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Review Article

TAURINE MODULATION OF RENAL EXCRETORY FUNCTION

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Taurine is an important regulator of cellular ion transport and osmotic balance, aspects that are pivotal to renal function. The kidney not only regulates body taurine status, but emerging information also suggests that body taurine status is of consequence for renal function. While reduction in endogenous taurine stores can attenuate renal excretory function, exogenous taurine supplementation is renoprotective and augments kidney function in several conditions that are associated with reduction in diuresis and natriuresis. Thus taurine treatment may be of potential benefit in conditions that are associated with impaired kidney function and the accompanying dysregulation of body fluid and electrolyte homeostasis.

Key words: taurine, kidney function

Taurine (2-aminoethanesulfonic acid) is an amino acid found in high concentration in mammalian cells. A number of physiological roles have been attributed to taurine including bile acid conjugation, neurotransmission/ neuromodulation, retinal cell stabilization, antioxidation, and regulation of ion transport and osmotic balance, with the regulation of ion transport being particularly important (Burg, 1995; Fugelli et al., 1995; Handler and Kwon, 1993; Huxtable, 1992; Pasantes-Morales and Martin, 1990; Pasantes-Morales et al., 1998; Schaffer et al., 2000; Uchida et al., 1991). The evidence in support of a role for taurine in the regulation of ion transport includes: a) the demonstration that taurine transport *per se* is directly coupled to sodium and chloride flux, a process involving the transport of taurine with a stoichiometry of 2-3 Na^+; $1Cl^-$; 1 taurine (Benyajati and Bay, 1994; Zelikovic et al., 1989) and b) during periods of osmotic stress, the cell modulates the levels of organic osmolytes, such as taurine, and inorganic osmolytes, such as sodium, in order to re-establish osmotic homeostasis (Fugelli et al., 1995; Handler and Kwon, 1993; Schaffer et al., 2000; Uchida et al., 1991). Clearly the effects of taurine on cellular ion transport and osmotic balance are of major relevance to kidney function. Thus, given the pivotal role of the kidney in regulation of body fluid and electrolyte balance, this review will focus on the role of endogenous taurine stores as well as exogenous taurine supplementation on kidney function.

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Role of endogenous taurine in regulation of kidney function

There is a heterogeneous distribution of taurine in the kidney with intracellular taurine concentration increasing along the corticomedullary axis (Amiry-Moghaddam et al., 1994). As a result, there in preferential localization of taurine to the inner medullary

regions of the kidney, where the extracellular milieu can become extremely hypertonic. The differential taurine distribution is believed to serve as an adaptive mechanism for renal tubular cells to cope with high osmotic gradient of the medullary interstitium (Nakanishi et al., 1994).

Recent studies suggest that taurine depletion is of consequence for kidney function. This information has been gleaned from studies with the drug-induced taurine-deficient rat. Reduction of tissue taurine content can be achieved by providing taurine uptake inhibitors such as β-alanine or guanidinoethylsulphonate (GES) in drinking solution (Lombardini, 1996; Mozaffari et al., 1986; Shaffer and Kocsis, 1981). While GES can be more effective in reducing tissue taurine content, it also accumulates in the tissue (Mozaffari et al., 1986). By contrast, β-alanine does not accumulate in the cell as it is readily metabolized to malonic semialdehyde and eliminated as carbon dioxide (Shaffer and Kocsis, 1981). Thus in order to avoid the potential confounding influence of accumulation of the taurine depleting agent in the tissue, we have used the β-alanine-induced taurine deficient rat to examine the impact of endogenous tissue taurine store on kidney function (Mozaffari et al., 1997; Mozaffari et al., 1998). Rats given 3% β-alanine in their drinking fluid for three weeks display a significant reduction (~ 40%) in taurine content of tissues such as the kidney, the heart and the submandibular gland (Lombardini, 1996; Mozaffari et al., 1986; Shaffer and Kocsis, 1981).

Utilizing the taurine-deficient rat, our initial studies focused on the ability of the animal to dispose of a saline volume load (Mozaffari et al., 1997). We found that while the initial rates of fluid and sodium excretion in response to intravenous administration of an isotonic saline load (equivalent to 5% of the animal's body weight) were reduced in the taurine deficient rat, the overall ability of the kidney to dispose of the volume challenge, over 90 minutes, was minimally affected (Mozaffari et al., 1997).

We next explored the possibility that while taurine deficiency does not affect the ability of the animal to dispose of an isotonic saline load, it may be of consequence for excretion of hypotonic and/or hypertonic saline solution (Mozaffari et al., 1998). This contention was based on several lines of evidence. First, there is a growing body of evidence firmly establishing a major role for taurine in cellular adaptation to osmotic stress. Exposure of a variety of cells to a hypotonic solution results in cellular extrusion of taurine, a process which contributes to regulatory volume decrease. Conversely, exposure of cells to hypertonic media results in cellular uptake of taurine, an important mechanism in regulatory volume increase (Burg, 1995; Fugelli et al., 1995; Handler and Kwon, 1993; Pasantes-Morales and Martin, 1990; Pasantes-Morales et al., 1998; Schaffer et al., 2000; Uchida et al., 1991). Second, renal tubular cells normally experience large changes in tonicity. The intracellular accumulation of organic osmolytes, i.e., taurine, by renal tubular cells serves as an adaptive mechanism to cope with an increase in interstitial osmolality; the high interstitial osmolality is established by the counter current multiplier system and is essential for the kidney to concentrate urine. Therefore, we expected taurine to contribute to the counter current mechanism of urinary concentration, a deficiency of which would affect renal excretory function. Third, taurine is invariably linked to regulatory volume changes because of its role as an osmolyte (Fugelli et al., 1995; Handler and Kwon, 1993; Pasantes-Morales and Martin, 1990; Pasantes-Morales et al., 1998; Schaffer et al., 2000; Uchida et al., 1991). Since major changes in taurine flux occur in response to altered osmotic conditions, we also expected taurine movement to influence fluid and sodium excretion by the kidney. Against this background, we determined whether a reduction in endogenous taurine stores would differentially affect renal excretory responses to an intravenous infusion of a hypertonic vs. a hypotonic saline solution (Mozaffari et al., 1998).

The results indicated that while taurine deficiency was associated with a reduction in the ability of the animal to dispose of a hypotonic saline load, the excretion of a hypertonic saline challenge was not affected despite the requirement to eliminate more sodium (Mozaffari et al., 1998). Taken together, the data suggested that it is unlikely that taurine deficiency adversely affects the ability of the kidney to concentrate urine. This may relate to the fact that β-alanine treatment reduces renal taurine content by ~ 40% and that greater reductions may be required to impair the urinary concentrating ability. In subsequent studies, we explored the basis for the differential responses of the taurine deficient rat to hypotonic saline solution by examining potential involvement of arginine vasopressin (AVP) system (Mozaffari and Schaffer, 2001).

Based on our observation of differential renal excretory responses of the taurine deficient rat to hypotonic and hypertonic saline solutions and those of other investigators regarding taurine-modulation of AVP secretion (Deleuze et al., 1998; Hussy et al., 1997; Miyata et al., 1997), we conjectured that the inhibitory influence of taurine in regulation of AVP secretion would be attenuated in rats deficient of taurine, resulting in an overactive AVP system. Therefore, we tested the hypothesis that taurine-depleted rats manifest increased plasma AVP concentration thereby causing augmented AVP-mediated renal responses, and determined whether these effects are reversed by taurine repletion. As a corollary, we also tested whether taurine supplementation attenuates AVP-mediated renal responses. Accordingly, renal effects of a peptide antagonist for the renal V_2 receptors were determined in the conscious control, taurine-depleted, taurine-repleted and taurine-supplemented rats along with determination of plasma AVP concentration (Mozaffari and Schaffer, 2001).

We found that control and taurine-supplemented rats displayed similar and significant AVP receptor antagonist-induced elevations in fluid excretion, sodium excretion and free water clearance but a marked reduction in urine osmolality; analysis of the data suggested that the effect of the antagonist on renal excretory function is related, primarily, to altered tubular reabsorption activity. These effects were consistent with inhibition of endogenous AVP activity. By contrast, in the taurine-depleted rats, the magnitude and the time course of drug-induced renal excretory responses lagged behind those of the control and taurine-supplemented groups. Further, baseline urine osmolality was significantly higher in the taurine-depleted compared to the control or taurine-supplemented groups. However, following administration of the antagonist, taurine-depleted rats manifested a delayed but more marked reduction in urine osmolality thereby eliminating the baseline differential that existed between the taurine-depleted rats and control or taurine-supplemented groups. Consistent with these observations, plasma AVP was significantly increased in the taurine-depleted compared to the control rats. Interestingly, taurine-repletion shifted all responses closer to the control group. These observations suggested that taurine modulates renal function, and thereby body fluid homeostasis, through an AVP-dependent mechanism. Although the impact of taurine on cellular adaptation to osmotic stress has been the focus of numerous investigations, our study was the first to also implicate a prominent role for endogenous taurine in regulation of body fluid homeostasis.

Effects of exogenous taurine supplementation on kidney function

While the impact of endogenous taurine stores on kidney function has received little attention, the impact of exogenous taurine supplementation on renal, and cardiovascular, function has been the focus of numerous reports (Chiba et al., 2002; Cruz et al., 2000; Dawson, Jr. et al., 2000; Dlouha and McBroom, 1986; Erdem et al., 2000; Gentile et al., 1994; Ideishi et al., 1994; Kohashi et al., 1989; Militante and Lombardini, 2002; Mozaffari et al., 2003; Schaffer et al., 2003; Trachtman et al., 1993;

Trachtman et al., 1995). These studies have addressed the effect of taurine therapy on blood pressure as well as in retarding/preventing renal abnormalities in disease states and aging. An antihypertensive effect of exogenous taurine therapy has been reported in most, but not all (Dawson, Jr. et al., 2000; Mozaffari et al., 2003), animal models of systemic hypertension as were recently reviewed by Milatante and Lombardini (Militante and Lombardini, 2002). Thus the following discussion will primarily focus on the effect of taurine on kidney function.

Taurine reportedly possesses antioxidant and membrane-stabilizing properties (Schaffer et al., 2003). Several studies have proposed that taurine is renoprotective by virtue of its antioxidative activity. In one such study, Trachtman and colleagues reported that rats supplemented with taurine became resistant to kidney damage and proteinuria caused by either aminonucleoside-induced glomerulopathy or streptozotocin-induced type 1 diabetes (Trachtman et al., 1993). In a related study, chronic taurine treatment prevented aging-related upregulation of TGF-β1, collagen types I and IV and fibronectin mRNAs, proteins involved in the development of renal fibrosis in aging rat (Cruz et al., 2000). The renoprotective effect of exogenous taurine therapy has also been confirmed utilizing several animal models of hypertension including the Dahl salt-sensitive rat (Chiba et al., 2002; Militante and Lombardini, 2002). While the antihypertensive effect of taurine supplementation has been attributed, in part, to suppression of the sympathetic nervous system activity and augmented natriuresis (Inoue et al., 1988), few studies have provided direct evidence for the impact of exogenous taurine on excretory function.

We initially examined the effect of acute taurine treatment on the ability of the conscious rat to dispose of an isotonic saline load (Mozaffari et al., 1997). We found that inclusion of taurine in the infusate increased the diuretic and natriuretic responses to a saline load and these effects were more prominent in animals maintained on a basal, compared to a high NaCl diet. These observations corroborated the findings of Gentile and colleagues (1994) who had reported that taurine causes significant improvement in renal excretory responses in cirrhotic patients with ascites.

Based on the reported renoprotective effect of chronic taurine treatment as well the effect of acute taurine supplementation on renal excretory responses to a saline challenge, we sought to determine whether long-term taurine therapy would benefit renal excretory capacity of a compromised kidney. We had previously shown that surgical removal of one kidney early in life, results in progressive decline in the ability of the remaining kidney to dispose of a saline volume challenge as the animal aged (Mozaffari and Wyss, 1999; Mozaffari and Schaffer, 2002a-b); this effect was evident earlier in animals that were injected with streptozotocin as a neonate at 2 days of age (Mozaffari and Schaffer, 2002a). It is noteworthy that injection of streptozotocin into an adult rat results in destruction of pancreatic β cells and a syndrome similar to type 1 diabetes (Schaffer and Mozaffari, 1999). By contrast, neonatal streptozotocin-treated rats develop a state of impaired glucose tolerance as they reach adulthood, in part, due to the ability of neonate rat to partially regenerate β cell mass (Schaffer and Mozaffari, 1999). Since impaired glucose tolerance is the "lead in" phase to overt type 2 diabetes (Mozaffari and Schaffer, 2002a), the neonatal stretptozotocin-treated rat is a logical animal model to explore the impact of glucose intolerance on target organs.

We found that chronic taurine treatment ameliorated the reduction in saline-induced diuresis and natriuresis by both the unilaterally nephrectomized (UNX) control and the UNX glucose intolerant rat (Mozaffari and Schaffer, 2002a). Both an increase in glomerular filtration and a reduction in tubular reabsorption of fluid and sodium caused this taurine-mediated improvement in renal excretory function. Interestingly, taurine supplementation also caused reduction in proteinuria in both the UNX

control and UNX glucose intolerant rats further indicating renoprotection (Mozaffari and Schaffer, 2002a).

A noted feature of the UNX control and UNX glucose intolerant rat is that blood pressure remains within the normal range as the animal ages; taurine treatment did not affect blood pressure in these rats (Mozaffari and Schaffer, 2002a). Given earlier reports of its antihypertensive effect as well as the beneficial effect of long-term taurine treatment in retarding the age-related reduction in renal excretory function of the UNX rat (Militante and Lombardini, 2002; Mozaffari and Schaffer, 2002a), we next examined the potential benefits of taurine supplementation on renal excretory function and blood pressure of the hypertensive and hypertensive-glucose intolerant rats (Mozaffari et al., 2003). The hypertensive animal models were produced in our laboratory by feeding the UNX control and UNX glucose-intolerant rats a diet which contains a high (8%) NaCl content (hypertensive and hypertensive-glucose intolerant rat, respectively) (Mozaffari et al., 2000; Mozaffari and Schaffer, 2002a-b; Mozaffari et al., 2003). The vehicle-treated hypertensive-glucose intolerant rats displayed reduced saline volume-induced diuresis and natriuresis relative to their hypertensive counterparts. While taurine treatment did not affect blood pressure in either group, it did increase renal excretory responses to saline volume loading in the hypertensive glucose intolerant, but not the hypertensive control, group (Mozaffari et al., 2003). As a result, the differential which existed between the vehicle-treated hypertensive and hypertensive-glucose intolerant groups was eliminated by chronic taurine treatment. The effect of taurine on renal excretory function of the hypertensive glucose-intolerant rats primarily related to reduced tubular reabsorption activity (Mozaffari et al., 2003). The lack of an effect of taurine on blood pressure despite augmentation of renal excretory function is suggestive of a beneficial resetting of the pressure-diuresis-natriuresis mechanism in the hypertensive glucose-intolerant rat. In addition, taurine treatment reduced protein excretion further confirming its renoprotective effect.

Perspective

Our studies to date indicate that endogenous taurine stores are of consequence for regulation of renal excretory function. Nonetheless, the contribution of regulatory mechanisms, other than AVP, to the effect of taurine deficiency on kidney function has not been explored. Of potential relevance are angiotensin II and the atrial natriuretic peptide which are considered as physiological antagonists with respect to regulation of renal and cardiovascular functions. There is growing evidence that taurine opposes some of the actions of taurine (Schaffer et al., 2000). In addition, atrial extracts of taurine-treated cardiomyopathic hamsters increase renal fluid and sodium excretion (Dlouha and McBroom, 1986). Thus the depressant effect of taurine depletion on renal excretory function may relate to modulation of mechanisms involved in regulation of glomerular function and tubular reabsorption activity. This contention is supported by our observation that exogenous taurine supplementation ameliorates the deficiency in diuresis and natriuresis by enhancing glomerular function and/or reducing tubular reabsorption activity. Thus investigation of the mechanisms by which taurine affects kidney function is of relevance to several disorders that are associated with dysregulation of body fluid and electrolyte balance (i.e., systemic hypertension, heart failure and diabetes mellitus).

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