Effects of Taurine on Stress-Evoked Hemodynamic and Plasma Catecholamine Changes in Spontaneously Hypertensive Rats

JIN YAMAMOTO, SATOSHI AKABANE, HIROKI YOSHIMI, MASATSUGU NAKAI, AND MASAO IKEDA

SUMMARY Cardiovascular hemodynamics (microspheres) and plasma norepinephrine and epinephrine levels at rest and during short-term shaker stress were investigated in conscious spontaneously hypertensive rats and Wistar-Kyoto rats, with or without oral taurine (1.5%) treatment for 8 weeks. Taurine effects were evaluated by comparing data on the taurine-treated and untreated rats. Taurine affected neither the resting hemodynamics nor the resting plasma catecholamine levels in spontaneously hypertensive and Wistar-Kyoto rats. Taurine slightly but significantly reduced the left ventricular/body weight ratio in the spontaneously hypertensive rats ($p < 0.05$) and caused an insignificant 10 mm Hg decrease in the resting mean arterial pressure. Spontaneously hypertensive and Wistar-Kyoto rats responded in a qualitatively similar manner to stress, as evidenced by resistance-dominated increases in mean arterial pressure and increases in heart rate, with a blood flow redistribution from splanchnic, cutaneous, and testicular to skeletal muscle and cerebral circulations and by increases in plasma norepinephrine and epinephrine levels. These changes were more marked in the spontaneously hypertensive rats. Taurine significantly reduced the stress values of mean arterial pressure (untreated, 189 ± 4 (SE) mm Hg; treated, 166 ± 4 mm Hg in the spontaneously hypertensive rats; $p < 0.05$), while it significantly reduced stress values of heart rate in spontaneously hypertensive and Wistar-Kyoto rats ($p < 0.05$). Taurine also blunted the stress values of splanchnic, testicular, and cutaneous vascular resistance in the spontaneously hypertensive rats. There were no or only slight regional effects in the Wistar-Kyoto rats. Taurine substantially decreased plasma levels of norepinephrine (untreated, 615 ± 76 pg/ml; treated, 383 ± 49 pg/ml) and epinephrine (untreated, 892 ± 187 pg/ml; treated, 232 ± 59 pg/ml) during stress in the spontaneously hypertensive rats. These results indicate that chronic taurine treatment attenuates short-term shaker stress-induced hemodynamic and plasma catecholamine changes in spontaneously hypertensive rats.

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KEY WORDS • shaker stress • systemic and regional hemodynamics • sympathoadrenomedullary activity

Patients with essential hypertension, and even their normotensive adolescent offspring, often show hyperresponsiveness to physical and psychological stress.1-2 Likewise, adult and young spontaneously hypertensive rats (SHR), the most extensively studied animal model of genetic hypertension,1-3-4 are hyperresponsive to many, though not all, stressful stimuli, in terms of hemodynamics, sympathoadrenal activity, and behavior.3-5-12 A search of the literature revealed no studies on multiple regional circulatory changes during stress determined simultaneously with systemic circulatory and endocrine changes.

The nonessential, sulfur-containing amino acid taurine (H,N-CH$_2$-CH$_2$-SO$_3$H) is present in high amounts in the heart, brain, muscle, and other parts of the body.13-16 Although its physiological importance has not been clarified, this compound possesses a variety of pharmacological actions, which include inhibitory modulation of neurotransmitters, anticonvulsion ac-
tivities, antiarrhythmia capabilities, and modulation of cation fluxes affecting calcium. Taurine exerts inotropic action in isolated, artificially perfused, and hypoxic cultured heart. There is a preventive effect on cardiac lesions in cardiomyopathic hamsters.

Intracerebroventricular injection of taurine produces hypotension and bradycardia in laboratory animals. Long-term oral administration of taurine produces a significant hypotensive effect in patients with essential hypertension. Similar treatment lowers blood pressure slightly in SHR, moderately in stroke-prone SHR, and strikingly in rats with deoxycorticosterone acetate-salt hypertension, but it has no effects in normotensive controls. Taurine was considered to be an effective component in fish or animal protein enriched diets, with regard to the hypotensive and stroke-preventive effects in stroke-prone SHR. In addition, long-term taurine treatment was shown to reduce spontaneous motile activity of SHR. Of interest also is a report indicating that short-term taurine administration diminished the immobilization stress-induced decrease in epinephrine contents in the rat adrenal gland.

We postulated that taurine might attenuate stress-evoked alterations in hemodynamics and sympathoadrenal activity in the hyperreactive SHR. In the present study, we assessed cardiovascular hemodynamics and sympathoadrenal activity at rest and during short-term shaker stress in conscious SHR and normotensive Wistar-Kyoto rats (WKY) with or without long-term taurine pretreatment.

Materials and Methods

Six-week-old male SHR and WKY were purchased from Charles-River Japan Inc. (Atsugi, Japan). When the rats were 7 weeks of age, we initiated taurine treatment by providing both strains of rats with drinking water containing 1.5% taurine. This dose was chosen because our preliminary experiments showed that treatment of SHR with 1.5% taurine for 8 weeks significantly lowered systolic blood pressure (tail cuff plethysmography) but did not affect body weight (BW); doubling the dose had the same effect but reduced BW. Rats from each strain given only tap water were also used. Thus, this study involved four groups of rats: 34 untreated SHR, 34 taurine-treated SHR, 33 untreated WKY, and 33 taurine-treated WKY. The rats were housed three to a cage and had free access to food (CE-2, Clea Japan Inc., Tokyo, Japan) and drinking solution. The food contained 7.6% water, 24.5% protein, 4.2% fat, 4.2% carbohydrate, and 7.7% minerals as well as other constituents. One rat was housed singly in a third set of experiments in which the daily taurine intake was checked. All animals were kept under controlled conditions of temperature (25 °C), humidity (45–50%), and lighting (cycle, 0600–1800 hours).

After 8 weeks of treatment with or without taurine (i.e., when the rats were 15 weeks old), three sets of experiments were performed. At 1800 to 2000 hours, the rats were cannulated with tip-tapered polyethylene catheters (PE-50) in the femoral artery and vein and in the left ventricle through the right carotid artery, under conditions of short-term ether anesthesia. All catheters were tunneled under the skin and brought out between the shoulder blades. The wounds were treated with 1% lidocaine (Xylocaine) and closed with sutures. A pair of SHR and WKY usually were prepared. In addition, several normal male Wistar rats also underwent arterial and venous cannulation and were used as donors for blood transfusion. In a third set of experiments, only a carotid artery catheter was inserted. The next morning, after a 15- to 17-hour recovery period, the conscious rat was placed in a small, nonconfining cage. This cage, accommodating one rat, was then mounted on a shaker (Model 77A; Yuyama, Osaka, Japan) and fixed on a tabletop by spring coils. Heparin (100 units) was given through the venous catheter, after which all catheters were connected to Statham transducers (Oxnard, CA, USA). Pulsatile and mean arterial pressure (MAP), left ventricular pressure, and heart rate (HR) were recorded directly on a polygraph (Model 360; Sannei, Tokyo, Japan).

Hemodynamics at Rest and During Acute Stress

Systemic and regional blood flow were measured using radioactive microspheres, as described elsewhere. In brief, 50,000 to 100,000 radioactive microspheres (15 ± 3 μm) labeled with 14C (New England Nuclear Corp., Boston, MA, USA) or 85Sr (3M, St Paul, MN, USA), which were suspended in a volume of 0.05 ml of physiological saline with 0.01% polysorbate 80 (Tween 80), were injected into the left ventricle and flushed with 0.4 ml of blood freshly obtained from donor rats over a 20-second period. Beginning 10 seconds before the microsphere injection, a reference sample was withdrawn from the femoral artery over a 50-second period, using a Harvard 901 pump (Millis, MA, USA). Blood loss was immediately replaced by approximately 0.6 ml of fresh donor blood.

After the rat had been accustomed to the experimental setting for at least 30 minutes, systemic and regional hemodynamics were measured under resting conditions. Thirty minutes was then allowed for the rat to recover from the first measurement. Acute stress was imposed by shaking at a rate of 90 oscillations per minute (horizontal displacement of about 4 cm per oscillation) for 5 minutes. With this shaker stress, in general, the MAP and HR increased immediately, peaked within 1 minute, reached a plateau, and decreased gradually around 4 minutes after the start of shaking. Since the hemodynamic parameters were most stable between 2 and 3 minutes, we measured systemic and regional hemodynamics during this period, but we used a different nuclide, as already described.

At the completion of the experiment, the rat was exsanguinated and tissue and organs were removed. More than 20 g of skin or skeletal muscle tissue was...
 Plasma Concentrations of Catecholamines, Renin, and Corticosterone at Rest and During Acute Stress

The rats were subjected to the same experimental setting as in the first experiment. Under the resting conditions, 1.5 ml of blood was withdrawn from the arterial line into a tube placed on ice while the same amount of blood was simultaneously transfused into the venous line from the donor rat at a rate of 0.5 ml/min. This transfusion was achieved by connecting the femoral arterial catheter in the donor to the femoral venous catheter in the experimental rat and introducing this catheter into a tube by way of a pump (Gilson, Viliers Le Bel, France). Our previous and preliminary studies demonstrated that this sampling method was suitable for assays of plasma levels of vasopressin, catecholamines, and renin.

After a minimum of 30 minutes of recovery, at which time hemodynamic parameters returned to pre-existing levels, the rat was exposed to short-term shaker stress, as already described. Between 2 and 3 minutes after the initiation of shaker stress, 1.5 ml of blood was withdrawn from the femoral artery into an ice-chilled syringe while the same amount of fresh blood was infused from a syringe into the femoral vein. This procedure was performed manually because use of the pump was hampered by the shaking action.

The plasma was immediately separated at 4 °C and stored at −80 °C. Plasma catecholamines were measured by high-performance liquid chromatography combined with the trihydroxyindole method. Catecholamines were separated by applying deproteinized and alumina-treated plasma to a Zipax SCX column connected in sequence with a continuous flow system and a spectrophotometer (Autoanalyzing System, Shimadzu Seisakusho, Co. Ltd., Kyoto, Japan). We used circulating norepinephrine levels as an index of the sympathetic activity, and the circulating epinephrine levels were used as an index of the adrenomedullary activity.

Plasma renin concentration was determined by radioimmunoassay. Samples were incubated at 37 °C with substrate-rich plasma prepared from nephrectomized rats, and the generated angiotensin I was measured using a radioimmunoassay kit (Sorin Biomedica S.p.a., Saluggia, Italy). Plasma corticosterone concentration was measured by radioimmunoassay. Methylene chloride-extracted corticosterone was incubated with anticorticosterone rabbit serum (Miles-Yeda Ltd., Rehovot, Israel) and [3H]corticosterone (New England Nuclear).

Results

As shown in Table 1, the SHR weighed less than the WKY. Taurine treatment did not alter the BW in either the SHR or WKY strains. The left ventricular/BW ratio was greater in untreated SHR and taurine-treated SHR as compared with that in untreated WKY and taurine-treated WKY respectively. This ratio was slightly but significantly less in taurine-treated SHR than in untreated SHR (2.97 ± 0.03 g/kg vs 2.80 ± 0.02 g/kg; p < 0.05). The right ventricular/BW ratio was not different among the groups. The adrenal/BW ratio was significantly smaller in untreated SHR than in untreated SHR (0.14 ± 0.01 g/kg vs 0.18 ± 0.01 g/kg; p < 0.05).

Systemic Hemodynamics at Rest and During Acute Stress

The MAP was significantly higher in the treated and untreated SHR than in the treated and untreated WKY, respectively (Table 2). The MAP showed a slight, insignificant decrease in the treated SHR compared with that in untreated SHR (144 ± 3 mm Hg vs 154 ± 3 mm Hg), but there was no difference between treated and untreated WKY. There was a tendency toward a higher HR in both groups of SHR. The resting cardiac index was similar in all groups. Total peripheral resistance at rest was significantly greater in treated and untreated SHR than in their respective counterparts. Total peripheral resistance was somewhat lower in treated SHR than in untreated SHR.

With short-term shaker stress MAP and HR increased significantly from resting levels in all groups (Table 2). Both values during stress were significantly greater in untreated SHR than in untreated WKY, as well as in treated SHR compared with those in treated...
TABLE 1. Body, Heart, and Adrenal Weights in Rats With or Without Taurine Treatment

<table>
<thead>
<tr>
<th>Variables</th>
<th>Untreated</th>
<th>Treated</th>
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<td>WKY (n = 14)</td>
<td>SHR (n = 13)</td>
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<tr>
<td></td>
<td></td>
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<td>WKY (n = 13)</td>
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<td>BW (g)</td>
<td>281 ± 3*</td>
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<td>286 ± 4†</td>
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<td>LV/BW (g/kg)</td>
<td>2.97 ± 0.03*</td>
<td>2.58 ± 0.04</td>
<td>2.80 ± 0.02†</td>
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<td>RV/BW (g/kg)</td>
<td>0.56 ± 0.02</td>
<td>0.64 ± 0.03</td>
<td>0.62 ± 0.03†</td>
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<td>Adrenals/BW (g/kg)</td>
<td>0.17 ± 0.01</td>
<td>0.18 ± 0.01</td>
<td>0.14 ± 0.01†</td>
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</table>

Data are means ± SE. SHR = spontaneously hypertensive rats; WKY = Wistar-Kyoto normotensive rats; BW = body weight; LV = left ventricle including the septum, RV = right ventricle.
* p < 0.05 compared with untreated WKY, † p < 0.05 compared with treated WKY, ‡ p < 0.05 compared with untreated SHR.

TABLE 2. Systemic Hemodynamic Data at Rest and During Short-term Shaker Stress in Rats With or Without Taurine Treatment

<table>
<thead>
<tr>
<th>Variables</th>
<th>Interval</th>
<th>Untreated</th>
<th>Treated</th>
<th>Whole (ANOVA)*</th>
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<td>WKY (n = 13)</td>
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<td></td>
<td>Whole (ANOVA)*</td>
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<td>MAP (mm Hg)</td>
<td>Rest</td>
<td>154 ± 3†</td>
<td>120 ± 2</td>
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<td>Stress</td>
<td>189 ± 4†</td>
<td>142 ± 2</td>
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<td>&lt; 0.05</td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>Rest</td>
<td>399 ± 7</td>
<td>362 ± 10</td>
<td>391 ± 10</td>
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<td></td>
<td>Stress</td>
<td>464 ± 8†</td>
<td>397 ± 10</td>
<td>427 ± 8§</td>
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<td>&lt; 0.05</td>
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<tr>
<td>Cardiac index (ml/min per 100 g BW)</td>
<td>Rest</td>
<td>29.3 ± 1.0</td>
<td>29.8 ± 0.8</td>
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<td>Stress</td>
<td>32.2 ± 1.2</td>
<td>31.9 ± 0.7</td>
<td>31.6 ± 1.6</td>
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<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
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<tr>
<td>TPR (mm Hg · ml⁻¹ · min⁻¹ per 100 g BW)</td>
<td>Rest</td>
<td>5.34 ± 0.17†</td>
<td>4.08 ± 0.11</td>
<td>4.77 ± 0.26†</td>
</tr>
<tr>
<td></td>
<td>Stress</td>
<td>5.93 ± 0.13†</td>
<td>4.48 ± 0.10</td>
<td>5.36 ± 0.22†</td>
</tr>
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<td>&lt; 0.05</td>
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</table>

Data are means ± SE. MAP = mean arterial pressure; BW = body weight; TPR = total peripheral resistance; ANOVA = analysis of variance; NS = not significant. Other abbreviations and number of rats are as shown in Table 1.
* Comparison of rest versus stress values in all rats as a whole by ANOVA.
† p < 0.05 compared with untreated WKY, † p < 0.05 compared with treated WKY, ‡ p < 0.05 compared with untreated SHR.

WKY. Taurine treatment significantly reduced MAP and HR during stress in the SHR, as shown by significant differences in these values in untreated SHR compared with those in treated SHR (MAP, 189 ± 4 mm Hg vs 166 ± 4 mm Hg; p < 0.05; HR, 464 ± 8 beats/min vs 427 ± 8 beats/min; p < 0.05). In addition, stress HR was significantly smaller in treated than in untreated WKY (367 ± 11 beats/min vs 397 ± 10 beats/min; p < 0.05). As a whole, cardiac index increased significantly from resting to stress levels (by analysis of variance), but the changes did not reach a statistically significant level in individual groups. Total peripheral resistance increased significantly with stress as a whole and individually in untreated and treated SHR. Stress total peripheral resistance values were greater in untreated and treated SHR, as compared with those in untreated and treated WKY, respectively. Taurine treatment lowered these values significantly only in the SHR (treated SHR, 5.36 ± 0.22 mm Hg · ml⁻¹ · min⁻¹ per 100 g BW vs untreated SHR, 5.93 ± 0.13 mm Hg · ml⁻¹ · min⁻¹ per 100 g BW; p < 0.05).

Regional Hemodynamics at Rest and During Acute Stress
There were no differences in resting values of blood flow and vascular resistance in the gastrointestinal tract (stomach plus gut), pancreas, spleen, and liver in any of the groups (Figure 1). With short-term shaker stress analyzed as a whole, blood flow decreased from a resting level in all these organs except the liver and vascular resistance increased in all organs. Individualiy, significant decremental responses of flow occurred in the gastrointestinal tract and pancreas of untreated SHR and in the spleen of untreated SHR, untreated WKY, and treated WKY. Blood flow during stress was significantly less in the pancreas of untreated SHR than in untreated WKY and treated SHR. Individually, there were significant incremental responses of vascular resistance in the gastrointestinal tract and pancreas of untreated SHR, in the spleen of untreated SHR and untreated WKY, and in the liver of treated SHR. Stress vascular resistance was significantly greater in the gastrointestinal tract, pancreas, and spleen of untreated SHR than in the untreated WKY and, importantly, in...
TAURINE AND STRESS IN SPONTANEOUSLY HYPERTENSIVE RATS/Yamamoto et al.

FIGURE 1. Blood flow and vascular resistance in hepatosplanchic organs. SHR = spontaneously hypertensive rats; WKY = Wistar-Kyoto normotensive rats; TSHR = taurine-treated SHR; TWKY = taurine-treated WKY. Open columns represent values at rest, and shaded columns represent those during stress. Data are means ± SE. Asterisks on the shoulder of shaded column indicate significant differences between resting and stress values in the same group of rats, and those with brackets indicate significant difference between values of different groups. *p < 0.05.

the treated SHR. Thus, taurine treatment appears to have significantly suppressed the stress-induced vascular resistance changes in these splanchnic organs (except the liver) in the SHR.

Adrenourogenital hemodynamic data showed no differences in blood flow and vascular resistance among the groups at rest (Figure 2). With stress, blood flow decreased from a resting level in the testes and tended to decrease in the kidneys, while vascular resistance increased in the kidneys and testes and tended to increase in the adrenals. Individually, testicular vascular resistance increased significantly with stress in the untreated SHR. This stress value in untreated SHR was significantly greater, as compared with that in untreated WKY and, importantly, treated SHR. Taurine treatment thus appears to have reduced testicular vascular resistance during stress in the SHR.

Resting values for blood flow and vascular resistance in the brain, left ventricle, right ventricle, and lungs were not statistically different, although vascular resistance in the brain and lungs tended to be larger in both groups of SHR than in their respective counterparts (Figure 3). With stress, cerebral blood flow significantly increased in the untreated SHR, untreated WKY, and treated SHR. Cerebrovascular resistance during stress did not differ among the groups. With stress, left and right ventricular blood flow tended to increase in the untreated SHR, untreated WKY, and treated SHR, and left ventricular vascular resistance increased significantly as a whole. Left ventricular blood flow during stress was significantly greater in untreated SHR than in untreated WKY, but was similar in both groups of SHR.

At rest, blood flow and vascular resistance in skeletal muscle and skin were not statistically different among the groups; vascular resistance in either bed tended to be elevated in both groups of SHR (Figure 4). With stress, skeletal muscle blood flow increased significantly from a resting value as a whole and also individually in untreated SHR, whereas skeletal muscle vascular resistance decreased significantly as a

FIGURE 2. Blood flow and vascular resistance in the kidneys, adrenals, and testes. Symbols and abbreviations are as shown in Figure 1. Whole: p < 0.05 (ANOVA) indicates significant differences between resting and stress values when all groups of rats were assessed as a whole using F statistics by analysis of variance. *p < 0.05.
whole. On the contrary, with stress, cutaneous blood flow decreased significantly as a whole and also individually in untreated SHR, whereas cutaneous vascular resistance increased significantly as a whole and also individually in both groups of SHR. Cutaneous vascular resistance during stress was higher in untreated SHR than in untreated WKY, and that of epinephrine during stress was significantly higher in untreated and treated SHR than in their respective counterparts. Taurine treatment reduced plasma norepinephrine and epinephrine levels during stress, on average, by approximately 50 and 70% respectively in the SHR (plasma norepinephrine: untreated SHR, 615 ± 76 pg/ml vs treated SHR, 383 ± 49 pg/ml; plasma epinephrine: untreated SHR, 892 ± 187 pg/ml vs treated SHR, 232 ± 59 pg/ml; p < 0.05). Taurine treatment considerably but insignificantly lowered the plasma epinephrine level during stress in the WKY (untreated WKY, 245 ± 60 pg/ml vs treated WKY, 113 ± 28 pg/ml).

Plasma renin concentration was not different among the groups, either at rest or during stress (Table 3). Plasma renin concentration did not significantly change from a resting level in response to short-term shaker stress. Plasma corticosterone concentration showed no difference among the groups, either at rest or during stress, and was not altered with stress.

Plasma Levels of Taurine and Other Amino Acids

Average daily intake of taurine was comparable in treated SHR and treated WKY (2.71 ± 0.41 g/kg vs 2.79 ± 0.46 g/kg). As shown in Table 4, the plasma
TAURINE AND STRESS IN SPONTANEOUSLY HYPERTENSIVE RATS/Yamamoto et al.

### TABLE 3. Plasma Concentrations of Catecholamines, Renin, and Corticosterone at Rest and During Short-term Shaker Stress in Rats With or Without Taurine Treatment

<table>
<thead>
<tr>
<th>Variables</th>
<th>Interval</th>
<th>SHR Untreated</th>
<th>WKY Untreated</th>
<th>SHR Treated</th>
<th>WKY Treated</th>
<th>Whole (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine (pg/ml)</td>
<td>Rest</td>
<td>320 ± 54</td>
<td>184 ± 32</td>
<td>246 ± 59</td>
<td>186 ± 33</td>
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</tr>
<tr>
<td></td>
<td>Stress</td>
<td>615 ± 76*</td>
<td>286 ± 41</td>
<td>383 ± 49</td>
<td>276 ± 49</td>
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<tr>
<td></td>
<td>p</td>
<td>&lt;0.05 (11) NS (11)</td>
<td>NS (11) NS (11)</td>
<td>&lt;0.05</td>
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<tr>
<td>Epinephrine (pg/ml)</td>
<td>Rest</td>
<td>125 ± 3</td>
<td>32 ± 6</td>
<td>54 ± 10</td>
<td>45 ± 9</td>
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<td></td>
<td>Stress</td>
<td>892 ± 187*</td>
<td>245 ± 60</td>
<td>232 ± 59†</td>
<td>113 ± 28</td>
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</tr>
<tr>
<td></td>
<td>p</td>
<td>&lt;0.05 (11) NS (11)</td>
<td>NS (11) NS (11)</td>
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<tr>
<td>Renin (ng/ml/hr)</td>
<td>Rest</td>
<td>5.68 ± 0.56</td>
<td>4.94 ± 0.55</td>
<td>6.02 ± 0.64</td>
<td>4.43 ± 0.40</td>
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<td>Stress</td>
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<td>6.12 ± 0.51</td>
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<td>6.85 ± 0.76</td>
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<tr>
<td></td>
<td>p</td>
<td>NS (10)</td>
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<td>NS (10)</td>
<td>NS (10)</td>
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<tr>
<td>Corticosterone (μg/ml)</td>
<td>Rest</td>
<td>0.271 ± 0.058</td>
<td>0.262 ± 0.040</td>
<td>0.213 ± 0.034</td>
<td>0.194 ± 0.030</td>
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<tr>
<td></td>
<td>Stress</td>
<td>0.318 ± 0.056</td>
<td>0.210 ± 0.037</td>
<td>0.229 ± 0.035</td>
<td>0.173 ± 0.024</td>
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<tr>
<td></td>
<td>p</td>
<td>NS (10)</td>
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</table>

Values are means ± SE. Abbreviations are as shown in Tables 1 and 2. Number of rats for each group is shown in parentheses.

*p < 0.05 compared with untreated WKY, †p < 0.05 compared with untreated SHR.

### TABLE 4. Plasma Levels of Taurine and Other Amino Acids in Rats With or Without Taurine Treatment

<table>
<thead>
<tr>
<th>Variables</th>
<th>SHR Untreated</th>
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<th>SHR Treated</th>
<th>WKY Treated</th>
<th>Whole (ANOVA)</th>
</tr>
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<tbody>
<tr>
<td>Taurine (nmol/ml)</td>
<td>152 ± 23</td>
<td>202 ± 28</td>
<td>364 ± 28*†</td>
<td>514 ± 62†</td>
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<tr>
<td>Methionine (nmol/ml)</td>
<td>54.9 ± 3.2</td>
<td>58.4 ± 8.4</td>
<td>53.5 ± 1.7</td>
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<tr>
<td>Cysteine (nmol/ml)</td>
<td>10.3 ± 2.3</td>
<td>8.3 ± 0.8</td>
<td>15.6 ± 2.7</td>
<td>10.1 ± 2.3</td>
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<tr>
<td>Lysine (nmol/ml)</td>
<td>294 ± 21†</td>
<td>410 ± 65</td>
<td>310 ± 20</td>
<td>404 ± 11</td>
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<tr>
<td>Urea (μmol/ml)</td>
<td>7.90 ± 0.50</td>
<td>6.67 ± 0.65</td>
<td>5.41 ± 0.75*</td>
<td>4.62 ± 0.35†</td>
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</tbody>
</table>

Values are means ± SE. n = 9 for each group. Abbreviations are as shown in Table 1. Only data for amino acids containing sulfur atom and those showing significant statistical differences among groups are given.

*p < 0.05 compared with untreated SHR, †p < 0.05 compared with treated WKY, ‡p < 0.05 compared with untreated WKY.

taurine level of untreated SHR was somewhat lower than, but statistically not different from, that of untreated WKY. Taurine administration significantly elevated this plasma level in both groups. However, the plasma taurine level was significantly lower in treated SHR than in treated WKY. Plasma levels of other sulfur-containing amino acids, methionine and cysteine, did not differ among the groups. Plasma lysine level was significantly reduced in the untreated SHR compared with untreated WKY. Plasma urea level was similar in untreated SHR and treated WKY. This level was significantly lowered with taurine treatment in both groups. There were no differences in other amino acids, either essential or nonessential, among the groups (data not shown).

**Discussion**

The notable findings from the present study are that 1) compared with age-matched WKY, conscious, 15-week-old SHR showed exaggerated responses in hemodynamics and plasma catecholamines to short-term shaker stress and 2) oral pretreatment with 1.5% taurine solution for 8 weeks attenuated most of these enhanced responses in the SHR.

The present observation that in resting SHR with established hypertension, cardiac index was unchanged and total peripheral resistance elevated, with almost uniform distribution in increased vascular resistance in various organs, corroborates earlier findings. Long-term taurine feeding had minimal and no effects on resting hemodynamics in the SHR and WKY respectively. Although the difference in MAP between untreated and treated SHR was not significant (i.e., 10 mm Hg), the difference in the left ventricular/BW ratio between both groups was significant albeit slight (Table 1). Since the left ventricular/BW ratio may reflect the average of long-standing cardiac afterload, one interpretation of this result is that taurine exerted marginal hypotensive effects during a course of treatment in the SHR, possibly by mechanisms described below.
Nara et al.\textsuperscript{22} noted that feeding the SHR with 3% taurine solution slightly decreased systolic blood pressure.

Another interpretation would be that taurine improved the partly compromised efficiency in the myocardium in the SHR, thereby leading to partial regression of hypertrophy. Taurine may interact with Ca\textsuperscript{2+}-binding sites through actions on the membranes and consequently adjust either the available Ca\textsuperscript{2+} or the myocardial sensitivity to Ca\textsuperscript{2+} in the heart when its contractility is altered.\textsuperscript{16-18} Either pretreatment of animals with taurine or in vitro addition of taurine to perfusion buffer has been reported to antagonize the negative inotropic state following lowered perfusate calcium in isolated heart preparations.\textsuperscript{16, 17} Chronic taurine ingestion has a prophylactic effect on calcium accumulation-related cardiac necrotic lesions in genetically cardiomyopathic hamsters.\textsuperscript{18}

Resting plasma concentrations of norepinephrine and epinephrine tended to be higher in the SHR than in the WKY, but the difference was not statistically significant, which agrees with previous findings.\textsuperscript{3, 6-9} The comparable resting levels of plasma renin concentration observed in SHR and WKY are in accord with earlier results;\textsuperscript{26} the decreased level was found in 2-month-old SHR.\textsuperscript{8} Our finding of unaltered plasma corticosterone level in the SHR is consistent with some reports,\textsuperscript{3-9} but not with others.\textsuperscript{9} There were no appreciable influences of taurine treatment on these resting levels.

The nature of the shaker stress employed in this study has been described.\textsuperscript{26} Our preliminary experiments indicated that, compared with a stimulus such as noise or flashing, shaker stress produced circulatory reactions varying much less in degree and duration from rat to rat during a certain period. We applied an acute, single stress to prevent the problems of habituation, which appear to differ in a complex way between the SHR and WKY.

This shaker stress acutely aroused the rats both mentally and physically. Hemodynamically, both the SHR and WKY reacted to stress with quantitatively dissimilar, but qualitatively similar, patterns (Table 2; Figures 1-4). Systemically, MAP, HR, cardiac index, and total peripheral resistance all increased on average, although the increase in total peripheral resistance rather than that in cardiac index was predominant. Regionally, there was a decrease or a tendency toward a decrease in blood flow to the splanchnic organs (except the liver), kidneys, testes, and skin, which was in contrast to an increase or a tendency toward an increase in blood flow to the skeletal muscle, brain, liver, and heart. These changes were more remarkable in the SHR. Furthermore, most of the values obtained in the SHR during stress were significantly different from those in the WKY. The hemodynamic patterns seen typically in stressed SHR resembled in many aspects those noted in stressed hypertensive patients.\textsuperscript{1, 2}

These findings are reminiscent of the so-called defense reaction.\textsuperscript{3, 5} This centrally mediated response may vary considerably, depending on the state of equilibrium among central-hypothalamic, reflex-bulbar, and local influences.\textsuperscript{1} Accordingly, the present finding that during stress the resistance-dominated increase in MAP was associated with increased resistance in splanchnic, renal, and cutaneous circulations, as opposed to unaltered vascular resistance in skeletal muscle and cerebral circulations, may be viewed as this type of manifestation.

Consistent with this view, plasma norepinephrine and epinephrine levels increased on average with stress in both the SHR and WKY (Table 3). The enhanced response seen in the SHR was comparable to that reported previously.\textsuperscript{6-9} On the other hand, the lack of change in plasma renin concentration and plasma corticosterone levels we noted during stress seems to be different from the expected activation of the renin-angiotensin and the pituitary-adrenocortical systems with the defense reaction.\textsuperscript{1, 5} Yet, since renin secretion is affected by a balance among increased pressure, decreased perfusion, and reflex adjustments, combinations of these factors may be responsible in part for the absence of plasma renin concentration responses. Another factor is the duration of stress until blood sampling. Sampling 2 to 3 minutes after the start of stress may be too early to detect substantial alterations. This would account entirely for the lack of corticosterone changes, as described.\textsuperscript{41}

Taurine treatment significantly reduced the stress values of MAP, HR, and total peripheral resistance in the SHR and also that of HR in the WKY (Table 2). Here, the stress values of vascular resistance were significantly lowered in splanchnic, cutaneous, and testicular beds in the SHR (Figures 1, 2, 4). The renal vascular resistance tended to decrease in the SHR. Importantly, taurine treatment significantly suppressed the stress values of plasma epinephrine, and substantially but insignificantly suppressed those of plasma norepinephrine in the SHR as well as of plasma epinephrine in the WKY (Table 3). These results strongly suggest a modulatory role for taurine in the stress-related sympathoadrenomedullary activation, particularly in the SHR.

The mechanisms by which taurine exerts significant antistress effects and marginal, if any, antihypertensive effects remain speculative. Most important is the effect of taurine on the epinephrine release from the adrenals. Kuriyama and Nakagawa\textsuperscript{25} showed that a 3% taurine feeding reduced the decrease in the adrenal epinephrine content following immobilization stress in rats. They also found that even spontaneous release of epinephrine was reduced in the adrenal granular fraction by topical addition of taurine and in that prepared from taurine-fed rats. This effect possibly was mediated through a direct action on adrenomedullary chromaffin granules, because neither exocytosis nor epinephrine synthesis was influenced.\textsuperscript{16, 20} These data also suggest that taurine's effect on epinephrine release may depend on its concentration in the adrenals in normal rats. The far more remarkable effects seen in the SHR compared with those in WKY are perhaps related to altered release mechanisms in the SHR.
Another noteworthy suggestion is that taurine acts as an inhibitory modulator of neuronal activity, either centrally or peripherally, probably by stabilizing the membrane excitability and hence diminishing the neurotransmitter release.14,15 For example, Ca2+-dependent, K+-evoked release of acetylcholine or noradrenaline from rat brain or superior cervical ganglion was lessened by in vitro addition of taurine or by short-term feeding of taurine.14,15 These and other observations that intracerebroventricular, rather than intravenous, injection of taurine more readily produced hypotension and bradycardia imply that taurine may result in peripheral sympathetic inhibition through central nervous system mechanisms.16,17 Relevant to such central nervous mechanisms is the reported reduction of spontaneous motile activity of SHR fed a high taurine diet.24

The key to these actions appears to reside in changes in intercellular or intracellular ion movement, including Ca2+ in the presence of taurine,13,16,17 although this unification lacks convincing evidence at present. Other antistress and antihypertensive mechanisms could be accounted for by the natriuretic and direct vascular actions of taurine.4,21 These aspects need to be studied in detail.

In the present study, long-term treatment of the SHR with 1.5% taurine neither suppressed resting plasma catecholamine levels nor resulted in impressive hypotensive effects. In contrast, Fujita and Sato23 found that long-term treatment of rats with 1% taurine almost completely precluded the development of deoxycorticosterone acetate–salt hypertension and normalized the accelerated cardiac norepinephrine turnover rate, which suggests inhibition of the sympathetic activity. The exact reason for the contrasting hypotensive effects obtained in the SHR and deoxycorticosterone acetate–salt hypertensive rats is unclear, but the effects of taurine appear to vary with the type of hypertension.

Despite identical levels of taurine ingestion, the plasma taurine level was lower in the treated SHR than in the treated WKY (Table 3), which suggests changes in taurine metabolism in the SHR.22 The decreased lysine level we observed in the SHR has already been noted (Y. Yamori, personal communication, 1985). Long-term lysine administration was found to lower blood pressure in the stroke-prone SHRs.4 Another intriguing finding is the decline in plasma urea level in both the SHR and WKY in the presence of taurine. The implications of these findings remain obscure.

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