Chronic taurine treatment ameliorates reduction in saline-induced diuresis and natriuresis

MAHMOOD S. MOZAFFARI and STEPHEN W. SCHAEFFER

Department of Oral Biology and Maxillofacial Pathology, Medical College of Georgia School of Dentistry, Augusta, Georgia, and Department of Pharmacology, College of Medicine, University of South Alabama, Mobile, Alabama, USA

Chronic taurine treatment ameliorates reduction in saline-induced diuresis and natriuresis.

Background. Taurine is an osmolyte found in high concentration in the kidney. Both the modulation of tissue taurine stores and the exogenous administration of taurine are known to affect renal function. Therefore, it is likely that taurine therapy could benefit the dysfunctional kidney.

Methods. To test this idea, the present study examined the effect of chronic taurine administration on the excretory responses to acute saline volume loading by the unilaterally nephrectomized (UNX) control and the UNX glucose-intolerant rat (ages 3 to 9 months).

Results. Sham-operated animals excreted similar amounts of the administered fluid and sodium loads with age. However, unilateral nephrectomy was associated with a significant reduction in the response to saline volume loading. This defect was prominent at a younger age (that is, 3 months) in the UNX glucose intolerant than the UNX control (6 months old) rat. Chronic taurine treatment ameliorated the reduction in saline-induced diuresis and natriuresis by both the UNX control and the UNX glucose intolerant rat. 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.

Conclusion. Taurine treatment protects the kidney of the UNX rat against an age-dependent decline in excretory efficiency.

Taurine (2-aminoethanesulfonic acid) is an amino acid found in high concentration in mammalian cells. Among its putative physiological roles in the kidney is the regulation of ion transport and osmotic balance, with the regulation of ion transport being particularly important [1–5]. Several mechanisms are involved in the regulation of ion transport by taurine. First, taurine transport per se is directly coupled to sodium and chloride flux [5–8]. Second, 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 [5]. Third, cellular taurine depletion alters body fluid and electrolyte homeostasis, a mechanism involving, among other factors, the regulation of renal excretory function by arginine vasopressin [9, 10].

There is a growing body of evidence indicating that taurine supplementation augments renal excretory function [11–13]. Although the mechanism underlying taurine-induced natriuresis and diuresis remains elusive, one likely taurine-linked factor is the renal kinin-kallikrein system [13, 14]. Another plausible explanation for the regulation of renal function by taurine relies on the transport of taurine via the renal taurine cotransporter, a process involving the transport of taurine with a stoichiometry of 2 to 3 Na⁺:1 Cl⁻:1 taurine [6–8]. To ensure body taurine homeostasis, the taurine cotransporter is very tightly regulated. During periods of dietary taurine excess, the activity of the renal taurine cotransporter is down-regulated [6, 15], causing the appearance of large amounts of taurine in the urine [10]. Since less taurine is taken up when cotransporter activity is reduced, it follows that less sodium is also transported into the cell. Thus, it is plausible that taurine supplementation could lead to taurinuria with attendant sodium and fluid excretion.

Based on the direct and indirect effects of taurine on renal excretory function, our study tested the hypothesis that chronic taurine supplementation preserves renal function under conditions of reduced diuresis and natriuresis. Recently, we found that the removal of one kidney early in life (that is, 4 weeks of age) led to a reduction in saline volume-induced diuresis and natriuresis of the control and glucose intolerant rats as the animals aged [16, 17]. This deficit was particularly apparent following acute plasma volume expansion (such as, infusion of a saline volume load), a maneuver that requires an immediate increase in renal excretory function in order to restore plasma volume [18]. Therefore, we determined the effect of chronic taurine treatment on saline-induced
diuresis and natriuresis by the uninephrectomized control and glucose-intolerant rats (ages 3 to 9 months).

METHODS

Wistar-Kyoto (WKY) rats, obtained from Harlan Laboratories (Indianapolis, IN, USA), were bred at the Medical College of Georgia animal facility. To produce the model of glucose intolerance, two-day-old male rats were injected intraperitoneally with 90 mg/kg of streptozotocin [17, 19–21]; control littermates received an injection of citrate buffer (0.1 mol/L, pH 4.5). It is noteworthy that injection of streptozotocin into an adult rat produces an insulinopenic condition that resembles type 1 diabetes [22, 18], while injection of streptozotocin into the neonate rat results in impaired insulin secretion and action [19, 20]. During the early stages of the disease, basal plasma glucose and insulin are similar between the control and the neonatal streptozotocin-treated rats [20, 21]. However, in accordance with the development of insulin resistance and impaired glucose tolerance, the neonatal streptozotocin-treated rats display a significantly greater elevation in plasma glucose and insulin levels after a glucose challenge than the control rats [20, 21]. With increasing age, an elevation in fasting plasma glucose level develops (Results section), heralding the onset of type 2 diabetes [23]. The neonatal streptozotocin-treated rat is neither obese nor hypertensive, thereby providing a unique opportunity to examine the effect of glucose intolerance/type 2 diabetes per se on organ function. The animals were weaned at 21 days of age and were maintained at constant humidity (60 ± 5%), temperature (24 ± 1°C) and light cycle (0600 to 1800 hours). Unless otherwise specified, the animals had free access to food and drinking fluid.

At four weeks of age, the streptozotocin-injected and the control rats underwent either sham operation or unilateral nephrectomy (UNX) with the procedure performed under ether anesthesia [16, 17, 22]. Following a period of two weeks for compensatory renal hypertrophy to occur, impaired glucose tolerance was confirmed by the administration of a glucose tolerance test. The test was repeated at about 3, 6 and 9 months of age, each time just prior to initiating the renal function studies. In the glucose tolerance test, time 0 (that is, fasting) blood samples were obtained after an overnight fast. The animals were then subjected to a glucose challenge (2 g/kg IP) and blood samples were taken at two-hours post-injection for glucose analyses [17, 21]. Following confirmation of glucose intolerance in the streptozotocin-injected rats, the UNX rats were further subdivided and were either maintained on tap water (UNX-vehicle) or were given water containing 1% taurine (UNX-taurine); the sham-operated rats were maintained on tap water (sham-vehicle). Therefore, the protocol yielded three groups of rats for each condition at each age. At about 3, 6 and 9 months of age, each rat was placed individually in metabolic cages and 24-hour urine samples collected for determination of daily protein excretion [22].

To prepare for the renal function studies in the conscious animal, each rat was instrumented with femoral vessels cannuli and a stainless steel bladder catheter, with all procedures performed under ether anesthesia [9, 10, 12, 16, 17]. Two days after surgery, each rat was placed in an environmental conditioning unit (Braintree, Braintree, MA, USA); all rats were conditioned to the units for three hours per day for seven days prior to administering the test. After the arterial and venous catheters were flushed with 0.2 mL of isotonic saline containing 5 U/mL of heparin, the recording of hemodynamic parameters was initiated (Blood Pressure Analyzer; MicroMed, Louisville, KY, USA).

To determine the glomerular filtration rate (GFR), each rat received an intravenous injection of 0.2 mL of isotonic saline containing a priming dose of 2 µCi of 3H-inulin (Dupont Co., Boston, MA, USA), followed immediately by a 20 µL/min intravenous infusion of isotonic saline containing 2.5 µCi/mL of 3H-inulin [10, 16, 17]. After a 45-minute equilibration period, which is sufficient to achieve a steady state radioactive level in the plasma, a 30-minute urine sample was collected for determination of baseline excretory parameters. A 30-minute volume expansion (equivalent to 5% of the animal’s body wt) was then initiated with isotonic saline containing 3H-inulin [16, 17]. This was followed by infusion of isotonic saline containing 3H-inulin at the rate of 20 µL/min for the remainder of the experiment. Urine samples were collected at 15, 30, 60, and 90 minutes after initiation of the saline volume load. At the midpoint of each urinary collection period, 0.2 mL of arterial blood sample was collected for determination of plasma radioactivity and electrolyte composition; the blood sample was replaced with an equal volume of isotonic saline. At the conclusion of renal function studies the animals were sacrificed with pentobarbital (50 mg/kg; IV); kidney weight was determined for each animal.

Sodium (Na+) and K+ were measured by flame photometry and used to calculate the sodium and potassium excretion rates. GFR and fractional excretion of fluid (FEH2O) and sodium (FENA+) were calculated by using standard clearance formulas [10, 16]. Plasma taurine concentration and the rate of daily taurine excretion were determined as described previously [10].

Statistics

All data were statistically analyzed by the analysis of variance (ANOVA; significance criteria of $P < 0.05$) with Duncan’s test used for comparison of the mean values. All data are reported as means ± SEM.
RESULTS

Fasting blood glucose concentration was similar in the 3- and 6-month-old glucose intolerant animals. However, the 9-month-old glucose intolerant groups manifested a higher fasting blood glucose concentration compared to their 3-month-old counterparts or their age-matched control counterparts ($P < 0.05$; Table 1). As expected, the intraperitoneal administration of a glucose load significantly increased blood glucose concentration in all groups. However, two hours after administration of the glucose load, the blood glucose concentration of the three glucose intolerant groups remained significantly higher than the levels found in the control groups ($P < 0.05$; Table 1). An elevation in fasting blood glucose level in association with impaired glucose tolerance is suggestive of type 2 diabetes [23]. While fasting blood glucose level was greater in the older streptozotocin-injected rats, impaired glucose tolerance was a feature of all streptozotocin-treated rats. Therefore, all streptozotocin-injected rats are referred to as glucose intolerant rats throughout this article.

The uninephrectomized control rats generally displayed similar body weights compared to their age matched sham counterparts. However, taurine treatment slightly reduced the body weight of the 6- and 9-month-old UNX control rats, although not that of the glucose intolerant rats (Table 1). As expected, total kidney weight (KW) and kidney size (KW normalized relative to body weight) were lower in the UNX rats than in the sham-operated groups ($P < 0.05$; Table 1). The remaining kidney of the 9-month-old UNX rat displayed a 54% increase in size relative to one of the two kidneys of the 9-month-old sham-operated rat. Uninephrectomy also led to renal hypertrophy of the remaining kidney in the 3-month-old and 6-month-old UNX animals, although the increase in kidney size was somewhat less than the older UNX rat (38% and 27% in 3- and 6-month-old animals, respectively). The corresponding values for the 3-month, 6-month and 9-month-old glucose intolerant rats were 64%, 47%, and 59%, respectively. Comparison of the glucose intolerant and control rats revealed that the younger glucose intolerant rats displayed a greater increase in kidney size in response to uninephrectomy than their control counterparts. Taurine treatment increased the kidney size of the 3- and 6-month-old UNX control rats and the 3-month-old UNX glucose intolerant rats compared to their vehicle-treated counterparts (Table 1).

Unilateral nephrectomy and taurine treatment had no significant effect on mean arterial pressure (range 122 to 133 mm Hg, data not shown). However, taurine treatment was associated with a reduction of 40 to 50 beats/min in heart rate in both the 3- and 6-month-old UNX control and the UNX glucose intolerant rats ($P < 0.05$; heart rate data not shown). Consistent with previous reports [16–18], the administration of an isotonic saline load did not significantly affect either the mean arterial pressure or the heart rate of any group (data not shown).

---

**Table 1. Several features of the experimental groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>Age months</th>
<th>N</th>
<th>Body wt</th>
<th>Kidney wt</th>
<th>KW/BW mg/g</th>
<th>Blood glucose mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham</td>
<td>3</td>
<td>9</td>
<td>277 ± 11</td>
<td>2.2 ± 0.0</td>
<td>7.8 ± 0.2</td>
<td>84 ± 2</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>5</td>
<td>371 ± 16</td>
<td>2.8 ± 0.0</td>
<td>7.7 ± 0.3</td>
<td>82 ± 3</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>6</td>
<td>435 ± 6</td>
<td>3.1 ± 0.1</td>
<td>7.0 ± 0.1</td>
<td>93 ± 4</td>
</tr>
<tr>
<td>UNX</td>
<td>3</td>
<td>7</td>
<td>294 ± 7</td>
<td>1.6 ± 0.0</td>
<td>5.4 ± 0.1</td>
<td>83 ± 2</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>5</td>
<td>401 ± 12</td>
<td>1.9 ± 0.1</td>
<td>4.9 ± 0.1</td>
<td>96 ± 2</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>8</td>
<td>469 ± 5</td>
<td>2.5 ± 0.0</td>
<td>5.4 ± 0.1</td>
<td>86 ± 2</td>
</tr>
<tr>
<td>UNX/taurine</td>
<td>3</td>
<td>7</td>
<td>285 ± 11</td>
<td>1.8 ± 0.1</td>
<td>6.3 ± 0.4</td>
<td>87 ± 3</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>8</td>
<td>354 ± 6*</td>
<td>2.3 ± 0.1</td>
<td>6.5 ± 0.3*</td>
<td>93 ± 3</td>
</tr>
<tr>
<td>Glucose intolerant</td>
<td>9</td>
<td>8</td>
<td>426 ± 10d</td>
<td>2.0 ± 0.1</td>
<td>4.8 ± 0.1</td>
<td>88 ± 3</td>
</tr>
<tr>
<td>Sham</td>
<td>3</td>
<td>6</td>
<td>255 ± 16</td>
<td>1.8 ± 0.1</td>
<td>7.2 ± 0.3</td>
<td>81 ± 2</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>5</td>
<td>359 ± 17</td>
<td>2.6 ± 0.2</td>
<td>7.2 ± 0.3</td>
<td>92 ± 4</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>6</td>
<td>406 ± 4*</td>
<td>2.8 ± 0.1</td>
<td>6.9 ± 0.3</td>
<td>121 ± 6*</td>
</tr>
<tr>
<td>UNX</td>
<td>3</td>
<td>7</td>
<td>264 ± 11</td>
<td>1.6 ± 0.1</td>
<td>5.9 ± 0.1</td>
<td>85 ± 2</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>8</td>
<td>349 ± 8</td>
<td>1.9 ± 0.0</td>
<td>5.3 ± 0.1</td>
<td>98 ± 4</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>6</td>
<td>393 ± 12*</td>
<td>2.2 ± 0.1</td>
<td>5.5 ± 0.3</td>
<td>107 ± 5*</td>
</tr>
<tr>
<td>UNX/taurine</td>
<td>3</td>
<td>7</td>
<td>230 ± 11</td>
<td>1.5 ± 0.1</td>
<td>6.8 ± 0.3*</td>
<td>73 ± 3</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>8</td>
<td>357 ± 9</td>
<td>2.0 ± 0.0</td>
<td>5.6 ± 0.1</td>
<td>101 ± 5</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>6</td>
<td>400 ± 10</td>
<td>2.0 ± 0.1</td>
<td>5.1 ± 0.2</td>
<td>119 ± 4*</td>
</tr>
</tbody>
</table>

*P < 0.05 compared to their control counterparts

aP < 0.05 compared to their vehicle-treated counterparts

bP < 0.05 compared to their 3-month-old counterparts
dP < 0.05 compared to age-matched UNX control groups
It has been well documented that unilateral nephrectomy is associated with a compensatory increase in fluid and sodium excretion by the remaining kidney [24–26]. This was reflected in the higher baseline rates of fluid and sodium excretion, normalized relative to KW, of the UNX control rats compared to their age-matched sham-operated counterparts \((P < 0.05; \text{data not shown})\). However, a similar phenomenon does not occur in the glucose intolerant rats, as the baseline rates of fluid and sodium excretion were similar in the UNX and sham-operated groups. While taurine treatment reduced the baseline rate of fluid, but not sodium, excretion in the 3- and 6-month-old UNX control groups, it had no apparent effect on the excretion profile of the UNX glucose intolerant animals (data not shown).

Figure 1 A, B (control) and Figure 2 A, B (glucose intolerant) illustrate the percent of an administered fluid and sodium load that were excreted 90 minutes after the initiation of the saline infusion while Figure 1 C, D (control) and Figure 2 C, D (glucose intolerant) show the same data after normalization relative to kidney weight. As expected, the administration of a saline volume load significantly increased fluid and sodium excretion in all of the groups. Aging alone had no effect on the absolute percentages of fluid and sodium that were excreted by the sham-operated control rats (Fig. 1 A, B). However, the 9-month-old control animal showed a reduction in renal excretory efficiency relative to the 6-month-old sham operated animal, as evidenced by the decline in natriuresis \((P < 0.05)\) and diuresis in the kidney weight normalized data (Fig. 1 C, D). Uninephrectomy appeared to accelerate the loss of excretory effi-
Fig. 2. Effects of chronic taurine treatment on saline-stimulated diuresis and natriuresis by unilaterally nephrectomized (UNX) glucose intolerant rats. (A and B) Diuretic and natriuretic responses to a saline load, expressed as the percent of the administered fluid and sodium loads that are excreted within 90 minutes of the saline load. (C and D) Excretion data normalized relative to kidney weight. Symbols are: (■) sham operated; (□) UNX; (▲) UNX/taurine; *P < 0.05 compared to their age-matched sham or UNX-taurine counterparts; **P < 0.05 compared to 9-month-old UNX group; #P < 0.05 compared to the 3-month-old sham group.

Fig. 2. Effects of chronic taurine treatment on saline-stimulated diuresis and natriuresis by unilaterally nephrectomized (UNX) glucose intolerant rats. (A and B) Diuretic and natriuretic responses to a saline load, expressed as the percent of the administered fluid and sodium loads that are excreted within 90 minutes of the saline load. (C and D) Excretion data normalized relative to kidney weight. Symbols are: (■) sham operated; (□) UNX; (▲) UNX/taurine; *P < 0.05 compared to their age-matched sham or UNX-taurine counterparts; **P < 0.05 compared to 9-month-old UNX group; #P < 0.05 compared to the 3-month-old sham group.

Fig. 2. Effects of chronic taurine treatment on saline-stimulated diuresis and natriuresis by unilaterally nephrectomized (UNX) glucose intolerant rats. (A and B) Diuretic and natriuretic responses to a saline load, expressed as the percent of the administered fluid and sodium loads that are excreted within 90 minutes of the saline load. (C and D) Excretion data normalized relative to kidney weight. Symbols are: (■) sham operated; (□) UNX; (▲) UNX/taurine; *P < 0.05 compared to their age-matched sham or UNX-taurine counterparts; **P < 0.05 compared to 9-month-old UNX group; #P < 0.05 compared to the 3-month-old sham group.

Fig. 2. Effects of chronic taurine treatment on saline-stimulated diuresis and natriuresis by unilaterally nephrectomized (UNX) glucose intolerant rats. (A and B) Diuretic and natriuretic responses to a saline load, expressed as the percent of the administered fluid and sodium loads that are excreted within 90 minutes of the saline load. (C and D) Excretion data normalized relative to kidney weight. Symbols are: (■) sham operated; (□) UNX; (▲) UNX/taurine; *P < 0.05 compared to their age-matched sham or UNX-taurine counterparts; **P < 0.05 compared to 9-month-old UNX group; #P < 0.05 compared to the 3-month-old sham group.

Fig. 2. Effects of chronic taurine treatment on saline-stimulated diuresis and natriuresis by unilaterally nephrectomized (UNX) glucose intolerant rats. (A and B) Diuretic and natriuretic responses to a saline load, expressed as the percent of the administered fluid and sodium loads that are excreted within 90 minutes of the saline load. (C and D) Excretion data normalized relative to kidney weight. Symbols are: (■) sham operated; (□) UNX; (▲) UNX/taurine; *P < 0.05 compared to their age-matched sham or UNX-taurine counterparts; **P < 0.05 compared to 9-month-old UNX group; #P < 0.05 compared to the 3-month-old sham group.

Fig. 2. Effects of chronic taurine treatment on saline-stimulated diuresis and natriuresis by unilaterally nephrectomized (UNX) glucose intolerant rats. (A and B) Diuretic and natriuretic responses to a saline load, expressed as the percent of the administered fluid and sodium loads that are excreted within 90 minutes of the saline load. (C and D) Excretion data normalized relative to kidney weight. Symbols are: (■) sham operated; (□) UNX; (▲) UNX/taurine; *P < 0.05 compared to their age-matched sham or UNX-taurine counterparts; **P < 0.05 compared to 9-month-old UNX group; #P < 0.05 compared to the 3-month-old sham group.

Fig. 2. Effects of chronic taurine treatment on saline-stimulated diuresis and natriuresis by unilaterally nephrectomized (UNX) glucose intolerant rats. (A and B) Diuretic and natriuretic responses to a saline load, expressed as the percent of the administered fluid and sodium loads that are excreted within 90 minutes of the saline load. (C and D) Excretion data normalized relative to kidney weight. Symbols are: (■) sham operated; (□) UNX; (▲) UNX/taurine; *P < 0.05 compared to their age-matched sham or UNX-taurine counterparts; **P < 0.05 compared to 9-month-old UNX group; #P < 0.05 compared to the 3-month-old sham group.

Fig. 2. Effects of chronic taurine treatment on saline-stimulated diuresis and natriuresis by unilaterally nephrectomized (UNX) glucose intolerant rats. (A and B) Diuretic and natriuretic responses to a saline load, expressed as the percent of the administered fluid and sodium loads that are excreted within 90 minutes of the saline load. (C and D) Excretion data normalized relative to kidney weight. Symbols are: (■) sham operated; (□) UNX; (▲) UNX/taurine; *P < 0.05 compared to their age-matched sham or UNX-taurine counterparts; **P < 0.05 compared to 9-month-old UNX group; #P < 0.05 compared to the 3-month-old sham group.

Fig. 2. Effects of chronic taurine treatment on saline-stimulated diuresis and natriuresis by unilaterally nephrectomized (UNX) glucose intolerant rats. (A and B) Diuretic and natriuretic responses to a saline load, expressed as the percent of the administered fluid and sodium loads that are excreted within 90 minutes of the saline load. (C and D) Excretion data normalized relative to kidney weight. Symbols are: (■) sham operated; (□) UNX; (▲) UNX/taurine; *P < 0.05 compared to their age-matched sham or UNX-taurine counterparts; **P < 0.05 compared to 9-month-old UNX group; #P < 0.05 compared to the 3-month-old sham group.
Taurine treatment significantly improved saline-stimulated diuresis and natriuresis of the UNX glucose intolerant rat, with the effect being more prominent in the 3-and 6-month-old groups (Fig. 2).

A decline in excretory function is generally caused by either a decrease in the glomerular filtration rate (GFR) or in the fractional excretion of the filtered sodium and fluid loads. Therefore, to examine the basis underlying the loss of excretory function of the UNX animals, the GFR and fractional excretion of fluid and sodium were measured before and following a saline-volume load. As expected, saline loading was accompanied by an elevation in the GFR in all of the animal groups (Fig. 3; 6-month-old rats). However, the rise in GFR following the saline load was greater for both the UNX control and UNX glucose intolerant rats that were treated with taurine compared to their vehicle-treated counterparts. Indeed, the GFR of the taurine-treated UNX animals was even greater than that of the sham-operated groups (Fig. 3 A, D). Among the UNX control rats, the major defect appeared to be a reduction in the fractional excretion of fluid and sodium (Fig. 3, B, C). Significantly, taurine treatment restored the fractional excretion of both fluid and sodium in these animals to nearly the levels seen in the sham-operated group (Fig. 3, B, C). Although the effect was less dramatic, taurine treatment also increased the fractional excretion of fluid and sodium in the UNX glucose intolerant group (Fig. 3 E, F). Moreover, while reduced tubular reabsorption is the primary contributor to the enhanced saline-induced diuresis and natriuresis in the taurine-treated, 3-month-old UNX glucose intolerant rat, the effect of taurine treatment on renal fluid and sodium excretion of the 9-month-old UNX control and glucose-intolerant rat is related to both augmented saline-induced rise in GFR and a reduction in tubular reabsorption (data not shown).

Consistent with other reports [24, 26, 27], unilateral nephrectomy was associated with a significant elevation in the baseline rate of potassium excretion in all of the control rats (~99%, 70% and 49% in 3-, 6- and 9-month-old rats; respectively), as well as the 3-month-old glucose-intolerant rats (~63%). Taurine treatment generally reduced the baseline rate of potassium excretion, leading to normalization in the excretion rate. In the 3-month-old UNX control group, total potassium excretion, defined as the excretion that occurred within 90 minutes of administration of the saline volume load, was significantly greater than their age-matched sham-operated counterparts; taurine treatment normalized potassium excretion in the control UNX rat (sham, 126.1 ± 7.7; UNX, 220.3 ± 6.8; UNX/taurine, 128.6 ± 12 μEq/g KW). However, taurine treatment had no significant effect on the total amount of potassium excreted by the glucose intolerant rats.

The 9-month-old UNX control rat manifested significant proteinuria compared to their sham-operated counterparts (UNX, 69.7 ± 4.9 vs. sham, 26.6 ± 1.0 mg/day). Taurine treatment reduced daily protein excretion in the UNX rats to 50.5 ± 2.1 mg/day (P < 0.05). By comparison, the UNX glucose-intolerant rats excreted more protein than their sham-operated counterparts by 6 months of age, an effect that was reversed by taurine treatment (UNX, 72.9 ± 8.0; sham, 47.2 ± 6.6; and UNX/taurine, 44.7 ± 4.6 mg/day).

The plasma taurine concentrations were similar between 9-month-old UNX control and UNX glucose intolerant rats (0.35 ± 0.09 vs. 0.38 ± 0.07 μmol/mL), but were lower than their counterparts treated with taurine (0.78 ± 0.06 vs. 0.66 ± 0.06 μmol/mL; P < 0.05). Similarly, daily taurine excretion was significantly (P < 0.05) higher in the 9-month-old taurine-treated control and glucose-intolerant rats (617.4 ± 35.9 vs. 782.6 ± 34.4 μmol/day, respectively) than in their age-matched counterparts that consumed tap water (118.5 ± 8.0 vs. 143 ± 3.3 μmol/day).

**DISCUSSION**

The present study demonstrates that chronic oral taurine supplementation ameliorates the age-related decline in saline volume-induced diuresis and natriuresis by the UNX control and UNX glucose intolerant rat. These findings corroborate our earlier report that taurine depletion in rat reduces the initial rate of saline volume-induced diuresis and natriuresis and that acute taurine administration augments these responses in the normal rat [12]. Both a potentiation in the glomerular filtration rate and a reduction in tubular reabsorption of fluid and sodium cause this taurine-induced improvement in the response to saline volume loading. These renal effects are evident at a time when proteinuria is not a prominent feature (that is, 6 and 3 months of age in control and glucose intolerant rats, respectively), suggesting that the effect of taurine may involve modulation of renal function by neurohumoral regulators.

Consistent with our previous observation [16, 17], Figures 1 and 2 reveal that saline-induced diuresis and natriuresis by the UNX rat declines with age. Interestingly, this impairment was prominent earlier in the UNX glucose intolerant rat than in the UNX control rat (3 vs. 6 months of age, respectively). Since aging is known to reduce renal reserve capacity [28], it is likely that the observed reduction in saline-induced diuresis and natriuresis reflects an impairment in the response of the aging kidney to the volume challenge, an effect that apparently is accelerated by impaired glucose tolerance. Since the kidney’s response to saline volume loading is regulated in part by neuronal and humoral factors released during the volume challenge [18], it is possible that the release of these factors is adversely affected in the older UNX
Mozaffari and Schaffer: Chronic taurine therapy

Fig. 3. Glomerular filtration rate (GFR), fractional excretion of fluid and sodium by sham-operated (○), unilaterally nephrectomized (UNX; ●) and taurine treated UNX (□) rats. (A–C) Six-month-old control rat data. (D–F) Six-month-old glucose intolerant rat data. *P < 0.05 compared to the UNX/taurine group at the same time point.

animals. However, this seems unlikely because the older sham-operated rat responds normally to the saline load. Rather, the data suggest that a chronic reduction in renal mass is associated with a defective responsiveness of the remaining nephrons to the released neuronal and humoral factors.

The reduced renal mass model used in the present study commonly has been utilized to examine the effect of reduced nephron mass on both remnant kidney function and the ability of therapeutic modalities to preserve remnant kidney function. Most investigations of remnant kidney function have explored renal adaptation to either subtotal nephrectomy (that is, 5/6) or unilateral nephrectomy [24–27, 29–31]. While subtotal nephrectomy is of-
ten associated with the development of systemic hypertension [29–31], uninephrectomy leads to hypertension when combined with other maneuvers (that is, deoxycorticosterone acetate-salt or high salt diet) [16, 22]. Therefore, to avoid the complication of systemic hypertension, uninephrectomy was used in the present study.

In agreement with previous studies [24–26], we found that the baseline rates of fluid and sodium excretion by the young UNX rat were elevated in the remaining kidney (data not shown). However, as the animal ages, a defect develops in the renal response to acute plasma volume expansion. A similar defect has been observed in the streptozotocin-treated type 1 diabetic rat that manifests marked impairment in acute saline volume-induced diuresis and natriuresis [18]. The impaired response to volume loading in the type 1 diabetic rat appears to be partially associated with reduced responsiveness to atrial natriuretic peptide, a regulatory factor released during volume expansion to enhance diuresis and natriuresis [18]. Based on the similarities between the aging UNX rat and the type 1 diabetic rat in renal responses to plasma volume expansion, it would be attractive to suggest that long-term uninephrectomy also leads to impaired responsiveness to atrial natriuretic peptide. Nonetheless, the response to volume loading is complex and involves several components including: (a) the afferent limb (that is, volume receptors, electromechanical coupling and afferent fibers); (b) the central sites for neuronal processing of afferent input; and (c) the efferent limb (that is, release and/or action of humoral factors and renal sympathetic nerve activity [18]). Modulation of any of these components would account for the observations with the aging UNX rat.

One of the important findings of this study is that taurine therapy ameliorates the age-related decline in saline volume-induced diuresis and natriuresis by the UNX control and UNX glucose intolerant rat. The taurine-induced improvement in renal fluid and sodium excretions in this and previous studies [11–13], is in apparent contrast to the findings of McBroom and Davidson, who reported on the impairment of sodium homeostasis following combined treatment with high NaCl and taurine [32]. In the latter study, rats that were provided dietary Na\(^+\) (0.2%), along with a 1.8% NaCl solution containing 0.1 mol/L taurine (∼1.25%) displayed significant hypernatremia in association with sodium retention. Thus, the relevance of these findings to the present investigation is not clear, since the animals in our study were only provided with a dietary source of 0.29% Na\(^+\). However, taurine reportedly exerts an antihypertensive effect in NaCl-induced hypertension, an effect that is partially attributed to taurine-induced natriuresis [14, 33, 34]. Thus, future studies are warranted to clarify the effects of taurine treatment and dietary NaCl manipulation on sodium homeostasis.

As illustrated in Figure 3, a combination of augmented glomerular function and reduced tubular reabsorption activity contribute to this beneficial effect of taurine. The reasons for the beneficial effect of taurine therapy are not known but the following aspects are noteworthy. First, taurine exerts sympatholytic effects [33–34], which should be capable of increasing sodium excretion. Therefore, chronic taurine therapy could attenuate adrenergically-mediated sodium retention, culminating in greater excretion. However, this scenario seems unlikely since reflex withdrawal of renal sympathetic nerve activity is an important contributor to saline volume-induced diuresis and natriuresis [18]. Second, taurine antagonizes several actions of angiotensin II [35]. Yet, the relevance of the taurine-angiotensin II interaction with respect to renal function remains to be established. Third, taurine promotes diuresis and natriuresis and the activation of the renal kallikrein system [11–14], and the latter could contribute to renal fluid and sodium excretion during volume expansion. Clearly, the relevance of the renal kallikrein system to the observed responses to taurine warrants further investigation. Fourth, aging is associated with an attenuation of the pressure-diuresis-natriuresis relationship [36], an effect that is likely accelerated with unilateral nephrectomy. Our data showed that one of the arms of this relationship, namely blood pressure, was not affected by age, uninephrectomy or taurine treatment. Therefore, it is likely that a blunting of the relationship contributed to the reduced renal responses of the UNX rats. Presumably, taurine treatment ameliorates this deficit. Finally, atrial natriuretic peptide release contributes to saline volume-induced diuresis and natriuresis [18]. Since atrial extracts from taurine-treated hamsters cause greater diuresis and natriuresis than those obtained from their vehicle-treated counterparts [37], it is likely that taurine promotes the release of atrial natriuretic peptide. It remains to be determined if taurine can potentiate the effects of atrial natriuretic peptide in the UNX rat also.

Aside from the putative renal effects of taurine mediated by the regulatory neural and humoral factors, taurine possesses antioxidant and membrane-stabilizing properties. Several studies have proposed that taurine is renoprotective by virtue of its antioxidantive activity [38–41]. In one such study, Trachtman, Lu and Sturman 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 [39]. In a related study, chronic taurine treatment prevented aging-related up-regulation of transforming growth factor-β1 (TGF-β1), collagen types I and IV and fibronectin mRNAs, proteins involved in the development of renal fibrosis [42]. In contrast to those studies, the UNX animals did not exhibit proteinuria until either 6 months (glucose intolerant) or 9 months (control) of age. Yet, taurine treatment
improved saline-induced diuresis and natriuresis in the 3-month-old UNX glucose-intolerant and the 6-month-old UNX control animals. Therefore, it is unlikely that the effect of taurine is related to renoprotection against renal fibrosis and overt renal damage. Nonetheless, it is noteworthy that loss in renal mass triggers adaptive changes in the renal tubules, resulting in a hypermetabolic state of the remaining nephrons and the generation of toxic free radicals in the renal parenchyma [39]. Moreover, abnormalities of glucose metabolism would be expected to augment renal oxidative injury [41]. Therefore, it is possible that some of the beneficial effects of taurine are related to its antioxidative activity. Nonetheless, it remains to be determined if the antioxidant property of taurine protects the renal tubulointerstitium against free radical-induced renal injury thereby preserving renal function of the UNX rat. Also to be determined is whether taurine exerts a differential effect in the control versus the glucose intolerant rat, thereby contributing to its more prominent effect in the former group.

It is noteworthy that uninephrectomy increased potassium excretion but taurine treatment decreased kaliuresis, with the latter effect being more prominent in the UNX control rat. The UNX-induced increase in potassium excretion is associated with adaptive up-regulation of the cellular mechanisms for renal potassium transport including the Na⁺,K⁺-ATPase and the amiloride-inhibitable potassium secretion [26, 27]. Whether chronic taurine treatment modifies these potassium regulatory mechanisms in the UNX rat remains to be determined. In this regard, it is significant that taurine-treated rats excrete less potassium following antagonism of the renal arginine vasopressin [10]. Therefore, an investigation exploring the modulation of potassium homeostasis by taurine may represent a fertile area of future investigation.

In conclusion, oral taurine supplementation ameliorates the age-related decline in renal excretory function of the UNX control and UNX glucose intolerant rat. Since taurine possesses a high degree of chemical stability, very low metabolic reactivity and no known major adverse side effect, its potential usefulness as a therapeutic modality in conditions of reduced renal excretory function warrants further investigation.

ACKNOWLEDGMENTS

This study was supported by a grant from Taiho Pharmaceutical Company of Japan. The authors thank Ms. Champa Patel for her expert technical assistance.

Reprint requests to Dr. Mahmood S. Mozaffari, Department of Oral Biology and Maxillofacial Pathology, CB 3710, Medical College of Georgia, Augusta, Georgia 30912-1128, USA.

E-mail: Mmozaffa@mail.mcg.edu

REFERENCES


