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INVITED REVIEW

The role of taurine in renal disorders

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Abstract This article examines the actions of taurine on models of renal dysfunction, the potential mechanisms of taurine action and the possible clinical significance of these findings. Our laboratory has written previously on the role of taurine in renal function and we have focused upon the normal physiology of the kidney and on the mechanisms and regulation of the renal transport of taurine. This review is a distinct change of emphasis in that we describe a number of studies which have evaluated various aspects of renal dysfunction, including hypertension and proteinuria, specific glomerular and tubular disorders, acute and chronic renal conditions, urinary tract conditions including infection and nephrolithiasis, and diabetic nephropathy. The subject of chronic kidney disease and renal transplantation will also be examined relative to β amino acid. The studies evaluated will be mainly recent ones, recognizing that older reviews of the role of this taurine in the kidney are available.

Keywords Taurine · Renal function · Glomerular nephritis · Acute kidney injury · Diabetic nephropathy · Chronic kidney disease

The role of taurine in renal function

Taurine can influence several physiologic functions of the kidney, including renal blood flow, glomerular filtration and its rate, osmoregulation, ion reabsorption and secretion, and composition of urine (Chesney et al. 2011). The role of taurine in renal function has recently been reviewed by Mozaffari (2003). Dividing the influences of endogenous and exogenous taurine, this report emphasized the role of dietary taurine reduction and tissue depletion using either β-alanine or guanidino ethane sulfonic acid (GES) as a depleting agent. The taurine-deficient rat was less capable of excreting a water or salt load. Taurine-depleted rats could not readily excrete a hypotonic NaCl load, but hypertonic loads were well handled (Mozaffari et al. 1998). They also demonstrated that taurine influenced body water homeostasis through an arginine vasopressin (AVP)-dependent mechanism (Mozaffari and Schaffer 2001), consistent with its role as an osmolyte in the renal medulla (Handler and Kwon 1993). In contrast, experiments using chronic taurine supplementation appeared to improve blood pressure (Dawson et al. 2000), favorably altering the reduction in saline-induced diuresis after uninephrectomy (Mozaffari and Schaffer 2002). It may also potentially reset the pressure–diuresis–natriuresis mechanisms in a hypertensive glucose-intolerant rat model with a reduction in tubular sodium reabsorption (Mozaffari et al. 2003). Mozaffari and Schaffer (2002) speculate that taurine therapy may be of value in instances of renal dysfunction and its attendant dysregulation of fluid and electrolyte homeostasis.

Taurine, along with betaine, myoinositol and α-glycerolphosphate, forms the major non-ionic osmolyte that assures operation of the renal medullary tonicity gradient and the countercurrent mechanism (Burg 1995). The movement of these osmolytes in and out of renal medullary cells is key to cell volume regulation following hypo- or hyperosmolar stress. In terms of renal function, this osmolarity regulating capacity is one of the most important

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biological properties of taurine. A hypertonicity response element in the promoter region of many of the osmolyte transporter genes provides a rapid acting molecular mechanism by which up- and down-regulation of the abundance of osmolyte transporter protein in relevant cell membranes can occur (Burg 1995; Handler and Kwon 1993). The tonicity response element (TonE) has been located proximal to −124 and distal to −99 of the taurine transporter gene (*TauT*) promoter region (Ito et al. 2009). Mutation of TonE abrogates this hyperosmolar stress response. This topic has been extensively reviewed, and so only recent relevant studies will be examined here.

Macromolecular crowding appears to regulate the assembly of mRNA stress granules after hyperosmotic stress (Bounedjah et al. 2012). The accumulation of taurine, as well as betaine and myoinositol, by renal tissues follows expression of the transcriptional factor NFAT5/TonEBP. Macromolecular crowding and high ionic strength favor the assembly of these RNA stress granules. After several hours, with the accumulation of organic osmolytes, macromolecular crowding and ionic strength fall and stress granules dissociate. The authors speculate that this stress granule mechanism may play a pivotal role in the adaptation to hyperosmolarity in renal tissues.

To probe the impact of hyperosmolarity on the kidney, a metabolomic approach using high-resolution nuclear magnetic resonance spectroscopy was used in rats exposed to low and high concentrations of nickel chloride (Tyagi et al. 2011). Damage was evident in both cortical and medullary renal regions, and depletion of renal osmolytes, including taurine, betaine, trimethylamine oxide and myoinositol occurred in a dose-dependent fashion. Only animals exposed to the lower dose of NiCl recovered the renal function of osmolyte uptake. This approach could be especially useful in probing metabolomic patterns after renal injury in deep medullary regions. Tight gap junctions between cells are crucial to the process of osmolyte uptake under hypertonic conditions. Clustered cells appear to accelerate the transfer of osmolytes to cycling cells, which is necessary in cell volume regulation during cell turnover (Desforges et al. 2011). A property of cancer cells is that they do not communicate via gap junctions, and, hence, the variety of medullary cell renal carcinoma cell types may be explained by the inability of cancer cells to cope with hyperosmolarity. It can be speculated that the failure of a neoplastic cell to be capable of a hyperosmolar response may lead to further differences between "normal" and "neoplastic" renal cells.

The impact of taurine availability on renal function has been probed by Roysommuti et al. (2010a, b) in a conscious adult rat model. While the glomerular filtration rate (GFR) was not different in taurine-supplemented or in taurine-depleted rats relative to controls, the mean renal vascular resistance was higher in both taurine-depleted and -supplemented animals. Thus, it appears that taurine status can alter renal hemodynamics. An interesting aspect of this influence of taurine supplementation or depletion is that prenatal exposure will alter the response to a 5 % body weight saline bolus.

Whether a high taurine load alters renal function in man is unclear. Reports of renal failure and death in association with ingestion of vodka and energy drinks have surfaced. A 17-year-old boy developed acute kidney injury (AKI) after ingesting 1 l of vodka and 3 l of energy drink, a combination that contained 4,600 mg taurine, 780 mg of caffeine and 380 g ethanol (Schoffl et al. 2011). Adolescents and young adults consume this mixture because they feel that the energy drink attenuates the effects of ethanol.

Other stressors may affect the taurine transporter mechanism. The JNK pathway is a major stress-signaling pathway in cells that plays important roles in many cellular processes, including cell growth, development and apoptosis. In non-stressed cells, JNK targets the ubiquitination and subsequent degradation of bound proteins such as c-Jun (Fuchs et al. 1997). In addition, JNK forms a complex with and degrades p53 (Fuchs et al. 1998). However, in stressed cells, JNK phosphorylates and activates associated c-Jun and p53 proteins and enhances their transcriptional regulation of stress-responsive genes (Buschmann et al. 2001; Derijard et al. 1994). Our previous studies have shown that *TauT* is a target gene of p53. Activation of p53 by a chemotherapeutic agent (cisplatin) suppresses *TauT* expression both in vitro and in vivo (Han and Chesney 2005; Han et al. 2009). We have proposed a model for p53/c-Jun-mediated regulation of the *TauT* gene (Han and Chesney 2010). Normally, both p53 and c-Jun bind to the *TauT* promoter and compete to regulate *TauT*. Therefore, the level of *TauT* protein is tightly regulated by p53 and c-Jun via the JNK signaling pathway. In stressed cells, JNK phosphorylates and activates c-Jun and p53 proteins and enhances their transcriptional regulation of *TauT*. Cisplatin-induced activation of p53 decreases *TauT* promoter activity via the p53-inhibited JNK-c-Jun pathway by competing with c-Jun for activation. Upon survival signaling, c-Jun substitutes for p53 function and enhances *TauT* expression.

Exposure of renal cells to cisplatin results in nephrotoxicity and AKI. Both autophagy and apoptosis are characteristic renal cell responses to cisplatin exposure. At low doses (10 μM), exposed NRK-52E cells develop autophagy, which appears to grant cytoprotection to renal cells. By contrast, 50 μM cisplatin causes cell death by apoptosis. Preconditioning of cells with taurine (25 mM) delayed apoptosis and maintained autophagy (Rovetta et al. 2012). The authors speculate that a role for endoplasmic reticulum-specific signaling could lead to cross talk between autophagic and apoptotic cell death mechanisms. They

further posit that taurine enhances autophagic protection counter to apoptosis by reducing endoplasmic reticulum stress.

Hypertension and proteinuria

Hypertension is common in renal disorders for a variety of reasons: renal vascular disease, abnormalities of the renin–angiotensin system (RAS), monogenic disorders of ion transporters, acute inflammation of the kidney and the late stages of progressive CKD. Along with proteinuria, hypertension has been shown to contribute to the progression of CKD, leading to the need for renal replacement therapy (dialysis and/or renal transplantation). Taurine influences renal blood flow and endothelial cell properties. Using a deoxycorticosterone acetate (DOCA) salt-loaded rat model, taurine was shown to reduce blood pressure, which may have involved sympathoadrenal inhibition and activation of an endogenous opiate (Sato et al. 1991). Others have demonstrated a salutary response in blood pressure in both rats and humans (Hu et al. 2009; Roysommuti et al. 2009; Satoh and Kang 2009). It appears that the effect of taurine is to reduce vascular resistance (Hu et al. 2009; Roysommuti et al. 2009; Satoh and Kang 2009) and autonomic nervous control of arterial blood pressure (Nara et al. 1978; Roysommuti et al. 2009). It can also reduce the renal response to high sugar intake-induced baroreceptor reflex dysfunction (Thaeomor et al. 2010).

Using an L-nitro-methyl ester (L-NAME) model of hypertension, taurine supplementation was shown to augment nitric oxide (NO) synthase activity and serum NO values (Hu et al. 2009) and blunt cytokine and endothelin concentrations. Taurine also reduced hypertension in the hypertension-prone Kyoto rat (Nara et al. 1978).

Taurine depletion of uninephrectomized rats actually accelerated the development of hypertension as a consequence of uninephrectomy. Signs of increased inflammation in the kidney were evident (Mozaffari et al. 2006). Taurine depletion during the fetal or prenatal period will lead to higher blood pressure during adulthood (Roysommuti et al. 2009). Because of the immaturity of the uphill taurine transport process in the kidney, with resultant elevated fractional excretion of filtered taurine, much of the taurine administered to rat pups will be excreted (Friedman et al. 1981). It is plausible that such taurinuria could lead to intravascular volume depletion, resulting in upregulation of the RAS (Gomez et al. 1993). The role of taurine supplementation in slowing the advance of CKD is most probably related to its impact on renal blood flow dynamics, hypertension and proteinuria.

Proteinuria is a sign of serious renal disease, and, if uncorrected, leads to progression of CKD. That taurine may diminish urinary protein excretion in various models of glomerular damage has been known for nearly three decades, as recently reviewed (Chesney et al. 2010). Recent work has furthered insight into this observation. Rats made nephrotic by the administration of adriamycin exhibited proteinuria and hyperlipidemia, and taurine treatment reduced urinary protein excretion (Venkatesan et al. 1997). Pretreatment with taurine for 7 days not only reduced proteinuria, but prevented lipidemia to a significant extent. These findings suggest a protective role for taurine in instances where proteinuria might occur: for example, as a side effect of certain drugs (e.g., penicillamine).

While studies in the adriamycin-treated rat suggest that taurine has an effect on lipid status, including lecithin cholesterol acyl transferase, lipoprotein lipase activity and glutathione values (Venkatesan et al. 1997), other mechanisms are suggested in studies of rats with Masugi model glomerulonephritis (Lian et al. 2003). Taurine administration reduced proteinuria in association with a reduction in platelet activating factor in serum, urine and renal tissue.

In the fawn-hooded hypertensive rat model of spontaneous hypertension, perinatal micronutrient supplementation with L-arginine, taurine, ascorbic acid and vitamin E led to increased urinary NO excretion as well as increased sodium and potassium excretion for the duration of treatment. However, development of proteinuria was attenuated in these rats after they reached adulthood (Koeners et al. 2010). While both sexes exhibited attenuation of proteinuria, only in female rats was there reduction in GFR, glomerular hyperfiltration and glomerulosclerosis. Hence, the anti-proteinuric mechanisms of micronutrient supplementation are unclear.

Renal disorders

Renal maldevelopment and cell cycles

The original hypothesis that taurine may be involved in renal development was derived from the observation that the taurine transporter gene (*TauT*) is a tentative target of the *WT1* gene (Han and Chesney 2003). It has been demonstrated that *WT1* plays a critical role in kidney development (Coppes et al. 1993). The *WT1* gene is restricted during development to mesenchymal tissues, occurring in specific cells of the collecting system within the kidney, non-germ cell components of the gonads, uterus, spleen and mesothelium (Pritchard-Jones et al. 1990). Knockout of the *WT1* gene results in embryonic lethality in the homozygous state, secondary to the failure of kidney and gonad development (Kreidberg et al. 1993). Recent studies from our laboratory using a *TauT* knockdown 293 kidney

cell model support the idea that taurine plays a role in renal development. Knockdown of *TauT* significantly decreased the growth rate, cell migration and colony formation of 293 cells. Microarray analysis showed that several genes that are involved in cell cycle regulation or cell division, such as CDK6 and CDC7, were significantly down-regulated in *TauT*-deficient 293 cells as compared to control 293 cells. Inhibition of *TauT* causes cell cycle G2 arrest, largely because of the down-regulation of pathways involved in the positive regulation of biological processes (unpublished data).

Acute kidney injury and nephrotoxicity

The role of taurine in AKI, formerly called acute tubular necrosis, is complex in that it may play a protective role or be a marker of injury. Acute kidney injury is a major health issue in humans, and AKI is an important cause of mortality in patients in intensive care settings, with mortality rates reaching 60–70 % (Parikh et al. 2011). Hence, if therapeutic agents can be found that prevent or reverse AKI, they can be of appreciable value.

The value of models of AKI is that both disease mechanisms and therapeutic strategies can be assessed. One of the classical models of renal injury is induced by the administration of maleic acid (Gunther et al. 1979), which results in the renal Fanconi syndrome and inhibition of amino acid reabsorption. It appears that maleic acid inhibits the saturable component of amino acid reabsorption, including reabsorption of taurine.

Among common nephrotoxins that result in AKI are heavy metals, including lead, cadmium, mercury, uranium and gold. Of these, lead causes the most common heavy metal exposure. In a subchronic lead intoxication model in rats, the effects of taurine and/or meso 2,3-dimercaptosuccinic acid (DMSA) were examined relative to lead-induced alterations in heme synthesis, hepatic, renal and brain oxidative stress, and tissue lead concentrations. Lead exposure diminished delta-aminolevulinic acid dehydratase (ALAD), reduced glutathione and increased zinc protoporphyrin. DMSA treatment increased the activity of ALAD, but taurine was able to reverse oxidant stress, including normalization of glutathione (Flora et al. 2004). Taurine enhanced the effects of a thiol chelator on relief of oxidative stress and the depletion of lead tissue levels. The other issue is that as lead is released from soft tissue deposits, it helps to have a concomitant antioxidant as therapy.

Antibiotic nephrotoxicity is a common cause of AKI in man. The aminoglycoside class of antibiotics is especially nephrotoxic, and gentamicin is frequently used in animal models of AKI. One study used a gentamicin/diclofenate combination that led to greater nephrotoxicity than gentamicin alone (Eldin et al. 2008). Evidence of kidney injury included elevated serum Cr, BUN and urinary *N*-acetyl-glucosamine (NAG) and reduced Na^+K^+ATPase activity. Co-administration of taurine and quercetin normalized creatinine clearance and reduced urinary excretion of protein, uronic acids and NAG. Levels of cortical lipid peroxidation products were raised after gentamicin dosing and declined after administration of taurine and quercetin.

Arsenic is a potent mediator of oxidative renal injury via MAPKs/NF-κB and mitochondria-dependent pathways. Measured changes include increased production of reactive oxygen and reactive nitrogen species, enhanced lipid peroxidation and protein carboxylation, and decreased antioxidant activity in renal tissue (Roy et al. 2009). Arsenic administration causes activation of MAPK and NF-κB and induces apoptosis via a mitochrondrial Bcl-2/Bad pathway. Pretreatment with taurine blocked these effects and prevented apoptosis with preservation of renal histology.

In an ischemic–reperfusion model using control (perfusion injury alone), and taurine-treated and taurine-depleted rats, the taurine-depleted rats actually recovered from ischemia–reperfusion injury by day 6 (Mozaffari et al. 2010). A possible mechanism to explain this observation is that taurine depletion results in up-regulation of the taurine transporter, which would enhance taurine entry into the renal medulla. Consistent with this finding, the tubules demonstrated up-regulation of aquaporin 2. The taurine-treated group showed dilated tubules that lacked immunostaining for aquaporin 2, but not aquaporin 1, which suggested a proximal tubular origin of dilatation. Control rats with perfusion injury showed loss of urinary concentrating capacity, which recovered slowly. The capacity of the kidney to regulate total body taurine status is demonstrated in this study (Mozaffari et al. 2010).

Another drug resulting in nephrotoxic AKI is acetaminophen. In a Swiss albino mouse strain, acetaminophen causes necrosis and reduction of GSH, increases in ROS and up-regulation of CYP2E1. Taurine pretreatment or concomitant treatment reduced nephrotoxicity and suppressed CYP2E1 up-regulation (Das et al. 2010), indicating that it might be useful in the treatment of this difficult-to-reverse cause of AKI.

Han and Chesney theorized that regulation of expression of the *TauT* gene is a stress-responsive mechanism to reduce nephrotoxic injury and AKI. Using the well-established nephrotoxic chemotherapeutic agent cisplatin, which down-regulates *TauT*, forced overexpression of *TauT* protects against cisplatin-induced apoptosis. Expression of *TauT* is negatively regulated by p53, which increases after administration of cisplatin, and up-regulation by cJun, which is mediated by the JNK signaling pathway. These results suggest that *TauT* may determine the fate of renal cells during stress-induced AKI (Han and Chesney 2010).

These studies, using different models of AKI with a variety of nephrotoxins, all indicate that taurine, both as a therapeutic agent and in terms of total body taurine status, can be renoprotective. With these studies serving as background, therapeutic trials of taurine as a renoprotective agent are warranted, especially because of the seriousness of AKI in man.

Renal stones (nephrolithiasis)

Renal stone disease in man includes the hyperexcretion of calcium oxalate, magnesium ammonium phosphate, uric acid or cysteine. When plasma and urinary amino acid profiles were examined in control and subjects with renal calculi, the excretion of taurine, glycine, serine and L-leucine was evaluated, especially in those who formed calcium oxalate and ammonium phosphate stones (Atanassova et al. 2010). The significance of this finding is uncertain. A potential protective role of taurine has been assessed in a rat model of calcium oxalate nephrolithiasis (Li et al. 2009). Rats were given ethylene glycol and ammonium chloride, which increased oxidative stress, reduced superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) and led to mitochondrial membrane injury. Taurine treatment of experimental animals led to less mitochondrial membrane injury, increased SOD and GSH-Px, and abrogated calcium oxalate damage to the kidney. These studies suggest that a prospective trial of taurine supplementation in patients who form stones might be of value.

Urinary tract infection

Urinary tract infections (UTIs) are common in man (Chesney et al. 2008) and can involve the bladder alone (cystitis) or the upper urinary tract. They can lead to infection of the kidney, termed pyelonephritis. Ordinarily, the bladder wall mucosa has an innate host defense mechanism that prevents bacteria from causing a UTI and keeps the urine sterile. Neutrophils will also assist in the elimination of bacteria in the bladder. While taurine can enhance neutrophil respiratory burst activity, in a female mouse model it appears to diminish the inflammatory response at the urothelial–endothelial interface and thus may diminish clearance of *Escherichia coli* from the bladder (Condron et al. 2004, 2010).

N-chlorotaurine is a natural product of human leukocytes that has weak antimicrobial oxidant properties. A 1.0 % *N*-chlorotaurine solution was infused into the bladder of a patient with an omniresistant *Pseudomonas aeruginosa* infection and intravesical concrements of the bladder. Although the organism was rapidly killed in vitro by this agent, the infection in the patient was not eradicated (Nagl et al. 1998).

Kidneys obstructed by anatomic abnormalities or renal stones are at risk for increased incidence of UTI. Obstructed kidneys also have well-described physiologic abnormalities that compensate for the obstruction. A recent study in rats with partial and complete obstruction demonstrated that taurine, among other osmolytes, is found in increased amounts in the urine of animals with obstructed kidneys (MacLellan et al. 2011). The authors speculate that certain urinary patterns of differentiating metabolites could serve as biomarkers of obstruction.

Glomerulonephritis: the role of myeloperoxidase

In the early, heterologous phase of anti-glomerular basement membrane (anti-GBM) globulin glomerulonephritis, proteinuria occurs and is mediated by neutrophilic infiltration (Kuligowski et al. 2006) that peaks within hours (Saleem et al. 1998). The autologous phase of the nephritis is initiated by T helper cells 1 (Th1)—polarized, delayed-type hypersensitivity over the next 1–3 weeks (Tipping et al. 1998). During the initial phase, myeloperoxidase (MPO), a product of azurophilic granules, is released and in the presence of H_2O_2 and intermediates (chloride, tyrosine and nitrite) catalyzes the formation of hypochlorous acid, tyrosyl radical and reactive nitrogen intermediates that damage lipids and/or proteins (Klebanoff 2005). The use of an $MPO^{-/-}$ mouse model indicates the extensive role that MPO plays in renal damage, particularly in the heterologous phase, with reduced production of reactive oxidant products (Odobasic et al. 2007). The well-known capacity for taurine to form an adjunct with hypochlorous acid and thereby diminish the impact of MPO activity suggests that taurine could be a potential therapeutic agent in anti-GBM glomerulonephritis (Goodpasture syndrome).

Another MPO-related disorder is pauci-immune crescentic glomerulonephritis, in which circulating antibodies (anti-neutrophil cytoplasmic antibodies (ANCA) to MPO form the basis for this systemic glomerulonephritis and vasculitis (Falk and Jennette 1988). The role of taurine in this pauci-immune glomerulonephritis is unclear.

Other glomerular disorders

A number of different diseases can cause glomerular disease. It may be the direct result of an infection or a drug that is toxic to the kidneys, or it may result from a disease that affects the entire body, like diabetes or lupus erythematosus. The most well-known study was carried out by Sturman's group in the early 1990s (Trachtman et al. 1992). They developed an animal model of glomerular disease by repeated administration of low doses of puromycin aminonucleoside (PAMN) to rats to induce a

proteinuric renal disease that resembles focal segmental glomerulosclerosis (FSGS). They demonstrated that chronic PAMN nephropathy decreases the magnitude of the renal functional injury and lessens the severity of the associated glomerular and tubulointerstitial damage. In these animals, inulin clearances were lower than simultaneously measured creatinine clearances; however, taurine administration attenuated PAMN-induced FSGS and improved GFR in rats with PAMN nephropathy.

The classification of systemic lupus erythematosus nephritis includes proliferative glomerulonephritis (Class III/IV), focal segmental glomerulonephritis and pure membranous nephropathy (Class V), and diagnosis generally requires a renal biopsy. Taurine appears to be one of several urinary metabolites that distinguish among these forms of nephritis (Romick-Rosendale et al. 2011). Class III/IV patients had a tenfold lower excretion of taurine compared to Class V patients, in whom taurine excretion was normal. Other metabolomic signals, such as levels of urinary citrate and hippurate, also were measured in these patients.

Nephrotic syndrome

Nephrotic syndrome is a nonspecific disorder in which the kidneys are damaged, causing them to leak large amounts of protein. Animal studies showed that rats made nephrotic with adriamycin had a high excretion of protein, albumin and *N*-acetyl-β-D-glucosaminidase compared to non-nephrotic rats (Venkatesan et al. 1997). Nephrotic rats manifested hyperlipidemia with significant elevation in all major lipoprotein fractions. Treatment with taurine significantly suppressed adriamycin-induced proteinuria, albuminuria and urinary excretion of *N*-acetyl-β-D-glucosaminidase.

Diabetic nephropathy

Of all renal disorders, none has been studied as extensively as diabetic nephropathy in terms of taurine status. End-stage renal disease requiring dialysis is most often caused by diabetic nephropathy (United States Renal Data System 2011). The thesis that taurine therapy can help alleviate or slow down the progression of diabetic nephropathy is not new (Hansen 2001; Trachtman et al. 1995), but recent studies have made progress relative to the mechanism(s) of protection.

It had been hypothesized that antioxidants could reverse diabetes-induced oxidative stress in the glomeruli of diabetic rats, but careful examination of several antioxidant enzymes after induction of diabetes has pointed mainly to heme oxygenase-1 (HO-1). Of all enzymes studied, including superoxide dismutase and glutathione peroxidase, HO-1 was increased 16-fold in glomeruli of diabetic rats (Koya et al. 2003). Taurine, with other antioxidants, reduced HO-1 expression and diminished proteinuria and hypertension. Glomerular pathologic changes were reversed.

Other potential mechanisms of taurine's antioxidant role were studied in renal tubular epithelial cells, in which high glucose inhibited cellular growth and induced hypertrophy. High glucose-induced Raf-1, p42/p44 mitogen-activated protein kinase (MAPK), Janus kinase 2 (JAK2) and signal transducer and activator of transcription 1 (STAT1) and STAT3 activation were markedly blocked by taurine. Taurine also blocked the high glucose-induced stimulation of fibronectin and type IV collagen synthesis, increased concentrations of cyclin D/cdk4, and suppressed p21 NafI/Cip1 and p2KIP1 in high glucose-treated cells (Huang et al. 2007). Advanced glycation end products (AGE) cause inhibition of cellular mitogenesis, but do not lead to cell death. In essence, cells exposed to high glucose undergo hypertrophy. Taurine and other Raf-1 kinase or ERK kinase inhibitors may have the capacity to induce cellular proliferation and cell cycle progression in AGE-treated cells (Huang et al. 2008). Taurine reduces cell size, cellular hypertrophy index and protein levels of RAGE, p27(Kip1), collagen IV and fibronectin. Hence, taurine may have anti-fibrotic activity due to its inactivation of Raf-1/ERK in AGE-induced hypertrophy.

Another potential mechanism may involve the activation of leukocyte adhesion molecules. As the principal receptor of oxidized low-density lipoprotein, LOX-1 induces the leukocyte adhesion molecule-1 (ICAM-1). In streptozotocin (STZ)-treated diabetic rats, co-administration of taurine with STZ diminished the histologic appearance of renal injury, and the levels of BUN, serum creatinine and renal malondialdehyde were reduced. The activity of renal glutathione peroxidase was higher and the over-expression of LOX-1 and ICAM-1 was blunted. In this model, taurine was protective against early renal injury (Wang et al. 2008).

What if diabetic nephropathy is established and heavy proteinuria is evident? In rats with STZ-induced diabetes that were evaluated after 4 months of diabetes, proteinuria was significantly higher in diabetic rats than in control rats, and it continued to increase to more than fivefold higher than in controls. Taurine administered in the drinking water (1 %) after 4 months prevented a further rise in proteinuria and was associated with improved renal histology and reduced TGF-β expression in the glomeruli. The renal levels of several oxidative stress markers, including pentosidine and nitrotyrosine, were lower than in untreated diabetic rats. These findings suggest that taurine slows down the progression of disease through its antioxidant properties, even in an animal with established diabetic nephropathy (Higo et al. 2008). This finding also suggests

that taurine could serve as a therapeutic agent in patients with established disease.

In an alloxan diabetic rabbit model, taurine administration reduced gluconeogenesis and serum glucose concentration. It also reduced serum creatinine and BUN, and attenuated the diabetes-associated decline in GSH/GSSG ratio, as well as the decline in hydroxyl free radicals. Taurine may also have a nephroprotective effect via diminished NADPH activity (Winiarska et al. 2009). In another study in rats with alloxan-induced diabetes, taurine administration reduced levels of glucose and proinflammatory cytokines TNF-α, IL-6 and IL-1β. Markers of oxidative stress were also lower. Another effect of taurine was to protect renal tissues from alloxan-induced apoptosis by regulation of the Bcl-2 pathway and caspase-9/3 proteins. The authors speculate that taurine could ameliorate diabetes-associated renal damage (Das and Sil 2012).

Cytochrome P450 2E1 is increased in STZ-induced diabetes. Taurine (2%) in the drinking water of diabetic rats reduced both CYP2E1 protein and mRNA in the kidney, but not liver. As shown by others, the diabetes-induced rise in heme oxygenase-1 was also suppressed in kidney, as were other markers of oxidative stress (Yao et al. 2009).

A study in an experimental rat model of type 2 diabetes mellitus induced by a high fat sugar diet and STZ indicated that taurine administration to diabetic rats improved glucose metabolism and reduced triglycerides, total cholesterol, serum creatinine, BUN, urinary N acetyl β-glucuronidase, protein and the expression of laminin B1 mRNA in the kidney. Also, the HDL cholesterol was elevated (Lin et al. 2010).

When mice are made diabetic by administration of STZ, they develop polyuria. There is then enhanced expression of aquaporin 2 to compensate for diabetic dehydration. Lithium carbonate was administered to diabetic rats to examine the relationship between renal aquaporin expression and urine volume. The urine volume nearly doubled and the expression of aquaporin 2 and 3 decreased in the lithium carbonate-treated animals. However, expression of the sodium myoinositol and taurine transporters was unchanged. Of note, the decreased aquaporin expression levels occurred without a change in urinary osmotic pressure, because the osmolyte transporters were unaltered (Satake et al. 2010).

When human renal tubular cells were cultured under diabetic conditions, the AGEs resulted in renal tubular cell hypertrophy. A molecular mechanism was sought to account for these findings. Advanced glycation end products significantly suppressed the NO/cGMP/PKG signaling. Various NO donors and antioxidants N-acetylcysteine and taurine attenuated the AGE-blocked NO production, cGMP synthesis and PKG attenuation. These antioxidants also inhibited AGE/RAGE-induced hypertrophic growth, probably through the induction of NO/cGMP/PKG (Huang et al. 2009).

The protective role of taurine in diabetic nephropathy occurs by several mechanisms including reversal of proteinuria, stabilization of GFR, inhibition of fibronectin and P21 (Waf1/Cip1) and suppression of heme oxygenase-1, all of which were up-regulated by AGEs. In terms of medullary function, taurine resists the glucosuria and polyuria of uncontrolled diabetes that can wash out the osmotic gradient. Taurine is also capable of overcoming glucose-induced renal tubular cell hypertrophy and inducing cellular proliferation and cell cycle progression. Most studies of diabetic nephropathy have focused on the capacity of taurine to overcome the effects of AGEs on renal fibrosis and glomerular hypertrophy, including reversal of histopathologic changes of all parts of the kidney. These studies indicate that taurine could be of potential use in what is one of the most serious complications of diabetes mellitus: namely, renal tubular cell hypertrophy.

Renal tubular disorders

Renal tubular disorders involve abnormal transport of ions and other organic solutes (Jones and Chesney 1992). They may affect transport of a single substance or group of substances—for instance, amino acids of a similar charge group or hexose sugars—or affect global transport, as in the Fanconi syndrome. These disorders may be monogenic and are inherited in a Mendelian fashion. In this instance, an altered transporter protein does not support normal tubular transport. Tubular damage by toxins or from disorders of mitochondrial DNA can also lead to the Fanconi syndrome (Zelikovic and Chesney 1989a). Taurinuria occurs as a component of a defect in renal tubular β-amino acid reabsorption (Zelikovic and Chesney 1989b; Chesney et al. 1976) or in the context of Fanconi syndrome. Taurine is also poorly reabsorbed in immature mammals, especially in preterm infants (Han and Chesney 2006; Zelikovic et al. 1990).

The most relevant example of activity of the β-amino acid transport mechanism is the inherited defect found in certain mouse strains, including C57BL/6J (the common strain used for transgenic and knockout mice) (Chesney et al. 1976). An example of interactions of this transporter is that adding 3 % β-alanine to the drinking water of rats or mice can deplete tissue of taurine stores (Mozaffari 2003; Roysommuti et al. 2010a, b).

The observation that taurine could be found in the urine of patients with renal tubular disorders or in hereditary aminoacidurias was discovered soon after the development of ion-exchange chromatography (Cusworth and Dent 1960). In a group of patients with diverse tubular disorders,

including adult Fanconi syndrome, cystinosis, nutritional osteomalacia and hypophosphatasia, taurine excretion was increased, but not massive (Cusworth and Dent 1960). In patients with Lowe syndrome, an X-linked condition characterized by a bulging forehead and sunken eyes with cataracts or glaucoma, and evidence of a partial Fanconi syndrome, taurinuria was common (Gardner and Brown 1976). Taurinuria is also common in animal models of tubular disease such as Dent disease, a monogenic tubular disorder with low molecular weight proteinuria, glycosuria, aminoaciduria and sometimes rickets (Wang et al. 2000). Dent disease is caused by inactivating disorders of a renal-specific voltage-gated chloride channel, CLC-5, expressed in proximal tubule, thick ascending limb of Henle and the collecting duct. Both mice and human subjects with Dent disease have hypercalciuria and nephrocalcinosis as well. CLC-5 probably plays an important role in endosomal acidification. While taurinuria is common in many of these hereditary tubulopathies, it is not a specific or solitary finding but rather a component of generalized aminoaciduria.

Fanconi syndrome can be caused by nephrotoxins such as heavy metals or solvents. Taurinuria, along with distal renal tubular acidosis, weakness, dysmetria and ataxia has been reported after chronic exposure to airplane glue containing toluene (Moss et al. 1980). Patients generally sniff fumes from a plastic bag or sock laced with glue (known as "huffing"). Since they demonstrate both aminoaciduria and distal renal tubular acidosis, there is evidence for both proximal and distal tubular dysfunction. These renal changes are reversible after cessation of toluene exposure.

Fanconi syndrome is a disease of the proximal renal tubules of the kidney in which glucose, amino acids, uric acid, phosphate and bicarbonate are passed into the urine instead of being reabsorbed. Ifosfamide is a chemotherapeutic agent that can result in proximal renal tubular injury that mimics Fanconi syndrome. Badary's study in an animal model has demonstrated that ifosfamide induced a Fanconi syndrome characterized by wasting of glucose, electrolytes and organic acids, along with elevated serum creatinine and urea, and decreased the creatinine clearance rate. Taurine markedly ameliorated the severity of renal dysfunction induced by ifosfamide, with a significant decrease in total and fractional excretion of Na^+, K^+, PO_4^{-3} and glucose, decreased serum creatinine, urea and albumin, and increased creatinine clearance rate (Badary 1998). In mice with Ehrlich ascites carcinoma treated with ifosfamide, the addition of taurine to drinking water had no impact on the effectiveness of treatment. Indeed, mice receiving taurine appeared healthier than those treated with ifosfamide alone. As has been seen with toluene exposure, Fanconi syndrome after ifosfamide may be reversible.

Several models of Fanconi syndrome have demonstrated increased taurinuria and reduced accumulation of taurine in vitro, including exposure to cystine dimethylester (Foreman et al. 1987) and vitamin D deficiency (Dabbagh et al. 1989; Dabbagh et al. 1990). Taurine therapy has not been evaluated in these models.

Defects in medullary transport generally involve the reabsorption or secretion of specific ions because of the abundance of sodium, chloride, potassium, bicarbonate and proton transporters in that portion of the kidney. As noted previously, the medulla is the location of the counter current multiplier system, and thus is where the highest intracellular taurine concentrations are found (Han et al. 2006). Taurine has been used as a biomarker in an animal model of juvenile neuronal ceroid lipofuscinosis type 3 (CLN3) (Stein et al. 2010). Lipofuscin is built up in several tissues including skin, colon, lung and kidney, where it appears in principal cells of the medulla. The mice stored increased amounts of nuclear localized β-galactosidase (β-gal) and responded to osmolar stress by increased β-gal abundance. Following furosemide administration, which reduces the osmolarity of the medulla, β-gal abundance fell. Primary culture of inner medullary cells from CLN3 null mice showed no defect in osmolyte accumulation or taurine efflux. However, these mice were hyperkalemic and showed reduced potassium excretion.

Lithium is used in a variety of bipolar affective disorders, but this agent can have renal complications. Rats chronically treated with lithium chloride develop nephrogenic diabetes insipidus (NDI). The metabolic response to chronic lithium therapy was explored using (1)H-nuclear magnetic resonance metabonomics profiling, and changes were identified in the concentrations of metabolites in three zones of the kidney and in the urine of rats who had developed Li-induced NDI. NDI was localized to the inner medulla and influenced the tissue concentrations of several osmolytes, including taurine, betaine, myoinositol and glycerophosphocholine. Products of glycolysis as well as other organic solutes were also found in both tissue and urine. In metabolic studies involving renal tissue, taurine appears to be an important marker.

Miscellaneous renal disorders

The hepatorenal syndrome is an extremely serious disorder in which progressive kidney failure occurs in the face of hepatic cirrhosis (Ng et al. 2007). In patients with liver failure, another precipitating event, such as sepsis, overuse of diuretics or gastrointestinal bleeding, often presages the onset of the syndrome. The classic pathophysiologic feature is vasoconstriction of renal vessels in the face of dilatation of splanchinic vessels, which may be due to increased liver disease with higher values of

prostaglandins, nitric oxide and other vasoactive substances (Gines and Arroyo 1999). Because of renal vasospasm, the juxtaglomerular apparatus of the glomerulus senses effective volume reduction with attendant increased secretion of renin and activation of the RAS. Notwithstanding, these RAS mediators cannot overcome splanchinic vasodilatation, and sustained underfilling of the renal blood flow results in worsening renal vasoconstriction and AKI. Moreover, because of increased aldosterone secretion, distal sodium reabsorption is enhanced, which worsens the ascites in these cirrhotic subjects (Mukherjee 2011). A remarkable feature of this disorder is that a renal biopsy sample is normal (Gines and Arroyo 1999). A typical patient has a reduced volume of urine that is darkly colored from bilirubin metabolites; confusion, delirium and dementia from hepatic failure; as well as worsening abdominal swelling from ascites. The mortality rate is more than 50 %. Treatment is usually hepatic transplantation, although treatment with a vasopressin agonist can be helpful.

The bile duct-ligated rat can be a model of hepatorenal syndrome (Fleck and Engelbert 1998). Plasma amino acid levels rose in these rats, and renal tubular reabsorption of 11 of the 16 amino acids examined increased. Infusion of leucine, glutamine or taurine increased fractional excretion of the administered amino acid. If animals were treated for 3 days with intraperitoneal dexamethasone or thyroxine, it appeared to enhance the renal absorption of amino acids in this model. Because many of the patients with the hepatorenal syndrome are malnourished, enhanced amino acid reabsorption may be of value.

Another group of hepatorenal conditions involving taurine action are the peroxisomal disorders, which include various autosomal recessive enzyme disorders. Group I (of four groups) disorders are of peroxisome biogenesis and generally are caused by mutation of the 13 genes that are needed for the normal formation and function of peroxisomes. Two disorders in Group 1 are Zellweger syndrome and infantile Refsum's disease (Abdel-Hamid 2010). Zellweger syndrome, usually fatal by 6–12 months, involves peroxisomal deficiencies, retention of long chain fatty acids, neurologic maldevelopment, especially of white matter, and numerous renal cysts. Abnormalities in bile acid synthesis are also evident. Death is due to profound hypotonia, lack of myelination, pneumonia and inanition.

Several of the hepatic (and renal) perioxisomal disorders, such as Zellweger syndrome and infantile Refsum disease, demonstrate evidence of abnormal bile acids due to the absence of peroxisomes in hepatocytes. In some of these patients, 27-carbon and 29-carbon carbon bile acids are present in plasma (Clayton et al. 1987), including trihydroxycoprostanic acid (THCA) and dihydroxycoprostanic acid (DHCA). Even more obscure taurine-conjugated bile acids are found in the urine of a patient with Zellweger syndrome, including 3α,7α,12α-trihydroxy-5β-cholestanoic acid (Une et al. 1987). Many of these di- and trihydroxycholestanoic diasterioisomers appear due to the absence of peroxisomal α-methylacyl-CoA racemase (Ferdinandusse et al. 2001). While taurine is unlikely to be of therapeutic value in Group 1 peroxisomal disorders, its bile acid conjugates are of potential diagnostic value in this renal cystic disorder.

The finding of these bile acids in the urine, especially those that are taurine conjugated (as detected by fast atom-bombardment mass spectrometry), can lead to rapid diagnosis of these conditions (Lawson et al. 1986). The usual means of diagnosis is analysis of the PEX genes of interest (McKusick 2011) rather than seeking bizarre taurine-conjugated bile salts.

Using a metabonomic approach, increased quantities of *N*-acetyltaurine (NAT) were found in the urine of Cyp2e1-null mice following ethanol exposure. NAT was identified as a urinary metabolite strongly responsive to ethanol. Of the three principal substrates of NAT synthesis (taurine, acetyl-CoA and acetate), the values for taurine fell, in contrast to increased levels of the other two metabolites. NAT production was demonstrated in renal tissue in vitro. Urinary NAT can serve as a potential biomarker for hyperacetatemia after alcohol ingestion (Shi et al. 2012).

A serious renal disorder of pregnancy is pre-eclampsia or eclampsia. This is a well-known cause of maternal and infant mortality. Some pregnant mothers have the metabolic syndrome with hypertension, obesity, dyslipidemia, hyperglycemia and hyperinsulinemia. Full-term infants do not tend to be small for gestational age (SGA) (Lindheimer et al. 1999); however, if the infant is preterm, he or she is more likely to be SGA (Xiong et al. 2002). One hypothesis of intrauterine growth retardation is that SGA infants have diminished placental transport of amino acids, resulting in lower cord blood amino acid values and stunting of growth. By contrast, metabolic syndrome is associated with normal-sized offspring and high cord blood amino acids (Evans et al. 2003). Transplacental amino acid transfer may account for 20–40 % of fetal energy requirements, and amino acid transfer exceeds the strict needs for protein synthesis (Battaglia and Regnault 2001). When maternal plasma and cord blood (fetal serum) were compared between normal and pre-eclampsia pregnancies, one could evaluate the associations between amino acid concentrations and fetal growth. Both maternal and cord blood amino acids were higher in pre-eclampsia, and the concentrations were inversely associated with indices of fetal growth, such as head circumference (Evans et al. 2003). Maternal and cord blood amino acid concentration was also even higher in SGA pre-eclampic pregnancies. Taurine values in maternal serum were not different between normal and pre-eclampsia samples, but in cord blood were

nearly twofold higher ($p < 0.01$). Mothers with pre-eclampsia had significantly elevated systolic and diastolic blood pressures, greater proteinuria and delivered earlier. These findings point to the metabolic syndrome as being important in the pathogenesis of pre-eclampsia and renal damage to the mother. Elevated plasma taurine may be a marker of these events.

Renal transplantation

Renal allografts restore renal function and the capacity to regulate taurine status. When 11 children with kidney transplants were compared to 10 age-matched control patients undergoing elective surgery, plasma taurine and leucine concentrations were lower in the transplanted children at 97 ± 14 days post-transplant. Several muscle amino acids, including taurine, were increased post-transplantation. The authors postulated that prednisone dosing might have affected plasma taurine status (Perfumo et al. 1994).

An issue in transplantation is the composition of the perfusion solutions administered to cadaveric kidneys prior to the allograft procedure. The addition of taurine to the "gold standard" perfusion solution, University of Wisconsin (UW) kidney solution, was able to prevent tissue alterations during hypoxia and reoxygenation and allowed recovery of energy metabolism in LLC-PK1 cells (Wingenfeld et al. 1995). Other properties in this in vitro system include improved calcium homeostasis and acceleration of cellular growth (Wingenfeld et al. 1996). The traditional ischemia/reperfusion model uses blood vessel clamping to induce antioxidant injury to renal vasculature, including the endothelium. When rats undergo 60 min of ischemia followed by 90 min of reperfusion, the serum creatinine rises and tissue ATP falls. Pretreatment with taurine at 40 mg/kg reduces injury, as reflected by lower serum creatinine values (Michalk et al. 2003), but ATP values still fell. In a human saphenous vein model, endothelial cell damage was reduced, with both apoptosis and necrosis being influenced, despite higher intracellular ROS and calcium and decreased endothelial nitric oxide synthase (Chen et al. 2009). Pre-and post-ischemia taurine was protective and endothelial damage was attenuated. Taurine has also been shown to reduce ischemia/reperfusion-induced increases in BUN and creatinine and to attenuate histopathologic evidence of renal injury in Wistar rats (Guz et al. 2007).

Donor preconditioning with taurine protects kidney grafts from injury after experimental transplantation. Taurine at different doses was infused and the grafts were cold stored in histidine–tryptophan–ketoglutarate solutions. After transplantation, the taurine-treated tissue showed reduced caspase-3 values compared to controls, while superoxide dismutase and heat shock protein increased. The serum levels of creatinine, aspartate aminotransferase and lactate dehydrogenase were significantly decreased in a dose-dependent manner. Preconditioning with taurine protects kidney grafts from injury, including apoptosis and necrosis (Guan et al. 2008).

The calcineurin inhibitors cyclosporine (CsA) and tacrolimus (FK506) result in renal damage even though they are highly effective anti-rejection agents that inhibit IL-2 release. ROS play an important role in mediating CsA-induced hypertension and nephrotoxicity (Hagar et al. 2006). In a rat model, CsA elevated blood pressure, reduced serum NO values leading to increased serum creatinine and proteinuria, and reduced creatinine clearance and urinary flow rate. Evidence of oxidative stress was evident by reduced GSH, glutathione peroxidase and SOD. Taurine markedly reduced elevated blood pressure and attenuated renal dysfunction and the decline in serum NO values. The changes in ROS after CsA administration were counteracted by taurine.

A metabolomic pattern has been determined after transplant in patients treated with CsA or tacrolimus (FK506). The metabolites for which the levels varied between CsA and FK506 groups, and which were also related to dosage duration, were glucose, hypoxanthine, lactate, succinate and taurine. These unique metabolites may provide a method of evaluating early patterns of renal damage with each immunosuppressive agent (Kim et al. 2010).

Using cultured distal tubular cells (MDCK), the effect of FK506 increases ROS products and promotes JNK and Bax with increased FK506-induced MDCK cell death. Taurine treatment reduced the FK506-induced ROS and activation of JNK and Bax (Jeon et al. 2010).

In effect, taurine may be a metabolic indicator of renal damage secondary to CsA and FK506 nephrotoxicity. These agents act by increasing ROS and the JNK and Bax pathways, an effect that is dampened by both pre- and post-treatment with taurine. Moreover, during the phase of cadaveric donor organ retrieval, the addition of taurine to the perfusion solution may have protective properties related to its antioxidant properties.

Using HPLC mass spectrometry, the influence of CsA and rapamycin (sirolimus) on high energy compounds (ADP, ATP) and 15-F(2t)-isoprostanes (as markers of oxidative stress) was measured in urine. Changes in urine metabolites followed the order of rapamycin < CsA < CsA/RAPA < -higher dose CsA/RAPA. The changes in urine creatinine, succinate, citrate and α-ketoglutarate were downward, but creatine, trimethylamine and taurine rose relative to controls. Immunosuppressive therapy with CsA or rapamycin induced changes in urinary metabolite patterns as an early sign of nephrotoxicity. 15-F(2t) isoprostane concentrations rose after drug dosing and also could be an early marker of nephrotoxicity (Schmitz et al. 2009).

Chronic kidney disease and dialysis

Plasma sulfur amino acids (SAA) were measured in chronic hemodialysis subjects with and without cardiovascular disease (CVD). Patients with CVD appear to have a greater prevalence of malnutrition, hypoalbuminemia and lower plasma total homocysteine concentrations. Malnutrition and hypoalbuminemia were associated with lower SAA. The ratio of cysteine to homocysteine was related to CVD in hemodialysis patients (Suliman et al. 2002b). In general, hemodialysis subjects with CKD have reduced plasma taurine values (Bergstrom et al. 1989). A trial of oral taurine for 10 weeks was undertaken in hemodialysis patients (Suliman et al. 2002a) at a dose of 100 mg/kg/day. Two of the four enrolled subjects had no side effects, but the other two reported dizziness and the trial was discontinued. Analysis of muscle at baseline showed taurine depletion in three patients and marginally low levels in the fourth patient compared to controls both plasma and acid tissue levels far exceeded what would be evident in a subject with normal renal function. The authors conclude that patients on hemodialysis should not imbibe taurine-containing energy drinks.

The taurine status of patients undergoing hemodialysis was evaluated in blood elements (Jung et al. 1991). Taurine values were elevated before dialysis and higher than in controls (90.16 vs. 54.2 μmol/L), but fell to subnormal (34.3 μmol/L) after dialysis. While erythrocyte taurine was higher than in controls pre-dialysis, platelet taurine was low and fell even further after the procedure. Granulocyte and lymphocyte concentrations were unaltered by CKD or hemodialysis. It appears that both CKD and hemodialysis alter plasma and blood cell taurine content, but the effect is very specific to the cell type.

The non-antibiotic antibacterial agent taurolidine has been used in situations where bacteremia could be anticipated. The use of uncuffed hemodialysis catheters is fraught with catheter-related bacteremia and thrombi. When taurolidine/citrate was used in a catheter-lock system and compared to gentamicin/heparin with heparin as a control, both taurolidine and gentamicin gave comparable results.

Taurolidine is a product of the chemical modification of taurine that has broad-spectrum antimicrobial properties in vitro (Shah et al. 2002) and has been used in cancer patients and to prevent recurrent bloodstream infections. To date, it has not been approved by the FDA. Taurolidine has not been successful in the treatment of fungal peritonitis, at least in a single patient with CKD, diabetes mellitus, HIV-positive status and fluconazole-resistant fungal peritonitis. The patient had severe burning pain during intraperitoneal infusion (Gallieni et al. 2011).

Taurine has been suggested as an osmotic agent for peritoneal dialysis solution in lieu of glucose, because glucose can lead to functional and morphologic damage to the peritoneal membranes. The net ultrafiltration coefficient of 3.5 % taurine in peritoneal dialysis fluid was equivalent to 3.86 % D-glucose, and was more biocompatible relative to mesothelial and fibroblast-like cell proliferation in peritoneal membrane biopsies (Nishimura et al. 2009).

Taurine status of patients with CKD or on hemo- or peritoneal dialysis is variable, but is generally depleted in malnourished patients. Because patients requiring renal replacement therapy are incapable of using the renal regulatory mechanisms to assure body pool size status, a given patient's taurine status is dependent on in vivo synthesis and dietary intake of taurine.

Clinical uses of taurine in renal disorders

Taurine as a therapeutic agent in renal disease has been underutilized, at least in trials in humans. By contrast, taurine has been used in numerous animal models, especially glomerular, tubular and nephrotoxic models of AKI. While the precise mechanism(s) of taurine action are not well understood, the roles of this SAA as an antioxidant or an osmolyte are common themes. The use of a *TauT* transgenic mouse model demonstrated that taurine was able to reduce the nephrotoxicity of cisplatin in a mouse model (Han and Chesney 2009b). The mechanism involves the augmentation of intracellular taurine content due to significantly higher amounts of taurine transporter protein in renal cell membranes (Han and Chesney 2009a).

Because taurine is found in the diet of man, it would be valuable to study large surveys, such as NHANES, to examine markers of renal injury such as serum creatinine, microalbuminuria and hypertension in relation to dietary meat and fish intake. The power of these large data sets is that epidemiologic associations can be assessed.

Conclusion

This review has examined the role of taurine relative to renal disorders. However, it is important to be mindful that another method of viewing taurine's role is in terms of the nephron segment or urinary structure in which the disorder lies (Table 1). Taurine has largely been seen as a neuromodulatory or cardioprotective agent, but its role in the kidney is considerable. Tissue taurine body pool size is regulated by the renal tubular epithelial surface, and when dietary intake is limited, upregulation of *TauT* expression occurs (Chesney et al. 2011). The inner medulla of the

Table 1 Genitourinary sites of action of taurine in renal disorders

Site	Function of taurine
Vasculature	Regulation of blood flow and stabilization of endothelial surface
Glomerulus	Scavenging reactive oxygen species
Proximal tubule	Na^+ co-transporter and regulation of taurine body pool
Renal medulla	Osmoregulation and cell volume regulation
Bladder	Assisting in neutrophil function or diminishing neutrophil respiratory burst

kidney is the location of the highest intracellular osmolarity in vertebrates. Because these steep osmolar gradients require uptake of osmolytes, the role of taurine as an osmolyte is important in many cell types, but it is in the renal medulla where the final urine osmolarity is established. This osmolytic role is also important in the cell cycle process (Chesney et al. 2011) and most likely accounts, in part, for protection of the kidney from nephrotoxins. The contribution of taurine to the scavenging of ROS is another major renoprotective feature. Thus, the interactions of taurine with kidney function are multifaceted.

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