The influence of oral tyrosine and tryptophan feeding on plasma catecholamines in man[1-3]

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ABSTRACT We investigated the effects of oral tyrosine (7.5 g/day) and oral tryptophan (3 g/day) feeding with regular meals in normal male volunteers using a double-blind cross-over design with a "run in" period for acclimatization. Oral tyrosine feeding significantly decreased both free and conjugated plasma norepinephrine concentrations while oral tryptophan feeding did not have such an effect. Since α adrenergic stimulation in certain areas of the CNS has been shown to decrease peripheral sympathetic tone, we postulate that dietary tyrosine supplementation in man causes an increase in brain catecholaminergic activity which in turn leads to a decrease in peripheral sympathetic activity as evidenced by the decrease in plasma catecholamines. *Am J Clin Nutr* 1983;38:429–435.

KEY WORDS Plasma norepinephrine, oral tyrosine and tryptophan feeding, conjugated and free catecholamines

Introduction

Studies over the past decade have shown that the synthesis of the neurotransmitters serotonin and catecholamines is partially controlled by the availability of their amino acid precursors tryptophan and tyrosine, respectively (1, 2). Furthermore, this precursor control of neurotransmitter synthesis has been shown to have physiological relevance in both experimental animals and man. For example, manipulation of tryptophan intake alters some of the putative functions of brain serotonin including the control of pituitary hormone secretion (3), sleep patterns (4, 5), and perception of pain (6, 7). Similarly the administration of tyrosine may modify blood pressure (8), ventricular fibrillation threshold (9), and the symptoms of Parkinson's disease (10).

Supporting the evidence that physiological or pharmacological doses of precursors have functional significance, there is some evidence for precursor control of neurotransmitter synthesis in human subjects. Tryptophan administration increases 5-hydroxyindoleacetic acid, the product of the serotonin breakdown, in cerebrospinal fluid (11, 12). Similarly, tyrosine feeding increases the cerebrospinal fluid concentration of homovanillic acid, a dopamine breakdown product, in patients with Parkinson's disease (10) and increases the daily excretion of dopamine, norepinephrine, and epinephrine in subjects given tyrosine for 1 day in a metabolic unit (13). There are no reports of the neurochemical responses to precursor amino acid administration to an ambulatory population using a double-blind cross-over design.

Materials and methods

Twelve healthy male volunteers aged 21 to 45 yr gave informed consent for participation in the study according to the protocol approved by the Toronto General Hospital Ethics Sub-Committee. Before admission and throughout the study period participants abstained from smoking, tea, coffee, alcohol, colas, bananas, cheese, chocolate, nuts, citrus fruits, and juices; none was on sympathetic agonists or antagonists. All the patients were studied as outpatients and continued on their regular meals and dietary pattern with the exception of the above mentioned food exclusions. The

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protocol was as follows: on day 1, all were started on placebo for 3 days (acclimatization period); on day 4, after evaluation, they were started on placebo or tryptophan (3 g/day) (six subjects) or placebo or tyrosine (7.5 g/day) (six subjects). Both amino acids were given as the free base of the L-form of the amino acid (Sigma Chemical Co, St Louis, MO). On day 7, after a second evaluation, subjects who had received either tryptophan or tyrosine were crossed over to placebo and those receiving placebo to either tryptophan or tyrosine. All the subjects returned for final evaluation on day 10 of the study. Supplements of tyrosine or tryptophan or placebo were taken with meals in three equally divided doses and the compliance was checked by determining the plasma levels of tryptophan by the method of Bloxam and Warren (14) or of tyrosine on an amino acid analyzer (Beckman Instruments, Palo Alto, CA) and by counting the number of capsules returned. The acclimatization period was single-blind and the rest of the study was performed as a double-blind protocol.

On day 4, 7, and 10, which were the days of evaluation, subjects came with a 24-h (0800 to 0800 h) urine collection about 60 to 90 min after breakfast which consisted of two slices of toast, Sanka coffee, plus the appropriate supplements of the previous 3 days. The antecubital vein was cannulated with the subjects standing and blood was drawn for plasma renin activity estimation. After resting supine for 30 min, resting heart rate and blood pressure (standard arm cuff) were determined and blood was drawn for platelet counts and for the determination of the concentrations of plasma norepinephrine (NE), epinephrine (E), dopamine (DA) and their conjugates, L-dihydroxyphenylalanine (Dopa), sodium, creatinine, platelet serotonin, and tryptophan or tyrosine. After standing for 10 min, blood pressure and heart rate were determined again and blood samples were drawn for plasma NE, E, and DA determination. The 24-h collection of urine was analyzed for urinary excretion of NE, E, DA, sodium, and creatinine. Samples taken during the acclimatization period were not analyzed.

Platelet 5HT content was measured by the radioenzymatic method of Hussain and Sole (15), plasma and urinary free catecholamines by the radioenzymatic method of Sole and Hussain (16) and plasma and urinary conjugated catecholamines by the method of Sole and Hussain using the adaptation described by Johnson et al (17). Plasma Dopa was measured by the method of Shum et al (18). Plasma renin activity was measured by the method of Stockigt et al (19). All values were reported as mean ± SEM and all the data were analyzed using "Student's" paired *t* test (two-tailed analysis). Data for the acclimatization phase were not analyzed and, thus, did not enter our calculations.

Results

Effect of tyrosine intake

All six subjects were male with an age range of 24 to 38 yr and their mean weight was 73.6 ± 4.7 kg. None of the subjects experienced any adverse effects and were able to function normally through the study period. The concentration of plasma tyrosine increased 153%, 60 to 90 min after taking the supplement of tyrosine ($p < 0.005$) (**Fig 1**). The increase was greater in individuals with smaller body weights. Plasma free NE declined 27% while plasma conjugated NE declined 20% with tyrosine intake (**Fig 2**). Both of these decreases were statistically significant at $p < 0.025$. The subject who exhibited the smallest increase in plasma tyrosine concentration also showed the smallest decline in plasma free and conjugated NE.

There were no significant changes in heart rate, blood pressure, plasma sodium level, 24-h urinary sodium excretion, or any of the other biochemical parameters with tyrosine feeding (**Table 1**). Plasma Dopa showed an increase but this increase was marginal ($p = 0.08$).

Effect of tryptophan intake

All six subjects were males with an age range of 22 to 45 yr. Their weight was 66.4 ± 6.2 kg. None of the volunteers experienced any adverse effect or drowsiness throughout the study period. Concentration of total plasma tryptophan increased 113%, 60 to 90 min after taking the supplement ($p < 0.005$) (Fig 1). Despite the increase in plasma tryptophan concentration there were no significant changes in heart rate, blood pressure, platelet serotonin concentration, plasma sodium level, 24-h urinary sodium excretion, or any of the other biochemical parameters measured (**Table 2**).

Discussion

Tyrosine is fairly abundant in dietary proteins with normal daily consumption amounting to 3 to 4 g. In addition, another 2 to 3 g/day is presented to body tissues because at least half of the ingested phenylalanine in protein is converted to tyrosine by the liver (20). Unlike tyrosine, tryptophan is scarce in most dietary proteins and dietary consumption is usually less than 1 to 2 g/day. Thus our volunteers received approximately 1.5 to 2 times the normal intake of tyrosine or tryptophan with their regular meals. With tryptophan administration we failed to show any change in any of our biochemical measurements despite a signif-

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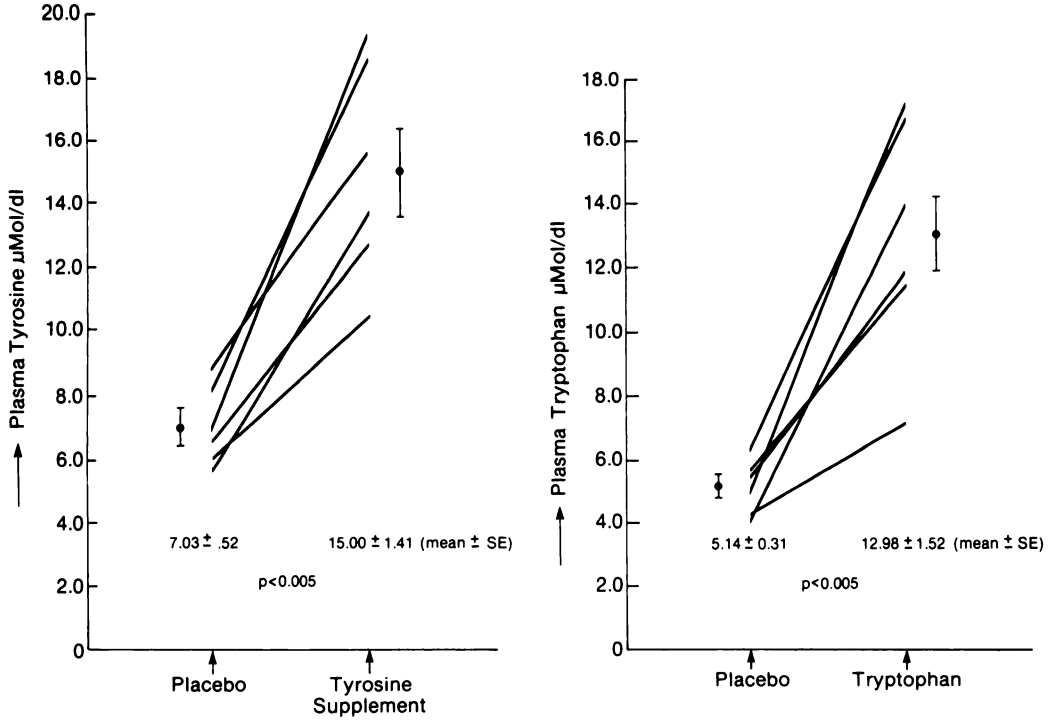

FIG 1. Increase in plasma tryosine and tryptophan concentrations with appropriate animo acid supplementation.

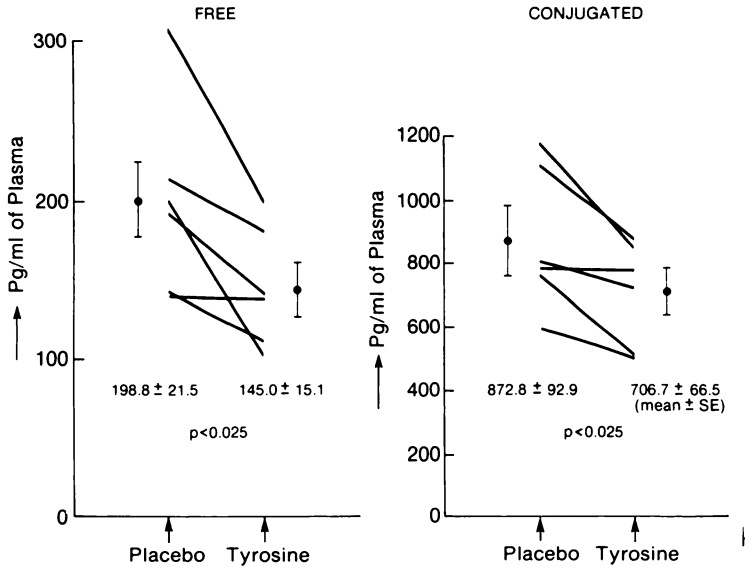

FIG 2. Changes in free and conjugated norepinephrine concentrations with tyrosine feeding.

icant increase in plasma tryptophan concentration; our observations are in contrast to some previous reports. A change in platelet serotonin content has been reported after the administration of 100 mg/kg of tryptophan in a single dose (21). Similarly, a small but significant increase in plasma catecholamines has been shown after a single dose of two grams of tryptophan to seven subjects (22). Also, Zimmerman and Ganong (23)

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TABLE 1
Changes in biochemical parameters (mean ± SE) in plasma and urine with tyrosine supplementation

	Placebo	Tyrosine
Plasma (supine; pg/ml)		
Free NE	198.8 ± 25.1	145.0 ± 15.1*
Conjugated NE	872.8 ± 92.9	706.7 ± 66.5*
Percentage change in free NE on standing	143.2 ± 30.6	118.2 ± 17.0
Free E	51.2 ± 11.2	38.7 ± 7.8
Conjugated E	202.8 ± 16.6	224.3 ± 22.8
Free DA	36.8 ± 3.9	24.2 ± 5.0
Conjugated DA	3987.0 ± 1217.9	3038.5 ± 557.0
Plasma renin activity (ng/ml/h)	4.2 ± 0.16	4.4 ± 0.28
Plasma Dopa	2.4 ± 0.32	3.2 ± 0.41
Urine (μg/g creatinine)		
Free NE	27.7 ± 6.4	22.9 ± 3.3
Conjugated NE	100.2 ± 34.9	82.5 ± 22.9
Free E	10.5 ± 2.3	8.8 ± 1.5
Conjugated E	31.0 ± 6.9	23.6 ± 4.9
Free DA	148.8 ± 26.5	165.4 ± 37.1
Conjugated DA	501.3 ± 119.2	539.1 ± 125.0
Urine sodium (mEq/24 h)	228.4 ± 19.2	229.7 ± 10.2
Mean blood pressure	75.3 ± 1.7	77.0 ± 1.3
Heart rate (beats/min)	61.7 ± 2.5	61.7 ± 2.3

* $p < 0.025$ versus placebo.

administered 20 mg/kg of tryptophan parenterally to dogs and noted a significant rise in plasma renin activity. It is possible that our failure to find alterations in platelet serotonin or plasma catecholamines or renin activity after 3 days of treatment was due to a compensatory change in the biosynthetic pathway for serotonin or some other adaptive neurochemical mechanism (24). Furthermore it appears that tryptophan administered daily in single doses greater than 50 mg/kg results in the induction of hepatic tryptophan pyrrolase (25). In addition to increased tryptophan catabolism it is worth noting that much of the tryptophan is converted to kynurenine (26). Increased levels of kynurenine interferes with tryptophan transport into rat brain (26, 27) with doses of tryptophan exceeding 50 mg/kg actually lowering the amount of tryptophan transported into the brain (28). Thus apparent physiological changes induced by single large doses may be related to excessive levels of kynurenine rather than to an induction of brain serotonin synthesis; it is also possible that such high levels of tryptophan could

TABLE 2
Changes in biochemical parameters (mean ± SE) in plasma and urine with tryptophan supplementation

	Placebo	Tryptophan
Plasma (supine; pg/ml)		
Free NE	232.0 ± 40.0	263.3 ± 34.2
Conjugated NE	825.0 ± 167.9	950.0 ± 88.1
Free E	75.5 ± 13.3	68.3 ± 10.8
Conjugated E	264.0 ± 41.3	231.2 ± 25.4
Free DA	32.3 ± 3.2	36.2 ± 6.7
Conjugated DA	3623.3 ± 290.7	2848.5 ± 269.2
Plasma renin activity (ng/ml/h)	3.6 ± 0.2	3.9 ± 0.3
Urine (μg/g creatinine)		
Free NE	30.7 ± 4.7	28.6 ± 4.9
Conjugated NE	80.2 ± 13.5	77.5 ± 20.0
Free E	14.1 ± 2.3	13.3 ± 2.9
Conjugated E	29.2 ± 5.2	26.5 ± 6.1
Free DA	186.3 ± 36.2	156.8 ± 40.0
Conjugated DA	543.8 ± 116.0	404.9 ± 107.2
Urine sodium (mEq/24 h)	242.8 ± 31.6	242.7 ± 37.1
Platelet serotonin ($ng/10^6$ platelets)	139.2 ± 18.9	148.1 ± 21.1
Platelet poor plasma serotonin	3.75 ± 0.85	4.82 ± 0.9
Mean blood pressure (mm Hg)	82.0 ± 2.5	79.0 ± 3.9
Mean heart rate (beats/min)	61.7 ± 2.9	63.3 ± 3.5

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competitively inhibit brain tyrosine transport. Our subjects received approximately 15 mg/kg of tryptophan with each meal which, although more than doubling plasma tryptophan concentration, was well below the blood levels apparently needed to induce tryptophan pyrrolase activity or inhibit brain tyrosine transport.

Although urine norepinephrine excretion roughly parallels plasma NE concentration the relationship between the two is complex. Plasma NE represents but a moment in time whereas that in the urine represents an integration over a longer period. Furthermore, a variety of factors such as renal glomerular and tubular filtration, tubular metabolism, and renal autonomic activity must all be considered when assessing urinary NE excretion. In this study, urinary free and conjugated NE showed nonsignificant declines which appear to parallel the changes seen in plasma. This result is at variance with the one single study reporting that tyrosine loading increased urinary DA, NE, and E (13).

In that study, volunteers were admitted to a clinical investigation unit, and given a specially prepared house diet for 2 days—tyrosine supplement was added to the diet of all subjects on day 2. Our study was double-blind and placebo controlled with patients remaining on a normal ambulatory diet throughout the period. It is probable that a difference in sodium ingestion accounts for the discrepancy between the two studies. Our subjects excreted approximately 230 mEq sodium per day in the urine throughout the study (Table 1) representing the relatively high levels of daily sodium ingestion in normal North American individuals. It is very unlikely that the specially prepared clinical investigation unit diet in the Agharanya study contained such levels. As a decrease in dietary sodium leads to an increase in plasma and urinary NE (29, 30), the increase in urinary norepinephrine excretion on day 2 of the Agharanya study may merely reflect a reduction in daily sodium intake. Tyrosine administration, if more effective on neurons with an increased firing frequency (eg, renal sympathetic nerves in this case) would be expected to augment such an effect (31).

Administration of a single oral dose of tyrosine to humans increases plasma tyrosine concentration and its ratio to plasma neutral amino acids for at least 8 h (32). The ingestion of tyrosine with each meal appears to increase urinary tyrosine for approximately the full 24 h (13). Therefore, it is likely that the three divided doses of tyrosine given to our subjects maintained a relative increase in plasma tyrosine levels over the entire 3-day period.

Tyrosine administration to a normal ambulatory population appears to significantly decrease both free and conjugated plasma NE with a tendency to increase plasma Dopa. These results represent the first measurement of circulating catecholamines after tyrosine feeding.

Plasma NE appears to be a useful index of peripheral sympathetic activity while plasma E appears to reflect the level of activity of the adrenal medulla (34). The significance of plasma DA and dopa are as yet unknown (35). However, the decline in plasma NE suggests a response in the CNS to tyrosine administration. Intraperitoneal administration of tyrosine to rats subjected to cold stress have been shown to increase brain tyrosine levels and cause the accumulation of sulphate conjugated MHPG (33) suggesting the increased synthesis of brain NE and possibly E. Tyrosine supplementation has been reported to increase the urinary excretion of MHPG in humans (36). These data would support the concept that an increase in plasma tyrosine concentration increases brain tyrosine concentration, which in turn, increases the synthesis and release of brain catecholamines.

An increase in bulbar noradrenergic activity can lead to a decrease in peripheral sympathetic tone; eg, the administration of either the α agonist clonidine or the dopaminergic agonist bromocriptine has been reported to reduce the level of circulating NE in man (37–39) presumably by their effects on the CNS (37, 40). These data are consistent with the hypothesis that the oral administration of tyrosine, by increasing the synthesis of brain catecholamines, results in the stimulation of central catecholaminergic receptors with a resultant decrease in the release of NE by peripheral sympathetic nerves.

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The changes in blood pressure and heart rate we observed were small despite the significant change in circulating NE. Sved et al (8) observed a similar lack of blood pressure and heart rate response in normotensive rats after the administration of tyrosine; spontaneously hypertensive rats, on the other hand, exhibited a marked decrease in blood pressure. Our findings warrant the investigation of the possible effects of tyrosine administration to patients with hypertension or other clinical conditions associated with excessive sympathetic nervous system activity.

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