Effects of increased adrenomedullary activity and taurine in young patients with borderline hypertension

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ABSTRACT Recent studies showed that taurine, a sulphonic amino acid, could decrease blood pressure and increase sympathoadrenal tone in DoCA-salt-treated hypertensive rats. To determine whether taurine exerts its antihypertensive action in man in a similar fashion, we studied the effect of oral administration of taurine (6 g for 7 days) on blood pressure and plasma catecholamines in 19 young patients with borderline hypertension in a double-blind, placebo-controlled fashion. Systolic blood pressure in the 10 patients who were treated with taurine decreased by 9.0 ± 2.9 mm Hg (mean ± SE; p < .05 by paired t test), compared with a 2.7 ± 2.3 mm Hg decrease (NS) in the nine patients treated with placebo and diastolic blood pressure in the taurine-treated patients decreased by 4.1 ± 1.7 mm Hg (p < .05) compared with 1.2 ± 3.0 mm Hg (NS) in the placebo-treated subjects. In the patients receiving taurine plasma epinephrine (E) decreased significantly, with a negligible decrease in plasma norepinephrine (NE). The effect of taurine on plasma catecholamines and the response of plasma E after the stimulation with glucagon was also studied in 12 borderline hypertensive and nine age-matched normotensive subjects. Basal plasma E was significantly higher in borderline hypertensive than in normal subjects, but basal plasma NE did not differ in the two groups. The intravenous bolus injection of glucagon (1 mg) caused a transient increase in plasma E in each subject studied; plasma E reached a peak concentration 2 to 5 min after the injection of glucagon and thereafter declined rapidly to the baseline level. The overall response of plasma E to glucagon stimulation was significantly (p < .01) greater in the borderline hypertensive than in the normotensive subjects. Taurine not only reduced mean blood pressure and basal plasma E, but also attenuated the increased response to glucagon in the borderline hypertensive subjects. In the normotensive subjects, however, the administration of taurine did not significantly change blood pressure, basal plasma catecholamines, or the response of plasma E to glucagon. Overall, there was a direct correlation (r = .670, p < .01) between the decrements in mean blood pressure and those in plasma E after taurine in the 22 borderline hypertensive subjects. Evidence presented suggests, therefore, that sympathoadrenal tone is increased in young borderline hypertensive individuals, and that oral administration of taurine attenuates increased tone, leading to the reduction of blood pressure.


YOUNG PATIENTS with borderline hypertension are at least three times more likely to develop established essential hypertension than age-matched normotensive subjects.1,2 Thus, young patients with borderline hypertension have been of particular interest to investigators because they may provide insight into the pathogenesis of essential hypertension. The majority of studies have reported increased average circulating norepinephrine levels in borderline hypertensive subjects,3,4 and more recently some studies have reported higher epinephrine levels in borderline or mildly hypertensive patients.5–7 An increase in plasma norepinephrine reflects increased sympathetic activity, whereas an increase in plasma epinephrine is likely to reflect an adrenal hyperactivity. Several investigators have demonstrated that in patients with borderline hypertension there is an increased response of plasma catecholamines to mental stress8,9 or orthostatic tilting,10 suggesting a net increase in the sympathoadrenal tone.11 These observations led us to the hypothesis that not only increased sympathetic activity but also adrenomedullary hyperactivity may be involved in the development of essential hypertension. To assess the
adrenomedullary activity in young patients with borderline hypertension, we therefore examined the response of plasma epinephrine after stimulation by the injection of glucagon in young borderline hypertensive and age-matched normotensive subjects.

Recently, there has been increased concern with ascertaining the importance of nutrients in the regulation of blood pressure and the pathogenesis of hypertension. Since the majority of patients with elevated blood pressure fall in the borderline and mildly hypertensive categories, there is a need to do research on nonpharmacologic strategies for management of these patients. It is well known that dietary nutrients such as sodium, potassium, and calcium influence blood pressure. Moreover, several investigators have suggested that dietary protein and amino acids could also influence blood pressure and thus affect development of hypertension. Recently emphasis has been focused on the relationship between taurine, a sulphonic amino acid, and cardiovascular disease. Our recent studies have indicated that supplementation of the diet with taurine could attenuate the development of DoCA-salt-induced hypertension in rats, possibly by the suppression of increased sympathetic activity. Moreover, previous studies have demonstrated that the administration of taurine in vitro not only suppresses the high-potassium-evoked release of norepinephrine from a variety of neuronal tissues, but also inhibits the stress-induced release of epinephrine from adrenal chromaffin granules. In contrast, neither methionine nor leucine (sulfur-containing amino acids metabolically related to taurine) have been shown to have any preventive effect on the release of epinephrine, suggesting that taurine has a specific preventive effect on stress-induced release of epinephrine in the adrenal gland.

To determine whether taurine is an efficacious therapeutic modality in young patients with borderline hypertension who are at risk for the development of established hypertension, we studied the effect of the oral administration of taurine on blood pressure in young borderline hypertensive subjects in a double-blind, placebo-controlled fashion. To clarify the role of sympathoadrenal function in the antihypertensive action of taurine, we also studied the effect of oral taurine on the glucagon-induced release of epinephrine from adrenal glands in our young subjects with borderline hypertension.

Methods

Forty male subjects (31 with borderline hypertension and nine age-matched normotensive subjects) were included in this study. Each subject underwent a physical examination and gave a medical history. Laboratory results, including those of urinalysis, tests for levels of serum electrolytes, creatinine, plasma renin activity (PRA), and aldosterone, and results of electrocardiographic examination were normal. Thus, there was no evidence of a known cause of hypertension in any of the subjects. Most had never been treated and in those few who had, antihypertensive drugs had been discontinued at least 2 months before the study. No patient was older than 25 years of age, and none had electrocardiographic or radiographic evidence of left ventricular hypertrophy, hypertensive retinopathy, or renal involvement. Each subject was informed of the nature of the study and gave written consent. Patients were considered to have borderline hypertension if, on examination in the outpatient department, their diastolic pressures at times exceeded but at other times were lower than 90 mm Hg. Subjects brought two complete 24 hr urine samples to each visit throughout the trial and sodium, creatinine, and taurine levels were determined in each sample. Body weight was recorded at each visit. When patients were supine, subjectively relaxed, and had a stable pulse rate, blood pressure was measured by sphygmomanometer.

Protocol 1. The subjects were studied on an outpatient basis. Each subject attended a special research clinic for examinations at a fixed hour and day of the week. After screening visits, patients with borderline hypertension who were 20 to 25 years old were admitted to the trial. They were randomly assigned to receive either taurine or placebo, 6 g/day, for 7 days. For each test procedure the subject was supine and had an indwelling catheter inserted in an arm vein. At least 30 min after insertion of the indwelling catheter, but not before the patient was subjectively relaxed and had a stable pulse rate, blood for the determination of catecholamines was drawn. This procedure was repeated in each patient before and after treatment with taurine or placebo.

Protocol 2. After screening visits, 12 patients with borderline hypertension and nine normal subjects were admitted to the trial. An indwelling catheter was placed in the antecubital vein through which isotonic solution was slowly infused at a rate of 1.0 ml/min while subjects were kept at rest in a supine position. This catheter was also used for blood sampling and the injection of glucagon. Blood pressure and pulse rate were measured serially by an automated sphygmomanometer (Dinamap 845XT, Critikon, FL) every 1 min. After a 30 min observation period, blood was drawn for the measurement of plasma catecholamines, PRA, aldosterone concentration, and taurine concentration, and then 1.0 mg of glucagon (Novo Industri A/S, Copenhagen, Denmark) was injected intravenously as a bolus. The blood pressure and pulse rate were then measured at 1 min intervals, and blood specimens for determination of plasma catecholamines were obtained at 1, 2, 3, 5, and 10 min after the injection of glucagon. The same procedure was repeated after taurine was administered in an oral dose of 6 g/day for 7 days.

Laboratory procedures. Adequacy of urine collection was checked by daily creatinine determinations. Sodium and potassium concentrations in the urine were determined by flame photometry, with the use of lithium as an internal standard. Circulating norepinephrine and epinephrine were determined by the radioenzymatic method, as previously reported. Plasma aldosterone concentration was measured by radioimmunoassay as previously reported. For the measurement of serum and urinary taurine concentrations, serum and 24 hr urine samples were deproteinized with sulfosalicylic acid and the deproteinized samples were analyzed on a Durrum D-500 amino acid analyzer. Statistical analysis. Values are expressed as the mean ± SE. A paired t test was used for analysis of data before and after the
administration of taurine. Comparison of results in the borderline hypertensive and normotensive subjects was by the unpaired t test. Total epinephrine release after stimulation with glucagon was determined by calculating the areas under the plasma concentration curves between 0 and 10 min. The areas under the curves were compared by paired or unpaired t tests. Data on responses of blood pressure, heart rate, and plasma epinephrine and norepinephrine to glucagon were analyzed by analysis of variance and the Bonferroni method for multiple comparisons.28 Statistical significance was defined as p < .05.

Results

Study 1. Table 1 shows the changes in blood pressure and plasma catecholamines after taurine in 19 young patients with borderline hypertension studied in a double-blind, placebo-controlled fashion. Systolic and diastolic blood pressure fell in the treatment group by 9.0 ± 2.9 and 4.1 ± 1.7 mm Hg, respectively, while blood pressure in the control group decreased by 2.7 ± 2.3/1.2 ± 3.0 mm Hg. Mean blood pressure decreased by 5.7 ± 1.8 mm Hg in taurine recipients (p < .05 by paired t test) compared with a decrease of 1.7 ± 2.0 mm Hg in placebo recipients (NS). In the 10 subjects receiving taurine, plasma epinephrine also significantly (p < .01) decreased (from 65.3 ± 6.3 to 50.7 ± 4.2 pg/ml), but plasma norepinephrine did not change (from 245.8 ± 18.6 to 223.5 ± 21.5 pg/ml, NS). In the nine subjects receiving placebo, neither plasma epinephrine nor norepinephrine changed significantly (65.3 ± 5.7 to 64.6 ± 4.0 pg/ml and 221.3 ± 22.1 to 202.0 ± 27.7 pg/ml, respectively). Thus, the average plasma concentration of epinephrine after taurine was significantly lower than that after placebo (50.7 ± 4.2 vs 64.6 ± 4.0 pg/ml, p < .05 by unpaired t test).

Study 2. Table 2 summarizes clinical and laboratory findings in borderline hypertensive patients and age-matched normal subjects before and after the administration of taurine. There were no significant differences with respect to age or body weight in the groups. In borderline hypertensive patients there was a significant increase in mean blood pressure as compared with that in the normotensive subjects. There were no significant differences in plasma creatinine, sodium, or potassium levels in the borderline hypertensive and the normotensive subjects. Plasma epinephrine was significantly (p < .05) increased in the borderline hypertensive as compared with the normotensive subjects (62.6 ± 9.0 vs 41.0 ± 5.4 pg/ml), although there were no significant differences in PRA, plasma aldosterone, or plasma norepinephrine in the two groups. There were also no significant differences in plasma taurine concentration or in urinary taurine excretion in the two groups. During the administration of taurine, both plasma and urinary taurine increased equally in both groups. More than 90% of daily taurine intake was excreted in the urine, indicating good compliance with therapy.

With the administration of taurine, mean blood pressure was significantly (p < .05) decreased from 101.0 ± 2.1 to 93.6 ± 2.4 mm Hg in the borderline hypertensive patients but it did not decrease significantly in the normal subjects (87.3 ± 2.0 to 83.5 ± 1.9 mm Hg, NS). With taurine, plasma epinephrine was significantly (p < .05) decreased (from 62.6 ± 9.0 to 45.8 ± 7.3 pg/ml) to a level similar to that in normotensive subjects (41.0 ± 5.4 pg/ml). However, in the normotensive subjects taurine did not significantly change plasma epinephrine (41.0 ± 5.4 to 35.3 ± 3.8 pg/ml, NS). Thus, the mean decrements in mean blood

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**Table 1**

<table>
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<th>Taurine (n = 10)</th>
<th>Placebo (n = 9)</th>
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<td>After</td>
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<tr>
<td>SBP (mm Hg)</td>
<td>147.9 ± 6.3</td>
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<td>95.6 ± 1.7^a</td>
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</tr>
<tr>
<td>Decrease in PE (pg/ml)</td>
<td>14.6 ± 4.7</td>
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Values are mean ± SE.

^p < .05 (vs before taurine, by paired t test).

^p < .05 (vs after taurine, by unpaired t test).
pressure were \(-7.4 \pm 2.8\) mm Hg \((p < .05)\) in the borderline hypertensive patients and \(-3.8 \pm 2.2\) mm Hg \((NS)\) in the normotensive subjects. Accordingly, the mean decrements from basal plasma epinephrine were \(-17.0 \pm 5.2\) pg/ml \((p < .05)\) and \(-5.7 \pm 4.5\) pg/ml \((NS)\), respectively, in hypertensive and normotensive subjects. There were no significant changes in serum and urinary electrolytes, PRA, plasma aldosterone, or plasma norepinephrine with the administration of taurine in either group (table 2).

Overall, there was a significant correlation \((r = .670, p < .01)\) between the decrements in mean blood pressure and those in plasma epinephrine in the 22 subjects with borderline hypertension receiving taurine (figure 1).

Figure 2 illustrates the changes in plasma epinephrine after stimulation with glucagon. Bolus intravenous injection of glucagon induced an immediate rise in blood pressure, heart rate, and plasma epinephrine in each subject studied. Plasma epinephrine reached a peak concentration 2 to 5 min after the injection of glucagon and thereafter declined rapidly to reach the baseline level by 10 min after the injection in both borderline hypertensive and normotensive subjects. Throughout the experimental period, however, plasma norepinephrine did not significantly change in either group. There was no apparent difference with respect to timing of the response of plasma epinephrine in the borderline hypertensive and normotensive subjects, but the response tended to be of greater magnitude earlier in the borderline hypertensive than in the normotensive subjects: the increments in plasma epinephrine at 2 and 3 min after glucagon were significantly greater in the borderline hypertensive than normotensive subjects \((44.0 \pm 12.3 vs 5.2 \pm 4.5\) pg/ml, \(p < .01\), and \(68.8 \pm 13.2 vs 32.1 \pm 8.9\) pg/ml, \(p < .05\).
respectively). When the areas under the plasma concentration curves were analyzed, the mean area after the injection of glucagon was $328 \pm 43$ pg·min/ml for the hypertensive subjects, which was significantly ($p < .05$ by unpaired t test) greater than $175 \pm 45$ pg·min/ml for normal subjects. However, there were no significant differences in the changes of mean blood pressure or heart rate with the injection of glucagon in the borderline hypertensive and the normotensive subjects.

With the administration of taurine, the response of plasma epinephrine to glucagon was significantly attenuated in the borderline hypertensive but not in the normotensive subjects. The increments in plasma epinephrine 2 and 3 min after glucagon were significantly less in the taurine-treated than the untreated subjects with hypertension ($3.0 \pm 6.3$ vs $44.0 \pm 12.3$ pg/ml, $p < .01$, and $26.4 \pm 4.5$ vs $68.8 \pm 13.2$ pg/ml, $p < .01$, respectively). When the areas under the plasma concentration curves were analyzed, the mean area was significantly decreased from $328 \pm 43$ to $147 \pm 30$ pg·min/ml ($p < .01$ by paired t test) after taurine treatment in young subjects with borderline hypertension. In the normotensive subjects, however, the administration of taurine did not significantly change the increments in plasma epinephrine 2 and 3 min after stimulation with glucagon ($2.4 \pm 3.9$ vs $5.2 \pm 4.5$ pg/ml, NS, and $16.9 \pm 7.4$ vs $32.1 \pm 8.9$ pg/ml, NS, respectively). Areas under the plasma concentration curves also did not change with taurine treatment in this group of subjects ($101 \pm 40$ vs $175 \pm 45$ pg·min/ml, NS). The administration of taurine did not change the responses of mean blood pressure, heart rate, or plasma norepinephrine to glucagon injection in either group.

Discussion
Our primary finding, in keeping with previous reports,5-7 was that plasma epinephrine was increased in young patients with borderline hypertension compared
with that in the age-matched normotensive subjects. Moreover, our study showed that there was an increased response of plasma epinephrine to stimulation with glucagon in young borderline hypertensive subjects as compared with that in normotensive subjects. This finding is consistent with the results of a previous study showing that the response of urinary catecholamines to the intramuscular injection of glucagon was significantly increased in young hypertensive patients but not in elderly hypertensives.29 The observations of increased levels of plasma epinephrine and an increased response of plasma epinephrine to glucagon in young subjects with borderline hypertension might suggest increased sympathoadrenal tone. Over the past 30 years, there has been a growing realization of the importance of the role of adrenomedullary function in the development and maintenance of animal and human hypertension.30-32 In DoCA-salt-induced hypertension the conversion of radioactive tyrosine into catecholamines was found to be increased in the adrenal glands,30 and the observed amelioration of hypertension resulting from bilateral adrenalectomy indicates that increased adrenal catecholamine synthesis might contribute to the maintenance of high blood pressure.31 Furthermore, a reduction in blood pressure was observed in a significant proportion of hypertensive patients undergoing sympathectomy, splanchcotomy, and partial adrenalectomy before oral preparations of antihypertensive drugs were available.32 Recently, much evidence has been presented suggesting that excessive release of peripheral catecholamines, especially epinephrine, in response to stressful stimuli may play a role in the development of essential hypertension.6-7 Several recent studies have demonstrated that in young borderline hypertensive patients there is not only an increased response of plasma norepinephrine but also of epinephrine to physical stress such as standing8 or to mental stress such as arithmetic, suggesting a net increase in the sympathoadrenal tone.8, 9

We performed another study in a double-blind, placebo-controlled fashion to determine whether oral administration of taurine would be an efficacious therapeutic modality in young patients with borderline hypertension. After 1 week of 6 g/day of taurine or placebo, blood pressure decreased by an average of 9.0 ± 2.9/4.1 ± 1.7 mm Hg in the taurine-treated group, as compared with a negligible decrease in blood pressure in the placebo-treated group. While small, this effect of taurine on mean blood pressure (a decrease of 5.7 ± 1.8 mm Hg compared with a decrease of 1.7 ± 2.0 mm Hg in the control group) may be clinically significant, since Rose33 has pointed out that decreasing the mean blood pressure in a large population by as little as 3 mm Hg will reduce the number of individuals with mild hypertension, and thus substantially reduce the number of people at excess risk of cardiovascular morbidity and mortality. Borderline hypertension appears to be an early predictor of future established hypertension, and it carries an excess of overall mortality and specific cardiovascular morbidity.1, 2 We speculate, therefore, that high dietary intake of taurine might be effective protection from the development of established hypertension and the excess risk of cardiovascular morbidity and mortality. However, in the present study the sample size was too small and the observation period too short to draw any conclusions about this issue.

Concomitant with the reduction of blood pressure, plasma epinephrine decreased significantly in the taurine-treated group while there was only a negligible decrease in plasma epinephrine in the placebo group. In another study, oral administration of taurine returned increased plasma levels of epinephrine toward normal in the young borderline hypertensive patients, but did not change it in the normotensive subjects. Overall, there was a significant relationship between the decrements in blood pressure and those in plasma epinephrine with taurine in 22 young patients with borderline hypertension, suggesting that the antihypertensive action of taurine may be attributable to the normalization of the increased sympathoadrenal tone. This hypothesis is supported by results of a study in vitro demonstrating that taurine inhibits the stress-induced release of epinephrine from adrenal chromaffin granules.24

In the present study, the oral administration of taurine attenuated the increased response of plasma epinephrine to stimulation with glucagon in the young patients with borderline hypertension when plasma taurine concentration was increased to five times that at baseline. In contrast, the administration of taurine did not significantly decrease blood pressure or basal plasma epinephrine concentrations, nor did it change the response of plasma epinephrine to glucagon in the normotensive subjects, although the increments in plasma taurine were the same in these subjects as in the borderline hypertensive patients.

Thus, our results suggest that taurine reduces blood pressure by the normalization of increased sympathoadrenal tone in the presence of borderline hypertension, but it does not affect adrenomedullary activity or blood pressure in normotensive subjects with normal sympathoadrenal tone. This finding is consistent with the results of our previous animal studies demonstrat-
ing that taurine supplementation attenuates the development of hypertension by the suppression of increased sympathetic activity in DOCA-salt-treated rats, but does not decrease blood pressure or sympathetic activity in vehicle-treated control rats.\textsuperscript{19}–\textsuperscript{21} Moreover, this hypothesis is supported by a previous study demonstrating that the addition of taurine in vitro significantly attenuates the Ca-dependent, K-evoked release of \( ^{3} \text{H} \)-norepinephrine from a variety of neuronal tissues without affecting uptake or unstimulated (spontaneous) release.\textsuperscript{22, 23}

It has been reported that the epinephrine in chromaffin granules of the adrenal medulla is released by the mechanism of exocytosis.\textsuperscript{34, 35} It is well known that the stress of administration of glucagon itself stimulates epinephrine release from adrenal glands.\textsuperscript{36, 37} In the adrenal medulla, calcium plays an important role in "stimulus-secretion coupling" because of its ability to form stable complexes with various constituents\textsuperscript{38} and its effects on membrane permeabilities. In this regard, it is of interest that taurine increases calcium content in the heart mitochondria and the affinity of various cellular components for calcium.\textsuperscript{39} Moreover, a recent study has suggested that taurine inhibits release of calcium from mitochondria,\textsuperscript{40} thus leading to a decrease in availability of intracellular calcium in sympathetic nerve. If these findings are applicable to the adrenal medulla, the administration of taurine might modulate the glucagon-induced release of epinephrine from adrenal medulla, possibly by interacting with retention mechanisms for calcium within adrenal granules.

In summary, young patients with borderline hypertension had significantly higher mean plasma levels of epinephrine under basal conditions and significantly larger increments in plasma epinephrine in response to glucagon than did age-matched normotensive control subjects. Oral administration of taurine abolished these differences. Evidence presented suggests, therefore, that sympathoadrenal tone is increased in young patients with borderline hypertension and that taurine attenuates this increased tone, leading to a reduction in blood pressure. Thus, taurine may be helpful in the management of these patients.

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