Decrease of Urinary Taurine in Essential Hypertension

Noriyuki Kohashi, M.D. and Ryo Katori, M.D.

SUMMARY

In order to evaluate how taurine relates to the pathogenesis of essential hypertension, the taurine content of plasma, whole blood and urine was measured in 18 normals and in 79 hypertensive patients. The patients included 32 untreated cases of essential hypertension, 32 treated cases and 15 cases with labile hypertension. There were no statistically significant differences between normals and essential hypertensives in either plasma or whole blood taurine content. However, in comparison to urinary taurine excretion in normals, 1594.0±143.7 µmol/day (mean±SE), that for untreated essential hypertensives, 708.1±57.1 µmol/day (p<0.001), and for treated essential hypertensives, 953.6±94.3 µmol/day (p<0.001), were significantly lower. Those with labile hypertension showed almost the same value, 1478.3±134.3 µmol/day, as normals. Taurine clearance and the taurine/creatinine ratio were also markedly decreased in essential hypertensives without treatment. For all subjects, taurine clearance had a positive correlation (r=0.327, p<0.01) with creatinine clearance, but there were significant negative correlations between systolic blood pressure and daily urinary taurine excretion (r=−0.472, p<0.01) and between diastolic blood pressure and daily urinary taurine excretion (r=−0.382, p<0.01). There were also significant positive correlations between daily urinary taurine excretion and serum high-density lipoprotein cholesterol (r=0.559, p<0.01) and between the former and cardiac index (r=0.547, p<0.01). These results suggest that a deficiency of taurine plays an important role not only in elevating blood pressure in essential hypertension but also in atherogenesis as well.

Additional Indexing Words:

Daily urinary taurine excretion Taurine clearance Creatinine clearance Cardiac index High-density lipoprotein cholesterol Pathogenesis of essential hypertension
Although, in spite of intensive studies, its biochemical functions have not yet been fully elucidated, a possible list could be summarized as follows: bile conjugator,\textsuperscript{4}) neuroinhibitor or neuromodulator,\textsuperscript{5}--\textsuperscript{7}) osmoregulator,\textsuperscript{8}) positive inotropic and antiarrhythmic agent, ion flux modifier,\textsuperscript{9,10}) membrane stabilizer,\textsuperscript{11}) and antiatherogenic agent.\textsuperscript{12})

It has been reported that a high protein diet rich in sulfur-containing protein decreased the incidence of stroke in spontaneously hypertensive rats (SHR) and in a stroke-prone SHR substrain (SHRSP), and also attenuated the increase in the incidence of stroke due to excessive salt intake.\textsuperscript{13}--\textsuperscript{17}) Nara et al\textsuperscript{18}) reported that the addition of taurine to the drinking water resulted in a significant reduction of blood pressure in SHRSP, while there was little effect on blood pressure in normotensive Wistar Kyoto rats (WKY). They found that taurine content in serum and liver were significantly lower in SHRSP. Murayama et al\textsuperscript{19}) reported that taurine significantly reduced blood pressure in essential hypertension. These studies suggest that taurine may act as an antihypertensive substance leading to a decrease in the incidence of stroke. The purpose of this study was to measure taurine content in the whole blood, plasma and urine of healthy persons and of hypertensives, and to examine the role it plays in the cause and maintenance of essential hypertension.

**Materials and Methods**

Seventy-six outpatients and 13 inpatients with hypertension (54.3±3.9 years old, mean±SE) at Kinki University Hospital as well as 18 normals (33.3±2.1 years old) were used in this study. Patients with hypertension were classified into 3 groups: Group 1 consisted of 32 patients (54.6±1.8 years old) with essential hypertension who were not receiving any antihypertensive drug treatment (WHO stage I, 10 cases; stage II, 12 cases; stage III, 10 cases), Group 2 included 32 patients with essential hypertension (54.5±2.0 years old) being treated with an antihypertensive drug; and Group 3 consisted of 15 patients (42.7±2.5 years old) with labile hypertension. Before treatment the blood pressures of Groups 1 and 2 were greater than 160/95 mmHg based on an average for 2 or more measurements in the recumbent or sitting position. All patients were screened so as to exclude those with secondary hypertension. Group 1 patients had received no antihypertensive medication prior to examination. Group 2 patients received either diuretics or beta-blocking drugs or both regularly without change throughout the study. Labile hypertension for Group 3 was defined as at least one diastolic blood pressure higher than 90 mmHg and also at least one normal reading
of the 3 outpatient visits.\textsuperscript{20)} The following conditions, which may make patients liable to hypertaurinuria, were excluded: radiation, trauma, muscle disorder, liver disease, renal aminoaciduria, proteinuria, infection, blood disease, and malignant tumor.\textsuperscript{13} Subjects over 71 years of age were also excluded because of decreased renal function.

As it has been reported that increases in taurine excretion were observed after a meat or protein-rich diet had been eaten for several days before the taurine measurement,\textsuperscript{21)-24)} we estimated the protein content in the diets of all subjects. The results showed no significant difference in protein content between the normals and the hypertensives, so we assume that diet was not a factor during this study.

Twenty-four hour urines were collected daily using a few drops of toluene as a preservative. Six ml of blood were sampled with a heparinized syringe early in the morning; 1 ml was removed for whole blood taurine measurement and the remaining 5 ml were quickly separated for purposes of plasma taurine measurement. Measurements were taken for plasma taurine, whole blood taurine, daily urinary taurine excretion, intrinsic taurine clearance, and intrinsic creatinine clearance.

Determination of taurine content was carried out using a modification of Orr's method.\textsuperscript{25)} Deproteinized samples (1 ml whole blood was added to 2 ml of 10\% trichloroacetic acid, and 1 ml plasma added to 1 ml of the same acid) were centrifuged at 10,000 g for 10 min. The supernatants were used for taurine assay. Urine samples were diluted with distilled water to an appropriate amount. These samples could be stored at $-20\degree$C until assay. An aliquot (100 $\mu$l) was removed from the samples and pipetted onto an approximate 5 mm internal diameter column packed with Dowex 50×8, 200-400 mesh in (H+) form over Dowex 1×2, 200-400 mesh in (Cl-) form to a height of 50 mm. The taurine was washed from the column with 1.5 ml of H$_2$O and collected. The taurine fraction (500 $\mu$l) was mixed with 1 ml of 0.25 M borate buffer (pH 9.5). Then 0.1\% fluorescamine (W/V) was added rapidly, followed by 1.5 ml of distilled water a few minutes later. Fluorescence was determined spectrophotometrically ($\lambda_{Ex}=390\ nm$, $\lambda_{Em}=470\ nm$) using a Hitachi 240 Fluorescence Spectrometer. The recovery of taurine through this column chromatography procedure was estimated to be almost 100\%. Authentic taurine, whole blood, plasma and urinary taurine appeared in the same fractions (Fig. 1). Estimations were duplicated for all measurements.

Serum high-density lipoprotein cholesterol was measured with a commercial enzyme method kit (Iatroset High Cholest, Iatron Labo Inc). Cardiac output was measured by the earpiece dye dilution method using a di-
Fig. 1. Taurine elution pattern from authentic taurine, whole blood, plasma, and urinary taurine from the same fraction. Samples (0.1 ml) were applied to a column with ion exchange resin: Dowex 50×8, 200–400 mesh in (H⁺) form, 5×25 mm, over Dowex 1×2, 200–400 mesh in (Cl⁻) form, 5×25 mm. This column was eluted with distilled water and a 0.5 ml fraction of the elute collected. Taurine recovery from this column was 100%. Estimations were duplicated.

Other materials were as previously reported. The fluorescamine (Fluran) was obtained from Roche Company.

Results are expressed as mean±standard error of the mean. Statistical significance has been determined by Student's t-test.

RESULTS

Clinical details are shown in Table I. Hypertensives were significantly older than normals. Blood pressures were significantly higher for hypertensives in comparison to normals.

As shown in Table I, no significant differences between normals and hypertensives were observed in plasma taurine or whole blood taurine. On the other hand, as shown in Table II and Fig. 2, there was a significant difference between normals and hypertensives in daily urinary taurine excretion. Daily urinary taurine excretion was 1594.0±143.7 μmol/day in normals; it was significantly lower (p<0.001) in Group I (708.1±57.1 μmol/day) and in Group 2 (953.6±94.3 μmol/day). The mean in Group 3 was 1478±134.3 μmol/day, nearly the same as in the normals. Daily urinary taurine excretion was similar for all WHO stages I, II, and III (data not shown here).
Table I. Age, Blood Pressure, Plasma, and Whole Blood Taurine of Subjects

<table>
<thead>
<tr>
<th>Classification</th>
<th>Number</th>
<th>Age (y/o)</th>
<th>Blood pressure (mmHg)</th>
<th>Taurine (amol/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
</tr>
<tr>
<td>Normals</td>
<td>18</td>
<td>33.3±2.1</td>
<td>123±3</td>
<td>75±2</td>
</tr>
<tr>
<td>Essential Hypertensives</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 (Without treatment)</td>
<td>32</td>
<td>54.6±1.8***</td>
<td>174±3***</td>
<td>102±3***</td>
</tr>
<tr>
<td>Group 2 (With treatment)</td>
<td>32</td>
<td>54.5±2.0***</td>
<td>155±4***</td>
<td>89±2***</td>
</tr>
<tr>
<td>Group 3 (Labile hypertensives)</td>
<td>15</td>
<td>42.7±2.5**</td>
<td>134±4***</td>
<td>85±2*</td>
</tr>
</tbody>
</table>

* = p<0.05, ** = p<0.01, *** = p<0.001.

Table II. Daily Urinary Taurine Excretion, Taurine Clearance, Creatinine Clearance, Taurine/Creatinine Ratio, and Urine Volume

<table>
<thead>
<tr>
<th></th>
<th>Daily Urinary Taurine Excretion (μmol/day)</th>
<th>Taurine Clearance (l/day)</th>
<th>Creatinine Clearance (l/day)</th>
<th>T/C Ratio</th>
<th>Urine Volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normals</td>
<td>1594.0±143.7 (18)</td>
<td>15.6±1.9 (18)</td>
<td>126.3±6.7 (10)</td>
<td>0.15±0.01 (14)</td>
<td>1178.3±105.4 (18)</td>
</tr>
<tr>
<td>Essential Hypertensives</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 (Without treatment)</td>
<td>708.1±57.1*** (32)</td>
<td>6.2±0.6*** (32)</td>
<td>97.4±5.1** (32)</td>
<td>0.10±0.01*** (32)</td>
<td>1205.6±76.8 (32)</td>
</tr>
<tr>
<td>Group 2 (With treatment)</td>
<td>953.6±94.3*** (32)</td>
<td>8.4±0.9** (32)</td>
<td>104.7±6.9* (28)</td>
<td>0.12±0.01* (28)</td>
<td>1371.4±8.7 (32)</td>
</tr>
<tr>
<td>Group 3 (Labile hypertensives)</td>
<td>1478.3±134.3 (15)</td>
<td>10.5±1.3* (15)</td>
<td>131.1±4.9 (13)</td>
<td>0.12±0.01 (13)</td>
<td>1289.3±104.3 (32)</td>
</tr>
</tbody>
</table>

* = p<0.05, ** = p<0.01, *** = p<0.001.
Fig. 2. Daily urinary taurine excretion in normals, Group 1 (essential hypertensives without antihypertensive drug treatment), Group 2 (essential hypertensives with antihypertensive drug treatment), and Group 3 (labile hypertensives). Results are expressed as mean±SE for each subject. There were significant differences between the normals and the 2 groups with essential hypertension (p<0.001). Bracket indication mean±SE.

Fig. 3. Relationship between creatinine clearance and taurine clearance in all subjects. Symbols as follows: (▲) normals, (●) Group 1, (○) Group 2, (△) Group 3, N=number of subjects.

There were no significant differences in daily urinary volume among normals, Groups 1, 2, or 3. Taurine clearances were decreased significantly in the essential hypertension groups. As shown in Table II, the values were 15.6±1.9 l/day in normals, 6.2±0.6 l/day in Group 1, 8.4±0.9 l/day in Group 2, and 10.5±1.3 l/day in Group 3.

Creatinine clearance was 126.3±6.7 l/day in normals, 97.4±5.1 l/day in Group 1, 104.7±6.9 l/day in Group 2, and 131.1±4.9 l/day in Group 3, also as shown in Table II. Taurine clearance was significantly correlated with creatinine clearance (r=0.327, p<0.01) in all subjects, as shown in Fig. 3. Since urinary taurine excretion, as well as creatinine excretion, may be influenced by impairment of renal function, clearances were compared only in
subjects with creatinine clearances of 90 to 160 l/day, indicating normal renal function. For these subjects, daily urinary taurine excretion was $1292.3 \pm 94.9 \mu \text{mol/day}$ in normals, $756.4 \pm 81.5 \mu \text{mol/day}$ in Group 1, $1105.4 \pm 181.4 \mu \text{mol/day}$ in Group 2, and $1509.6 \pm 125.4 \mu \text{mol/day}$ in Group 3. Taurine clearance was significantly lower in Group 1, $5.4 \pm 0.5 \text{l/day}$, as compared to normals, $12.6 \pm 1.5 \text{l/day}$, as shown in Fig. 4. The taurine/creatinine ratio was $0.15 \pm 0.01$ in normals, $0.10 \pm 0.01$ in Group 1, $0.12 \pm 0.01$ in Group 2, and $0.12 \pm 0.01$ in Group 3. There was a statistically significant difference ($p<0.001$) only between normals and Group 1.

Significant negative correlations were found between systolic blood pressure and daily urinary taurine excretion ($r=-0.472, n=97, p<0.01$).

![Fig. 4. Comparison of urinary taurine and taurine clearance in normals, essential hypertensives without treatment, essential hypertensives with treatment, and labile hypertensives. All creatinine clearances ranged from 90 to 160 l/day. (): Number of subjects. Results are expressed as mean±SE for each subject. Significant differences between normals and hypertensives are as follows: *=p<0.05, **=p<0.01, and ***=p<0.001. Brackets indicate mean±SE.]

![Fig. 5. Relationships between systolic blood pressure and daily urinary taurine excretion and between diastolic blood pressure and daily urinary taurine excretion in all subjects. Symbols are the same as in Fig. 3.]

Fig. 6. Relationships between cardiac index and daily urinary taurine excretion and between stroke index and daily urinary taurine excretion in untreated hypertensives and labile hypertensives. Symbols are the same as in Fig. 3.

Fig. 7. Relationships between serum high-density lipoprotein cholesterol and daily urinary taurine excretion in all subjects. Symbols are the same as in Fig. 3.

and between diastolic blood pressure and daily urinary taurine excretion \((r = -0.382, n=97, p<0.01)\) in all subjects, as shown in Fig. 5. There were significant positive correlations between daily urinary taurine excretion and both cardiac index \((r=0.547, n=28, p<0.01)\) and stroke index \((r=0.368, n=28, p<0.05)\) as shown in Fig. 6. Serum high-density lipoprotein cholesterol correlated significantly \((r=0.559, n=38, p<0.01)\) with daily urinary taurine excretion as shown in Fig. 7.

**DISCUSSION**

We demonstrated that daily urinary taurine excretion was markedly decreased in patients with essential hypertension and significantly related to
cardiac output and serum high-density lipoprotein cholesterol. It has been reported that daily urinary taurine excretion increased after ingestion of a protein-rich diet such as meat or fish.\textsuperscript{11,21–24} As we did not find any significant differences in dietary protein or sulfur containing amino acids among subjects in our study, it is unlikely that our results were significantly influenced by any dietary effect.

Because taurine clearance had a positive correlation with creatinine clearance, daily urinary taurine excretion is supposedly related to degree of renal function. However, daily urinary taurine excretion and taurine clearance were significantly decreased in untreated essential hypertensives even in those patients whose renal function was normal as shown by creatinine clearances of 90 to 160 l/day. This suggests that in essential hypertension the decrease in urinary taurine excretion may be due to a depression of taurine formation.

Taurine biosynthesis is complex, involving several routes and the distribution of taurine varies from species to species and organ to organ.\textsuperscript{11} Recently, Yamaguchi et al\textsuperscript{29} has reported that in the rat liver cysteine dioxygenase is a regulatory enzyme in the taurine pathway. This enzyme was induced by cysteine, methionine, or a high protein diet, and decreased by glucagon, CAMP or a low protein diet.\textsuperscript{27–30} As mentioned above, taurine content in the liver and serum was markedly decreased in SHRSP.\textsuperscript{18} These reports imply that taurine synthesis, probably by cysteine dioxygenase, may be attenuated in SHRSP rat liver. We presume that in this study, as well as in the experimental study on SHRSP, the decreased urinary taurine in essential hypertension may have been due to a defect in taurine metabolism.\textsuperscript{18} This, however, has never been investigated in SHRSP, SHR, or human beings.

On the other hand, the kidneys, also very important organs in the regulation of blood pressure, have two regulatory systems: One is the renin-angiotensin system which acts as a vasopressor with vasoconstrictive and antinatriuretic functions, and the other is the kallikrein-kinin system which acts as a vasodepressor with vasodilatory and natriuretic functions. Since taurine acts as a vasodepressor in essential hypertension,\textsuperscript{19} it may be suspected that taurine would participate in the kallikrein-kinin system to regulate renal blood flow. Margolius et al\textsuperscript{31} reported that urinary kallikrein is decreased in essential hypertension. In the present study, urinary taurine excretion had significant negative correlations with both systolic and diastolic blood pressures. If, in essential hypertension, a decrease in urinary taurine correlates with a decrease in urinary kallikrein, the regulation of taurine will add more important evidence for the role of the kallikrein-kinin system in the patho-
It has been reported that taurine has a vasodilatory function. In this study, there was a significant correlation between urinary taurine excretion and cardiac output. This suggests that either the inotropic action of taurine on the myocardium or the effect of afterload reduction on left ventricular ejection, or both, result in an increase in cardiac output.

As described above, high-density lipoprotein cholesterol had a positive correlation with daily urinary taurine excretion. The participation of taurine in bile salt formation is its most firmly established physiological function. It is reported that taurine may affect cholesterogenesis as a taurocholate. Recently, Ozaki et al reported that administration of taurine increased plasma high-density lipoprotein cholesterol in SHRSP to such an extent as to bring it to almost the same level as in Wistar Kyoto rats. Yamori et al reported that administration of taurine lowered cholesterol in arteriolipidosis prone rats (ALR), which quickly develop hypercholesterolemia on a high cholesterol diet. The significant correlation between serum high-density lipoprotein cholesterol and daily urinary taurine in this study is extremely interesting in this regard.

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REFERENCES


