Chronic Dietary Tyrosine Supplements Do Not Affect Mild Essential Hypertension

MICHAEL J. SOLE, CLAUDE R. BENEDICT, MARTIN G. MYERS, FRANS H.H. LEENEN, AND G. HARVEY ANDERSON

SUMMARY The blood pressure and plasma norepinephrine response to oral tyrosine, the precursor of norepinephrine, supplementation (2.5 g t.i.d.) of regular meals was examined in 13 untreated patients with mild essential hypertension. Using a randomized double-blind crossover design, each 2-week treatment was followed by a 2-week supplement-free interval. Supine and standing blood pressure and plasma norepinephrine levels were measured at the beginning and end of each 2-week treatment. Plasma tyrosine levels increased \((p<0.001)\) from 71.2 ± 8.0 nM/ml at baseline to 152.8 ± 17.4 nM/ml 2 hours after the tyrosine supplement. Blood pressure under control conditions was 144 ± 3 mm Hg systolic, 91 ± 2 mm Hg diastolic (109 ± 2 mm Hg mean) after 30 minutes in the supine position and 148 ± 4 mm Hg systolic, 102 ± 3 mm Hg diastolic (117 ± 3 mm Hg mean) after 5 minutes of standing. Plasma norepinephrine levels were 191 ± 18 pg/ml in the supine subjects and 390 ± 33 pg/ml in the standing subjects. No differences in systolic, diastolic, or mean blood pressure, heart rate, or plasma norepinephrine levels were seen between the beginning and end of each period or between groups. Individual changes in blood pressure showed no correlation with individual changes in norepinephrine levels. These results indicate that the addition of a tyrosine supplement to the usual diet of mild hypertensive subjects has no beneficial effect on blood pressure.

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KEY WORDS • plasma norepinephrine • diet • amino acid • catecholamines

The synthesis of catecholamines by the brain\(^1\) and sympathoadrenal system\(^3\) appears to be partially controlled by the availability of their amino acid precursor tyrosine. This relationship has been reported to be of functional importance in animals; for example, short-term administration of tyrosine can increase the ventricular fibrillation threshold in dogs\(^4\) and reduce blood pressure in hypertensive rats,\(^5\) apparently by increasing brain norepinephrine synthesis and reducing cardiovascular sympathetic tone. These data have suggested therapeutic approaches to the treatment of human disease involving modifications in the dietary content of tyrosine. Although the reduction of blood pressure in patients with hypertension prevents premature cardiovascular disease, the risk/benefit ratios of the pharmacological approaches differ; in particular, the value of medicating patients with mild or borderline hypertension but without target organ damage is the subject of considerable debate.\(^6\) In these circumstances a therapeutic approach involving a modification of diet has particular appeal.

Tyrosine is readily available as a free amino acid (for example, in health food stores) and can be consumed alone or added to food as a supplement. The new sugar substitute aspartame (1-methyl N-L-alpha-aspartyl-L-phenylalanine), approved as an additive to foods and beverages, provides such a dietary source through the conversion of phenylalanine to tyrosine by the liver.\(^9\) Indeed, the suggestion has been made that aspartame ingestion has the potential to induce changes in brain or sympathoadrenal neurochemistry with resultant behavioral or functional sequelae.\(^9\) We therefore thought it important to examine the functional consequences of increased tyrosine ingestion by humans. We recently reported a decrease in plasma norepinephrine concentration during short-term tyrosine feeding in normotensive men,\(^10\) which supports the suggestion that tyrosine ingestion may be a beneficial therapeutic strategy for the control of human hypertension. Thus, in the present study, we examined the
blood pressure and plasma norepinephrine responses to oral tyrosine supplementation of regular meals in humans with mild essential hypertension.

Methods
Thirteen patients (9 men, 4 women), ranging in age from 20 to 64 years, with mild essential hypertension gave informed consent for participation in the study, previously approved by the Human Ethics Committee of the University of Toronto. All of the patients either were receiving no therapy or had discontinued all therapy at least 1 month before the study. None of the patients had evidence of renal or hepatic disease, evident atherosclerotic heart disease, or known secondary causes of hypertension. All subjects were studied as outpatients and were instructed to continue their regular meal and dietary patterns. The study employed a randomized, double-blind, crossover design. On entry each subject underwent a series of baseline measurements including a 12 lead electrocardiogram and blood sampling for routine hematological and biochemistry tests. Each subject then received L-tyrosine (2.5 g of the free base three times a day) or matching placebo (lactose) in capsules, which they were to take with their usual meals for a 2-week period; there was then a 2-week supplement-free interval followed by crossover to the final 2-week treatment. The order of treatments was randomly allocated. To encourage compliance the patients were asked to maintain their normal diet. Compliance was tested by pill count and plasma tyrosine levels.

The patients were studied at the beginning and end of each treatment period. On the study day, the supplement or placebo was taken at 0800 hours with breakfast; the study began at 1000 hours. Samples for venous plasma norepinephrine and tyrosine levels were taken from an indwelling cannula, and blood pressure was measured by cuff and mercury sphygmomanometer; these measurements were made after the subject had been supine for 30 minutes and again after 5 minutes of standing. Free plasma norepinephrine was measured by the radioenzymatic method of Sole and Hussain with modifications. Tyrosine was measured on an amino acid analyzer (Beckman Instruments, Palo Alto, CA, USA). Values are reported as mean ± SEM, and the data were analyzed using a Student's paired t test (two-tailed analysis). We also tested for treatment by period interaction.

Results
None of the subjects experienced any adverse effects, and all were able to function normally throughout the study; no overt changes in dietary habit were noted. The concentration of plasma tyrosine increased almost twofold 2 hours after the tyrosine supplement period (Figure 1). None of our patients exhibited plasma norepinephrine concentrations outside of the normal range (<400 pg/ml); 5 minutes of standing led to an approximate doubling of the supine value (see Figure 1). There was a small but insignificant reduction in the levels of plasma norepinephrine (see Figure 1) after tyrosine administration.

We did not observe any differences in heart rate or in systolic, diastolic, or mean blood pressure, either supine or standing, between the beginning and end of each period or between placebo and tyrosine treated groups (Figures 2 and 3; B < 0.20 for a 6 mm Hg decrease with tyrosine relative to placebo). Individual changes in blood pressure showed no correlation with individual changes in plasma norepinephrine levels.

Discussion
The normal Western diet contributes 5 to 9 g of tyrosine daily to the body's tyrosine pool through the digestion of proteins containing tyrosine or phenylalanine (which can be hydroxylated to tyrosine by the liver) or both. Strategies for the treatment of disease that alter the composition of an individual's daily diet may be limited in their success because of poor patient compliance. We therefore elected to allow our volunteers to maintain their usual dietary regimen and employed supplements of tyrosine calculated to approximately double their daily intake of this amino acid; this was reflected by the twofold increase in tyrosine concentrations we observed in their plasma. A similar dietary program of supplemental tyrosine has been reported to maintain this relative increase for most
of each 24-hour period\textsuperscript{13,15} and to enhance urinary excretion of metabolites of both norepinephrine and dopamine.\textsuperscript{1}

Brain tyrosine concentration reflects that in plasma.\textsuperscript{16,17} Although this concentration appears to exceed the $K_m$ (25 $\mu$M) for tyrosine hydroxylase,\textsuperscript{18} the rate-limiting step for norepinephrine biosynthesis, studies have shown that an increase in brain tyrosine can lead to an increase in brain norepinephrine synthesis.\textsuperscript{1,2,16,18} A twofold increase in plasma tyrosine is reported to be optimal for this biosynthetic enhancement in rats, whereas larger increases may actually inhibit brain norepinephrine synthesis.\textsuperscript{19} Although indirect, two lines of evidence suggest that tyrosine supplements can alter brain norepinephrine synthesis in the human. First, in one study in which quantities of tyrosine identical to those used in the present study were added to diets of normal weight women, both plasma levels and the 24-hour urinary excretion of 3-methoxy-4-hydroxyphenylglycol were increased.\textsuperscript{3} There is good evidence that a proportion of this metabolite is of central origin.\textsuperscript{3,16,20} Second, in a recent study,\textsuperscript{10} we found that similar supplements of tyrosine given over a 3-day period decreased plasma norepinephrine levels. A similar plasma norepinephrine response can be seen following the stimulation of either central noradrenergic receptors by clonidine\textsuperscript{21,22} or central dopaminergic receptors by bromocriptine\textsuperscript{23,24} in both normotensive and hypertensive patients. In the latter group of patients, a fall in blood pressure was also observed. These data suggest that dietary tyrosine supplements may be useful as a therapeutic approach for the treatment of hypertensive patients. Such a hypothesis is supported directly by studies showing that the short-term administration of tyrosine by intraperitoneal\textsuperscript{5,7} or intraventricular\textsuperscript{25} injection is effective in decreasing blood pressure in hypertensive rats.

All of our patients had mild essential hypertension. The levels of supine and standing venous plasma norepinephrine in all of the participants were within normal range, with none falling into the so-called hyperadrenergic category.\textsuperscript{26,27} Our experiments clearly demonstrated that in this particular category of hypertensive patients a doubling of plasma tyrosine levels by dietary supplements has no effect on either plasma catecholamines or blood pressure when patients are evaluated after 2 weeks. Our failure to observe a decrease in plasma norepinephrine in these hypertensive subjects after tyrosine, as compared to the decrease found in our previous short-term study of normal volunteers,\textsuperscript{10} is difficult to explain. It might be attributed to an altered responsiveness to tyrosine in hypertensive patients; however, as both hypertensive and normotensive patients exhibit decreases in plasma norepinephrine following pharmacological stimulation of bulbar noradrenergic activity by clonidine\textsuperscript{21,22} or bromocriptine,\textsuperscript{21,22} such a qualitative difference in response seems unlikely. Tyrosine administration has been hypothesized to be more effective in neurons with an increased firing frequency.\textsuperscript{20} Perhaps brain noradrenergic activity in our hypertensive patients, like that in some hypertensive paradigms,\textsuperscript{28} was depressed sufficiently to mitigate a marked tyrosine effect. It is also possible that, although short-term tyrosine administration affects blood pressure in spontaneously hypertensive rats and plasma norepinephrine concentration in humans, homeostatic mechanisms obviate these effects in the longer term.
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