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ELEVATION OF PLASMA TYROSINE AFTER A SINGLE ORAL DOSE OF L-TYROSINE[1]

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Summary

Plasma tyrosine concentrations in twelve normal, fasting human subjects were significantly elevated 2-8 hours after they ingested 100 mg/kg or 150 mg/kg tyrosine. Mean plasma tyrosine levels were maximal after 2 hours, rising from 69 ± 3.9 to 154 ± 9.5 nmols/ml ($\bar{X}$ ± SEM) after the 100 mg/kg dose and to 203 ± 31.5 nmols/ml after the 150 mg/kg dose ($p \leq 0.001$ for both doses). The mean tyrosine ratio (defined as the ratio of plasma tyrosine concentration to the sum of the concentrations of six other neutral amino acids that compete for the same blood-brain barrier uptake system) increased from 0.10 ± 0.02 to 0.28 ± 0.04 ($\bar{X}$ ± SEM) 2 hours after the 100 mg/kg dose ($p \leq 0.001$) and to 0.35 ± 0.05 2 hours after the 150 mg/kg dose ($p \leq 0.005$). No side effects of orally-administered L-tyrosine were noted.

Circulating tyrosine is the major physiological precursor of brain dopamine and norepinephrine (1); its availability to brain neurons can influence the rates at which neurons synthesize these transmitters (2,3). Tyrosine enters the brain by an uptake system in the blood-brain barrier that is shared with other neutral amino acids (NAA) such as valine, leucine, isoleucine, phenylalanine, methionine, and tryptophan (4). The flux of tyrosine into the brain, as well as steady-state brain tyrosine levels, generally depend on the ratio of the plasma tyrosine concentration to the

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sum of the plasma concentrations of the competing NAA (i.e., the tyrosine ratio) (2,3). Thus, tyrosine administration to rats increases the plasma tyrosine ratio, elevates brain tyrosine levels, and, under appropriate conditions, accelerates dopamine and norepinephrine synthesis (5,6). If a similar sequence occurred in humans, L-tyrosine might be useful for treating diseases in which physicians wished to enhance catecholaminergic neurotransmission. Few data are available on the chemical or clinical consequences of administering tyrosine to humans. In this study, we measured the effects of single oral doses of L-tyrosine on plasma tyrosine levels in normal, fasting subjects.

Materials and Methods

Twelve normal subjects, ages 18-21, participated in the study according to a protocol approved by the MIT Subcommittee on the Use of Humans as Experimental Subjects. They fasted overnight and blood was drawn for amino acid analysis at 8 a.m. the next morning. Six of the subjects (group A) ingested a single oral 100 mg/kg dose of L-tyrosine (Ajinomoto Co., Tokyo, Japan) mixed in water; the other six (group B) took a single oral 150 mg/kg dose. Both groups fasted for the next 8 hours and gave blood samples 1, 2, 3, 4, 6, and 8 hours after drinking the tyrosine mixture. All plasma samples were frozen at -20°C until they could be subjected to amino acid analysis. We monitored each subject's blood pressure (in supine and standing positions) and pulse rate every hour during the study. Plasma tyrosine levels were measured by the fluorometric method of Waalkes and Udenfriend (7); plasma tryptophan levels were measured by the method of Denckla and Dewey (8) as modified by Lehman (9) and Bloxam and Warren (10). Levels of other NAA in plasma samples deproteinized by adding sulfosalicylic acid were measured on a Beckman amino acid analyzer (Beckman Instruments, San Diego, Calif., model #119) (4).

Data were analyzed by a 3-way analysis of variance and covariance, including repeated measures (11); factors compared were dosage, hours, and concentration (or ratio). A paired t-test was used to compare data from different time segments.

Results

Plasma tyrosine levels after a single dose of L-tyrosine. The mean tyrosine level at 8 a.m. was 69 $\pm$ 3.9 nmols/ml ($\bar{X} \pm$ SEM); it rose to a peak concentration of 154 $\pm$ 9.5 nmols/ml 2 hours after ingestion of the 100 mg/kg dose of tyrosine ($p \leq 0.001$) and gradually approached fasting levels after 8 hours (Fig. 1, top panel). Mean plasma tyrosine levels were higher after the 150 mg/kg dose: they rose to 203 $\pm$ 31.5 nmols/ml within 2 hours, and were still significantly elevated after 8 hours ($p \leq 0.001$).

Plasma neutral amino acid levels after a single dose of L-tyrosine. Plasma tryptophan levels decreased slightly during the day, from an 8 a.m. mean of 65 $\pm$ 3.6 to lowest values of 53 $\pm$ 4.1 nmols/ml ($\bar{X} \pm$ SEM) in group A, and 56 $\pm$ 3.6 nmols/ml in group B (Fig. 1, middle panel). These changes in plasma tryptophan levels were not significantly correlated with tyrosine dosage or with hours elapsed after tyrosine administration. Mean plasma levels of the other NAA (valine, methionine, leucine, isoleucine, phenylalanine) also decreased slightly in both groups of subjects (Table 1), as

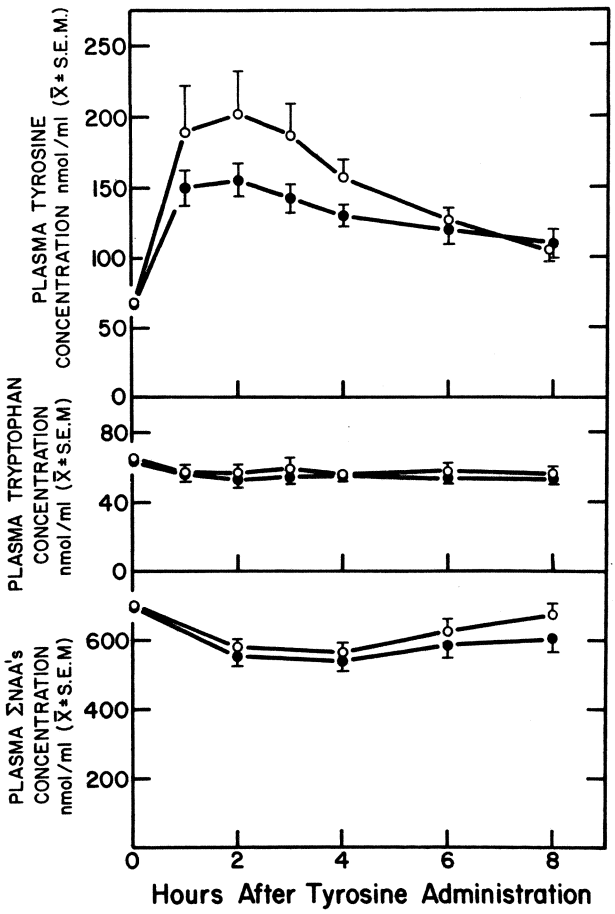

FIGURE 1

Top panel: Plasma tyrosine concentrations after L-tyrosine administration (100 mg/kg [•] and 150 mg/kg [○]). Plasma tyrosine concentrations are given as nmols/ml ($\bar{X}$ + SEM) 0, 1, 2, 3, 4, 6, and 8 hours after L-tyrosine administration.
Middle panel: Plasma tryptophan concentrations after L-tyrosine administration (100 mg/kg [•] and 150 mg/kg [○]). Plasma tryptophan concentrations are given in nmols/ml ($\bar{X}$ ± SEM) 0, 1, 2, 3, 4, 6, and 8 hours after L-tyrosine administration.
Bottom panel: Effects of L-tyrosine administration (100 mg/kg [•] and 150 mg/kg [○]) on the sum of plasma neutral amino acids. NAA included in this sum are valine, methionine, leucine, isoleucine, phenylalanine, and tryptophan. Data represent blood levels 0, 2, 4, 6, and 8 hours after L-tyrosine administration. Results are expressed in nmols/ml ($\bar{X}$ + SEM).

TABLE 1

Plasma Amino Acid Concentrations after L-Tyrosine Administration

Tyrosine dose	Hour	Valine	Methionine	Iso-leucine	Leucine	Phenyl-alanine	Tryptophan	Tyrosine
100 mg/kg	0	314 ± 19.7	36 ± 2.3	85 ± 5.6	167 ± 9.4	68 ± 2.1	65 ± 3.6	69 ± 3.9
	2	241 ± 18.0	32 ± 0.8	61 ± 3.7	131 ± 7.3	55 ± 14.5	53 ± 4.1	154 ± 9.5
	4	228 ± 17.4	30 ± 1.1	56 ± 3.4	102 ± 6.7	52 ± 2.8	55 ± 4.0	129 ± 7.7
	6	244 ± 19.3	29 ± 1.8	64 ± 3.7	138 ± 7.4	57 ± 2.5	53 ± 2.6	121 ± 11.7
	8	253 ± 18.8	30 ± 2.1	72 ± 4.0	149 ± 8.5	62 ± 3.3	53 ± 2.4	110 ± 10.4
150 mg/kg	0	314 ± 19.7	36 ± 2.3	85 ± 5.6	167 ± 9.4	68 ± 2.1	65 ± 3.6	69 ± 3.9
	2	240 ± 10.3	26 ± 3.7	58 ± 2.2	129 ± 4.3	53 ± 4.1	57 ± 4.0	203 ± 31.5
	4	242 ± 7.9	29 ± 3.2	59 ± 2.8	130 ± 5.3	49 ± 6.9	54 ± 2.5	158 ± 12.8
	6	252 ± 16.7	35 ± 2.9	70 ± 4.6	153 ± 8.2	62 ± 4.8	57 ± 4.5	128 ± 8.5
	8	266 ± 11.2	34 ± 3.0	75 ± 6.3	160 ± 10.6	63 ± 4.4	56 ± 3.6	106 ± 6.2

Plasma amino acid concentrations are given in nmols/ml ($\bar{X}$ ± SEM) 0, 2, 4, 6, and 8 hours after L-tyrosine administration (100 mg/kg and 150 mg/kg).

did the sum of their plasma concentrations (Fig. 1, bottom panel). In group A, this sum fell from 704 ± 29.2 to 543 ± 31.2 nmols/ml ($p \leq 0.001$) after 4 hours, subsequently rising to 588 ± 33.5 ($p \leq 0.05$) after 6 hours, and to 609 ± 34.2 nmols/ml after 8 hours. In group B, the sum fell to 566 ± 22.9 ($p \leq 0.05$) after 4 hours and then rose to 675 ± 24.4 nmols/ml after 8 hours (Table 1). The tyrosine ratio increased markedly in both groups 2 hours after tyrosine administration (Fig. 2), rising from 0.10 ± 0.02 to 0.28 ± 0.03 in group A ($p \leq 0.001$) and to 0.35 ± 0.05 in group B ($p \leq 0.005$). Tyrosine administration caused no significant changes in blood pressure or pulse rate; no subjects complained of side effects.

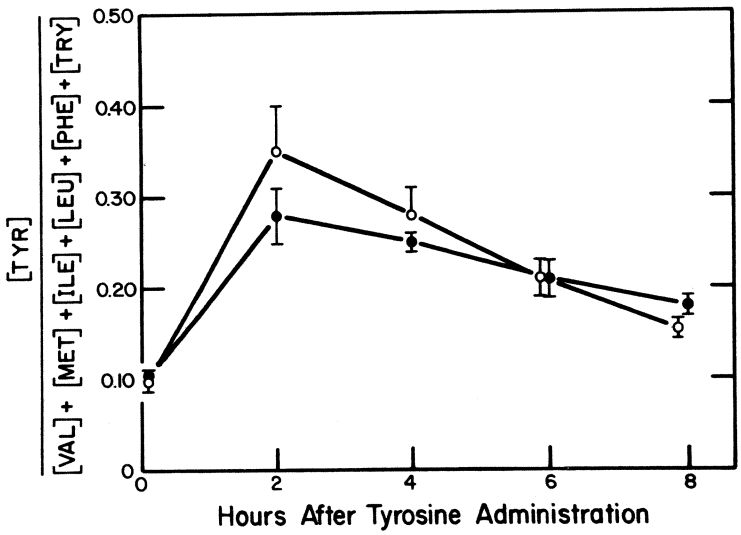

FIGURE 2

Tyrosine ratio after a single load of L-tyrosine

The plasma tyrosine ratio is presented for 0, 2, 4, 6, and 8 hours after L-tyrosine administration (100 mg/kg [•] and 150 mg/kg [o]). The tyrosine ratio is defined as the ratio of the plasma tyrosine concentration to the sum of six other NAA (valine, methionine, leucine, isoleucine, phenylalanine, and tryptophan).

Discussion

These data demonstrate that oral administration of L-tyrosine produces dose-related increases in plasma tyrosine levels in fasting subjects; these increases are maximal after 2 hours and persisted significantly for 6-8 hours. This time course is similar to those previously noted by Tocci et al. (12) in two patients given 100 mg/kg doses of tyrosine, and by Leeming et al. (13) in one patient given a 7 g load. Our basal fasting tyrosine levels are in close agreement with levels reported by Barbeau et al. (14).

The sum of the NAA did decline significantly after tyrosine administration; however, the observed change was similar to the decline seen after consumption of a protein-free diet (15). Therefore, tyrosine administration increased the tyrosine ratio (Fig. 2) proportionately more than it increased tyrosine levels (Fig. 1, top panel), and thus would be expected to facilitate markedly tyrosine's entry into the brain (4). If this facilitation also enhances brain catecholamine synthesis (1-3), tyrosine may be useful in treating patients with disorders that may be associated with deficient central catecholaminergic transmission, such as Parkinson's Disease and hypertension. Recently, Sved et al. (16) showed that tyrosine administration decreased blood pressure in hypertensive experimental animals; this effect was correlated with enhanced brain norepinephrine release and was blocked by concurrent administration of other large NAA. Tyrosine's utility in treating human hypertension apparently has not yet been examined.

The doses of tyrosine used in the present study did not produce clinically-discernible side effects. Furthermore, they did not significantly change blood pressure or pulse rate. Patients with hereditary tyrosinemia or persistent hypertyrosinemia may develop skin and eye lesions; however, their plasma tyrosine tends to be elevated to levels ten or more times greater than the peak concentrations noted in our subjects ingesting 150 mg/kg of the amino acid (17,18).

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