreting taurine depending on its availability. This phenomenon occurs at the renal brush border membrane surface by means of up- and down-regulation of the amount of TauT, the taurine transporter protein.
The ontogeny of renal transport of taurine in rats was measured in renal cortex slices, isolated tubules and brush border membrane vesicles [62-64]. Net renal tubular reabsorption is reduced and the percent excretion is higher in young animals compared to adolescent and adult rats [63, 64]. The results in vitro indicate reduced uptake in renal cortex slices. Kinetic analysis reveals a reduced $V_{\text{max}}$ but no alteration in the $K_m$ of taurine uptake by cortex slices or brush border membrane vesicles. Of note, efflux of taurine out of slices is slow, indicating that the reduction in taurine reabsorption may also represent back flux into urine, thus contributing to taurinuria [63-66].

The renal adaptive response to dietary intake was examined in rats of 1, 2, 3 and 4 weeks of age whose mothers had been fed LTD, NTD or HTD [54]. The renal adaptive response was observed between 7 and 14 days of age. Seven-day-old rats exposed to LTD in their mother’s milk did not reduce urinary excretion of taurine, nor did those exposed to HTD excrete more taurine than did animals exposed to NTD. However, rats 14, 21 and 28 days of age who were nursed by mothers fed the LTD conserved taurine while those fed by mothers on HTD hyperexcreted taurine [65].

The reabsorption and excretion of taurine was examined in pre-term and full-term human infants fed by mouth or by total parenteral nutrition (TPN) [67]. The TPN solution was devoid of taurine and thus the total body taurine pool size was dependent on the infants’ biosynthetic capacity. As noted in Figure 7, pre-term infants do not adapt to a decline in plasma taurine with reduced urinary excretion of the amino acid. Term infants on TPN do show evidence of the adaptive response. Pre-term and term infants fed enterally show higher urinary taurine excretion rates relative to taurine intake. Hence the renal adaptive response appears to be evident soon after a term birth, although excretion rates continue to fall over the first several weeks of life. In conclusion, the finding of renal immaturity in rodent species is also evident in man.

Among factors that might contribute to up-regulation or down-regulation of taurine transport after dietary change or as a maturational event could include membrane-related events [68]. Using various fluorescent dyes membrane fluidity could be evaluated. There were no changes in membrane fluidity brought about by dietary change or by immaturity. The lipoprotein content of renal tubule membranes can be measured as well as the proportion of each of the major lipoprotein classes. Again, dietary changes and immaturity do not change these proportions, although phosphotidyl ethanolamine is more prevalent in the membranes from younger animals [68].

The concentration of taurine was measured in plasma, blood and kidney cortex of rats fed LTD, NTD or HTD [69]. The plasma and blood concentrations of taurine are lower in LTD-fed rats than in NTD-fed animals.
but not significantly so; levels in the HTD-fed rats are higher, but not reaching significance. By contrast, the levels in cortex are significantly lower in LTD (~8 mmol/kg) than in NTD kidney (~10 mmol/kg) and significantly higher in HTD (12 mmol/kg). Dietary taurine intake affected the taurine concentrations in multiple organs, including liver, heart and muscle, but the concentration of taurine was the same in six areas of brain regardless of diet. In essence, rats fed a low, normal or high taurine diet maintain roughly the same plasma or blood values, but diet influences the plasma concentration in many tissues, including kidney. The constancy of brain taurine content is consistent with its role as a central nervous system osmolyte [69].

1.9. The role of taurine in the pathophysiology of kidney disease

Taurine has been shown to play a role in four different forms of kidney disease: glomerulonephritis, diabetic nephropathy, chronic renal failure, and acute kidney injury (AKI). Much of the work on the role of taurine in relation to kidney disease has been performed in animal models, especially murine
species. Many studies were performed nearly two decades ago and are descriptive, with the exception of the studies involving taurine chloramine. Only in the area of protection of the kidney against AKI have intracellular and molecular mechanisms been explored with the use of transgenic and knockout mouse models and knockdown cell lines.

1.9.1. Protection against glomerulonephritis

Trachtman has reviewed the evidence that taurine functions as a protective agent against immune- or toxicity-induced forms of glomerulonephritis [29]. In the Masugi glomerulonephritis model, rat kidney homogenates are injected into rabbits. After several weeks, rabbit serum is injected into rats. There occurs a heterologous phase in which injected antibodies lead to the migration of neutrophils into rat glomeruli. Myeloperoxidase (MPO) located in neutrophils causes generation of radicals, including hypochlorous acid [28, 30, 70, 71]. Hypochlorous acid activates tyrosine phosphorylation signal pathways, leading to calcium signaling and tumor necrosis factor α (TNFα) production [71]. In MPO-/− mice, fewer reactants are generated [70].

Subsequently, in an autologous phase, T cells and macrophages invade. The addition of taurine chloramine to the diet appears to inhibit the function of antigen-presenting cells and T cells in T cell-induced crescentic glomerulonephritis [70]. Lian et al. showed that taurine in drinking water reduced urinary protein excretion, and both serum and urine platelet-activating factor (PAF) levels [72]. Renal cortex and medulla PAF values are also lower than in control rats.

Another component of glomerulonephritis is an increase in glomerular albumin permeability (GAP). In a model using isolated rat glomeruli, which are infiltrated by neutrophils, \( \text{H}_2\text{O}_2 \) alone does not increase GAP, but \( \text{H}_2\text{O}_2 \) and MPO together do increase GAP [73]. This increase can be inhibited by superoxide dismutase, catalase or taurine.

A model of chronic puromycin aminonucleoside nephropathy that resembles human focal segmental glomerulosclerosis (FSGS) can be induced in rats. When rats are given 1% (w/v) taurine in their drinking water, urinary albumin excretion, segmental glomerulosclerosis and tubulointerstitial injury are significantly diminished. The urine albumin/creatinine ratio is lower in taurine-supplemented animals, as are levels of the oxidant malondialdehyde in renal cortex. While the presumed mechanism of nephroprotection is the formation of taurine chloramine from taurine, this was not directly measured [74].
1.9.2. Protection against diabetic nephropathy

Taurine has afforded renal protection against models of diabetic nephropathy [31]. The importance of this observation relates to the fact that diabetes mellitus (type 1 and type 2) is the predominant cause of end stage renal disease and the need for dialysis in North America [75]. In rats with streptozocin-induced diabetic nephropathy, addition of taurine to the drinking water and exogenous insulin inhibited the increase in glomerular planar area and ameliorated the condition, as did vitamin E [31]. Administration of vitamin E and taurine is associated with a reduction in advanced glycosylation products and the extent of lipid peroxidation. Taurine and its congeners reduce the formation of intracellular oxidants and afford protection against erythrocyte membrane damage [76], which could also reduce the fragility of erythrocytes within glomerular capillaries.

Another hypothesis concerning the importance of taurine in diabetic nephropathy involves the increased production of sorbitol. Simply stated, the elevated extracellular concentration of glucose disturbs cellular osmoregulation and sorbitol is synthesized intracellularly via the polyol pathway [77]. Intracellular accumulation of sorbitol crowds out other intracellular osmolytes, including taurine and myo-inositol. This disturbance of cell volume regulation might be altered by taurine supplementation, but this has not been tested [77].

1.9.3. Protection against chronic renal failure

In general, human patients with chronic renal failure have reduced plasma and muscle intracellular concentrations of taurine [78]. However, an open label, non-randomized trial of taurine supplementation (100 mg/kg/day) in 10 hemodialysis patients resulted in extremely high taurine levels in plasma and muscle [79]. The plasma concentration rose from 50 μM to 712–2481 μM after 10 weeks of therapy, and muscle values more than doubled [79], likely because no renal adaptive response is possible in these patients and taurine cannot be excreted. Clearance by dialysis was not measured.

1.9.4. Protection against acute kidney injury

Several models of AKI have been used to examine the influence of taurine in this process. In a gentamicin toxicity model, rats are injected with the aminoglycoside antibiotic, leading to a rise in serum creatinine and histologic features of acute tubular necrosis. Administration of taurine attenuated the rise in creatinine and there was less accumulation of
gentamicin [80]. In this model, the content of glutathione peroxidase and superoxide dismutase are similar in kidneys of taurine-treated rats and controls.

Acute kidney injury is a major problem in patients with sepsis, toxic injury and shock. The overall mortality rate is approximately 50% [81]. In cancer patients receiving chemotherapeutic agents, evidence of kidney injury, as defined by elevation of biomarkers, is common. Cisplatin is a frequently used chemotherapeutic agent, limited mainly by its nephrotoxicity. As many as 25% to 35% of patients experience a significant decline in renal function after a single dose of cisplatin [82].

Elevated expression of the tumor suppressor gene p53 has been detected in the kidneys of rats with cisplatin-induced AKI [83]. Jiang et al. have shown that p53 is an early signal in cisplatin-induced apoptosis in renal tubular cells [84]. These findings suggest that altered expression of distinct p53 target genes may be responsible for p53-induced progressive renal failure.

Our studies have shown that TauT is negatively regulated by p53 in renal cells [85]. Cisplatin, which stimulates p53 production, accumulates in all cell types of the nephron but it preferentially taken up by highly susceptible cells in the S3 segment of the proximal tubule [86], which is also the site where adaptive regulation of TauT occurs [87]. Cisplatin has been shown to impair the function of the taurine transporter and to down-regulate expression of TauT at the transcriptional level in a dose-dependent fashion [88]. We hypothesized that TauT plays a role as an anti-apoptotic gene and functions to protect renal cells from cisplatin-induced nephrotoxicity in vivo.

Transgenic mice over-expressing human TauT and wild-type mice were injected with cisplatin or saline; renal failure biomarkers (blood urea nitrogen, creatinine, urinary protein excretion) were measured and the mortality rate recorded [88]. Over-expression of TauT in the transgenic mice conferred significant protection against renal damage and death caused by cisplatin as compared to drug-treated control animals. Histological analysis of kidneys from cisplatin-treated transgenic mice showed greater amounts of membrane-bound TauT protein, higher levels of intracellular taurine, and less necrosis and apoptosis than the kidneys of cisplatin-treated control mice. The histological findings were similar to those found in saline-injected control animals [38].

Elevated levels of p53 have been found in the kidneys of animal models of acute renal failure induced by cisplatin administration [89]. Negative regulation of TauT gene expression by p53 may play a role in the action of cytotoxic drugs, such as cisplatin-induced renal failure. Cisplatin accumulates in cells from all nephron segments but is preferentially taken up by the highly
susceptible proximal tubule cells within the S3 segment (the site for renal adaptive regulation of \( \text{tauT} \)), which bear the brunt of the damage [86, 87]. A recent study showed that taurine was able to attenuate cisplatin-induced nephrotoxicity and protect renal tubular cells from atrophy and apoptosis [38]. The promoter region of the taurine transporter gene contains a consensus binding site for the p53 tumor suppressor gene, which functions as a cell cycle checkpoint, blocking cell division in the G1 phase to allow repair of damaged DNA or even triggering apoptosis in cells that have defective genomes [90]. Numerous stimuli trigger increases in the level of p53 expression, including DNA-damaging drugs, ionizing radiation, ultraviolet light, and hypoxia [91-94]. Varmus’ group has found that transgenic mice over-expressing p53 undergo progressive renal failure through a novel mechanism by which p53 appears to alter cellular differentiation, rather than by growth arrest or the direct induction of apoptosis [95]. These findings suggest that altered expression of certain p53 target gene(s) involved in renal development may be responsible for p53-induced progressive renal failure in p53 transgenic mice. Interestingly, the progressive renal failure found in p53 transgenic mice is similar to observations made regarding the offspring of taurine-deficient cats, which showed ongoing kidney damage in addition to abnormal renal and retinal development, suggesting that the taurine transporter gene may be an important target of p53.

A recent study shows that the Fas (CD95) cell surface receptor is up-regulated by DNA-damaging agents that appear to be p53-dependent [96]. Stimulation of Fas receptor with Fas antibody leads to release of cellular taurine, which coincides with cell shrinkage and precedes DNA fragmentation. However, Fas receptor-mediated apoptosis is blunted by increases in extracellular osmolarity [97], suggesting that taurine uptake mediated by the taurine transporter plays a role in the cell volume regulatory mechanism during apoptotic cell death. This hypothesis is strongly supported by observations in \( \text{tauT}^{-/-} \) mice, in which the progressive retinal degeneration was found to be caused by apoptosis [98]. Therefore, regulation of TauT by p53 may also be important in Fas-mediated apoptosis.

Studies have shown that taurine can prevent cell apoptosis through several mechanisms, including inhibition of the generation of reactive oxygen species (ROS), nitric oxide (NO), tumor necrosis factor alpha (TNF-\( \alpha \)), and regulation of intracellular calcium flux [99-101]. Recently, Takatani et al. demonstrated that taurine can effectively prevent myocardial ischemia-induced apoptosis by inhibiting the assembly of the Apaf-1/caspase-9 apoptosome [102]. They found that taurine treatment had no effect on mitochondrial membrane potential and cytochrome c release. However, it inhibited ischemia-induced cleavage of caspase-9 and caspase-3, and the interaction of caspase-9 with Apaf-1.
Studies have shown that relatively normal levels of \textit{TauT} and/or taurine are able to protect against cisplatin-induced AKI [38]. The mechanisms by which functional \textit{TauT} protects animals from cisplatin-induced AKI are unknown. However, results from this study suggest that over-expression of \textit{TauT} protects against cisplatin-induced AKI, possibly through modulation of a p53-dependent pathway rather than changing the transport of cisplatin by renal cells. This speculation was supported by the observation that cisplatin induced p53 to a similar degree in the kidneys of both wild-type and \textit{TauT} transgenic mice. Furthermore, we have shown that PUMA, a p53 downstream target gene, is up-regulated in the kidneys of both wild-type and \textit{TauT} transgenic mice after cisplatin treatment. Interestingly, the vast apoptosis observed in the proximal tubules of cisplatin-treated wild-type mice was where the strong signals of immunostaining for PUMA were found. Jiang et al. have recently demonstrated that PUMA is involved in cisplatin-induced injury, which could be attenuated in p53-deficient animals and PUMA knockout cells [103], suggesting that the p53/PUMA pathway plays an important role in cisplatin-induced AKI. Functional \textit{TauT} plays an essential role in maintaining normal kidney functions. Activation of p53 represses \textit{TauT} expression, which in turn renders animals more sensitive to cisplatin-induced AKI. Forced over-expression of \textit{TauT} is capable of protecting against cisplatin-induced AKI, possibly through attenuating the p53-dependent pathway.

### 1.10. Physiologic roles for taurine relative to the kidney

It is possible to develop a structural-functional map of the kidney based upon information presented in this review. The nephron, the basic unit of the kidney, has several different cell types that behave in a variety of ways when interacting with taurine. The major characteristics of taurine in terms of kidney function are shown in Table 1. Although many of these roles may overlap in different renal tissue types, the function of each structural part sets the paradigm within which taurine will operate.

The effect of taurine on renal blood vessels is to alter blood flow, and probably to stabilize the endothelium of the extensive renal vascular network [33]. Taurine influences blood flow within all types of vessels (capillaries, venules and arterioles) through several mechanisms discussed previously, such as NO synthase activity, the rheology of erythrocytes, the renin-angiotensin system activity and vascular tone [15, 16, 21]. In the glomerulus,
Table 1. The role of taurine in various renal structures.

<table>
<thead>
<tr>
<th>Renal Structure</th>
<th>Role of Taurine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasculature</td>
<td>Regulate blood flow</td>
</tr>
<tr>
<td>Glomerulus</td>
<td>Scavenge ROS (reactive oxygen species)</td>
</tr>
<tr>
<td>Proximal tubule</td>
<td>Na⁺ transport</td>
</tr>
<tr>
<td></td>
<td>Regulate taurine body pool size</td>
</tr>
<tr>
<td>Medulla</td>
<td>Osmoregulation</td>
</tr>
<tr>
<td></td>
<td>Cell volume regulation</td>
</tr>
</tbody>
</table>

where inflammatory cytokines evoke leukocyte migration, T cell activation, fibrosis, sclerosis and scarring, the value of taurine as an antioxidant is paramount. Taurine scavenges ROS that can influence podocyte function and increase protein excretion. In the proximal tubule, the site of bulk reabsorption of ions, organic solutes and water, taurine influences sodium transport and is taken up itself to maintain the body pool size in an adaptive response to variations in dietary availability. The taurine transporter system maintains the steep plasma (extracellular, μM) to intracellular (mM) concentration gradient despite huge variations in taurine intake. In the medulla, taurine is critical to cell volume regulation, moving into or out of collecting duct cells relative to external osmolarity. Taurine’s role as an osmolyte is likely important in many cell types in nearly all organs, but it is especially evident in renal medullary cells, where final urine concentration is established.

1.11. References


11. Sagun KC, Carcamo JM, Golde DW. Vitamin C enters mitochondria via facilitative glucose transporter 1 (Glut1) and confers mitochondrial protection against oxidative injury. FASEB J 2005, 19:1657-1667.


