J. Neural Transmission 47, 299—306 (1980)

Journal of
Neural Transmission

Plasma Tyrosine in Normal Humans: Effects of Oral Tyrosine and Protein-Containing Meals

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With 1 Figure

Received January 14, 1980

Summary

To test the effects of tyrosine ingestion and concurrent food consumption on plasma tyrosine levels and on the plasma tyrosine ratio, we measured plasma neutral amino acid levels in 11 subjects who consumed a diet containing 113 g protein and who also took 100 mg/kg/day of L-tyrosine (in three equally divided doses) before meals. Plasma tyrosine levels rose significantly ($p < 0.025$) during the day when subjects consumed the diet alone; they increased markedly after tyrosine ingestion ($p < 0.005$). Tyrosine administration did not affect plasma concentrations of the other neutral amino acids that compete with tyrosine for entry into the brain. Thus, the plasma tyrosine ratio increased from 0.13 to 0.21 ($p < 0.001$) on the day fed subjects received the tyrosine. These observations indicate that tyrosine administration might increase brain tyrosine levels and perhaps accelerate catecholamine synthesis in humans with diseases in which catecholamine synthesis or release is deficient.

Introduction

Plasma amino acid levels fluctuate during the day in response to food consumption (*Wurtman*, 1970; *Fernstrom et al.*, 1979); these changes in turn affect brain tryptophan and tyrosine concentrations

0300-9564/80/0047/0299/$ 01.60

and thereby influence the rates at which neurons synthesize serotonin (*Fernstrom et al.*, 1973; *Fernstrom* and *Wurtman*, 1971 a, b) and the catecholamine neurotransmitters dopamine and norepinephrine (*Wurtman et al.*, 1974; *Gibson* and *Wurtman*, 1977; *Scally et al.*, 1977; *Gibson* and *Wurtman*, 1978). Oral tryptophan, without the other amino acids present in protein, has been used to treat diseases, such as posthypoxic intention myoclonus (*Delean et al.*, 1976), depression (*Maas*, 1975; *Mendels et al.*, 1975), and insomnia (*Hartmann*, 1976), which may result from deficient serotoninergic neurotransmission. The possible use of oral tyrosine to enhance catecholamine synthesis in humans has not, to our knowledge, been evaluated. Tyrosine administration is known to accelerate neuronal synthesis and release of catecholamines in rats (*Wurtman et al.*, 1974; *Gibson* and *Wurtman*, 1977; *Scally et al.*, 1977; *Gibson* and *Wurtman*, 1978), which suggests that it might also be useful in restoring catecholamine-dependent functions in human diseases associated with deficient catecholaminergic neurotransmission. Before testing tyrosine's utility in specific diseases, we examined the effects of short-term tyrosine administration on plasma levels of tyrosine and other large neutral amino acids in normal subjects. We previously showed that a single oral dose of L-tyrosine (100 mg/kg) produced a two-fold increase in plasma tyrosine levels and a corresponding increase in the ratio of plasma tyrosine to the sum of the plasma levels of the other neutral amino acids (the plasma tyrosine ratio) in fasting subjects (*Glaeser et al.*, 1979). In the present study, we have extended these observations to normal subjects who consumed a diet containing protein and who also took multiple doses of tyrosine. Since tyrosine's entry into the brain depends on plasma levels of other neutral amino acids present in dietary protein (*Fernstrom* and *Faller*, 1978), we compared the diet-induced changes in the plasma tyrosine ratio to those changes following the consumption of both tyrosine and protein-containing meals.

Materials and Methods

Eleven healthy male subjects, aged 18—21, participated in the study according to a protocol approved by the MIT Subcommittee on the Use of Humans as Experimental Subjects. All were admitted to the MIT Clinical Research Center for two consecutive days and nights; they entered at 7 a.m., having fasted from 8 p.m. on the previous night. On both days, the participants ingested three equal portions of a specially prepared diet at 8 a.m., 12 noon, and 5 p.m. Each meal contained 38 g protein, 112 g carbohydrate, and 44 g fat. On the second day, the subjects also consumed an aqueous suspension of L-tyrosine (100 mg/kg/day in three equal doses) at

7 a.m., 11 a.m., and 4 p.m. (Fig. 1). Blood samples were collected each day at 9 a.m., 1 p.m., 5 p.m., 9 p.m., 1 a.m., and 5 a.m.; plasma samples were frozen and stored at −20 °C until assayed. Fasting blood samples from the same subjects were obtained on a separate occasion at 8 a.m. after an overnight fast that started at 8 p.m. the previous evening. Urines were collected from 7 a.m. to 7 p.m. and from 7 p.m. to 7 a.m. on the two consecutive days. Pulse rates and arterial blood pressures were monitored in all subjects in the supine and standing positions every 3 hours during the day, and at 9 p.m. and 1 a.m. during the night. Plasma tyrosine was determined by the fluorometric technique of *Waalkes* and *Udenfriend* (1957). Plasma tryptophan was measured by the method of *Denckla* and *Dewey* (1967), as modified by *Lehman* (1971) and *Bloxam* and *Warren* (1974). Plasma levels of the other neutral amino acids were measured using a Beckman amino acid analyzer (Beckman Instruments, Cedar Grove, NJ) as previously described (*Fernstrom* and *Faller*, 1978). Data were analyzed by two-way analysis of variance and Student's *t*-test.

Results

1. Plasma Tyrosine Levels

During day I, when the subjects consumed only protein-containing meals, plasma tyrosine concentrations were highest (94—96 nmol/ml) between 1 p.m. and 9 p.m., and lowest (70 nmol/ml) at 5 a.m. (Fig. 1). Except at 1 a.m., all plasma tyrosine levels were significantly higher than the 5 a.m. plasma concentration ($p < 0.025$). During day II, when supplemental tyrosine was consumed in addition to the protein meals, all plasma tyrosine levels, except at 5 a.m., were significantly higher than the respective levels on day I ($p < 0.005$). Major increases in plasma tyrosine levels on day II persisted until at least 9 p.m., or 5 hours after the last tyrosine dose. Peak levels (178 nmol/ml at 1 p.m. and 5 p.m.) were more than double the levels observed at 5 a.m. (79 nmol/ml), and almost double the levels at comparable times on day I.

2. Plasma Neutral Amino Acids

On day I, the plasma concentrations of the large neutral amino acids valine, leucine, isoleucine, methionine, phenylalanine, and tryptophan were all higher at 1 p.m. than at 5 a.m. (Table 1). Levels of the individual amino acids (Table 1) at 1 p.m. on day I were similar to those at 1 p.m. and 5 p.m. on day II, when peak increases in plasma tyrosine levels were observed. The sums of the plasma levels of the six neutral amino acids (Fig. 1) were also very similar at 1 p.m. on days I

Table 1. *Effect of consuming protein-containing meals alone or with ingestion of tyrosine on plasma levels of the neutral amino acids and on the plasma tyrosine ratio**

Day/hour	Plasma neutral amino acid levels in nmol/ml (mean ± S.E.M.)						Plasma tyrosine ratio
	Valine	Methionine	Isoleucine	Leucine	Phenylalanine	Tryptophan	
I/1 p.m.	329 ± 16.5	41.8 ± 2.3	108.5 ± 7.2	212 ± 12.7	69 ± 2	61 ± 4.1	0.13 ± 0.004
I/5 a.m.	222 ± 16.8	29.5 ± 2.8	79.2 ± 5.9	150 ± 10.2	57.5 ± 3.8	52.2 ± 2.6	0.12 ± 0.010
II/1 p.m.	346 ± 20.3	41.3 ± 3	116.1 ± 8	224 ± 9.8	70.8 ± 3.7	64.4 ± 3.7	0.21 ± 0.08
II/5 p.m.	334.5 ± 3.3	33.9 ± 2.5	107.3 ± 6.4	212 ± 10.2	67.8 ± 2.7	86 ± 4.2	0.21 ± 0.15

Eleven normal subjects consumed identical protein-containing meals (38 g protein per meal) at 8 a.m., 12 noon, and 5 p.m. on days I and II of the study. On day II, L-tyrosine (33 mg/kg body weight) was ingested one hour before each meal.

* The ratio of plasma tyrosine level to the sum of the plasma concentrations of the other six neutral amino acids measured.

and II and at 5 p.m. on day II; all three were significantly higher than the fasting 5 a.m. value on day I ($p < 0.005$).

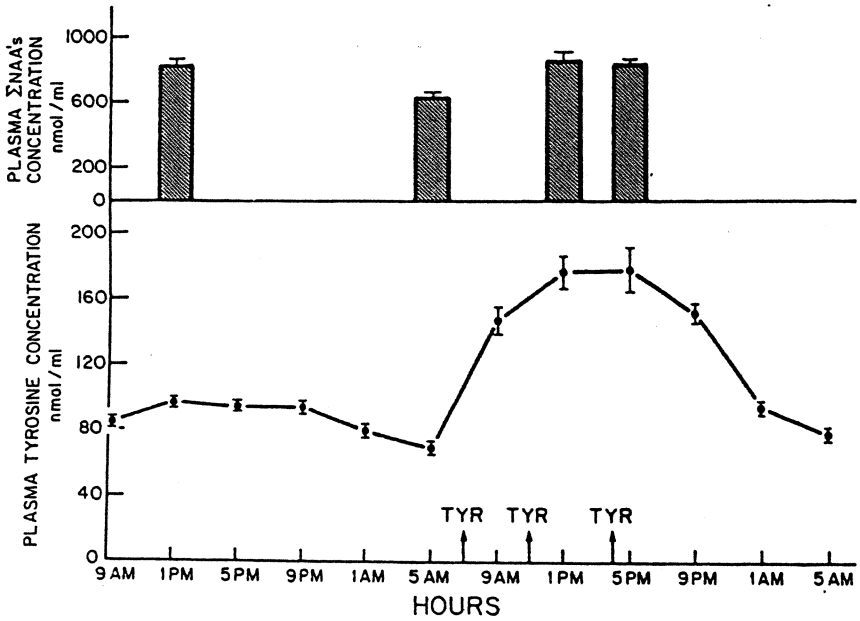

Fig. 1. Diurnal variations in plasma tyrosine levels (lower part) and in the sums of the plasma concentrations of the large neutral amino acids valine, leucine, isoleucine, methionine, phenylalanine, and tryptophan (upper part) in 11 normal, human subjects ingesting protein-containing meals alone (day I of the study) or with tyrosine supplementation (day II of the study). Identical meals, each containing 38 g protein, were consumed at 8 a.m., 12 noon, and 5 p.m. on the two consecutive days of the study. On day II, tyrosine was administered orally one hour before each meal at a dose of 33 mg/kg body weight. All amino acid levels are expressed in nmol/ml and the vertical bars represent standard errors of the mean

3. Tyrosine Ratio

In the fasting state, the mean ratio of the plasma tyrosine concentration to the sum of the six other neutral amino acids at 8 a.m. was 0.10 ± 0.05 (mean $\pm$ S.E.M.). On day I of the study, the tyrosine ratios at 1 p.m. and at 5 a.m. were 0.13 and 0.12, respectively (Table 1), and rose significantly ($p < 0.001$) to 0.21 at 1 p.m. and 5 p.m. on day II. The increases in the tyrosine ratio on day II resulted almost entirely from the greater rise in plasma tyrosine concentration, reflecting tyrosine's addition to the diet.

4. *Clinical Signs*

No significant changes were observed in blood pressure, pulse rate, or urinary volume after tyrosine administration. There were no gastrointestinal complaints, nor were abnormal neurologic or psychologic phenomena observed during this study.

Discussion

This study confirms previous reports (*Wurtman*, 1970; *Fernstrom et al.*, 1979) that plasma tyrosine levels, like those of other amino acids, normally fluctuate during the day in response to food intake. Thus, consumption of protein-rich meals causes daytime, postprandial plasma amino acid levels to rise, whereas these levels generally fall during the night, during a fast, or after low-protein, high-carbohydrate meals. In the present study, a diet that supplied 113 g protein/day produced the expected elevations in plasma levels of the neutral amino acids after meal consumption; highest plasma tyrosine levels occurred at 1 p.m., 5 p.m., and 9 p.m.; the lowest levels occurred at 5 a.m.

Ingestion of L-tyrosine one hour before each meal elevated plasma tyrosine levels much more than did an unsupplemented protein meal. Tyrosine is transported from blood to brain by a specific uptake system that it shares with other neutral amino acids, including valine, leucine, isoleucine, methionine, phenylalanine, and tryptophan (*Fernstrom* and *Faller*, 1978). The amount of tyrosine that enters the brain therefore depends on the ratio of tyrosine to the sum of the competing neutral amino acids: more tyrosine enters and is available for catecholamine synthesis when the tyrosine ratio is high, and less enters when the ratio is low. Repeated doses of tyrosine did not significantly alter the normal fluctuations in the plasma levels of the other neutral amino acids that occur during the day in response to meals. Thus, tyrosine administration increased the plasma tyrosine ratio despite the diet-induced increases in plasma levels of the other competing neutral amino acids. Since the amount of tyrosine that enters the brain depends on the plasma tyrosine ratio (*Fernstrom* and *Faller*, 1978), tyrosine administration may increase brain tyrosine levels and perhaps also catecholamine synthesis in humans consuming normal meals, as is the case with rats (*Wurtman et al.*, 1974; *Gibson* and *Wurtman*, 1977; *Scally et al.*, 1977; *Gibson* and *Wurtman*, 1978). Therefore, tyrosine may be helpful in treating diseases, such as Parkinson's disease, depression, hypertension, and hyperprolactinemia, that may involve inadequate central catecholaminergic tone.

Acknowledgements

This study was supported in part by grants from the National Institutes of Health (AM-14228) and the National Aeronautics and Space Administration (NGR-22-009-627). Dr. Melamed is an NIH-Fogarty International Fellow (FO5 TWO2579-01). Dr. Growdon is the George Cotzias Fellow of the American Parkinson's Disease Association. We are grateful to the nursing staff of the MIT Clinical Research Center for their assistance and cooperation.

References

Bloxam, D. L., Warren, W. H.: Error in the determination of tryptophan by the method of Denckla and Dewey. Anal. Biochem. *60*, 621—625 (1974).

Delean, J., Richardson, J. C., Hornykiewicz, O.: Beneficial effects of serotonin precursors on postanoxic action myoclonus. Neurology *26*, 863—868 (1976).

Denckla, W. D., Dewey, H. K.: Determination of tryptophan in plasma, liver and urine. J. Lab. Clin. Med. *69*, 160—169 (1967).

Fernstrom, J. D., Faller, D. V.: Neutral amino acids in the brain: changes in response to food ingestion. J. Neurochem. *30*, 1531—1538 (1978).

Fernstrom, J. D., Larin, F., Wurtman, R. J.: Correlations between brain tryptophan and plasma neutral amino acid levels following food consumption in rats. Life Sci. *13*, 517—524 (1973).

Fernstrom, J. D., Wurtman, R. J.: Brain serotonin content: physiological dependence on plasma tryptophan levels. Science *173*, 149—152 (1971 a).

Fernstrom, J. D., Wurtman, R. J.: Brain serotonin content: increase following ingestion of carbohydrate diet. Science *174*, 1023—1025 (1971 b).

Fernstrom, J. D., Wurtman, R. J., Hammarstrom-Wiklund, B., Rand, W. M., Munro, H. N., Davidson, C. S.: Diurnal variations in plasma concentrations of tryptophan, tyrosine and other neutral amino acids: effect of dietary protein intake. Am. J. Clin. Nutr. *32*, 1912—1922 (1979).

Gibson, C. J., Wurtman, R. J.: Physiological control of brain catechol synthesis by brain tyrosine concentration. Biochem. Pharmacol. *26*, 1137—1142 (1977).

Gibson, C. J., Wurtman, R. J.: Physiological control of brain norepinephrine synthesis by brain tyrosine concentration. Life Sci. *22*, 1399—1406 (1978).

Glaeser, B. S., Melamed, E., Growdon, J. H., Wurtman, R. J.: Elevation of plasma tyrosine levels after a single load of L-tyrosine. Life Sci. *25*, 265—272 (1979).

Hartmann, E.: L-tryptophan: effects on sleep. Monogr. Neural Sci. *3*, 26 to 32 (1976).

Lehman, J.: Light—a source of error in the fluorimetric determination of tryptophan. Scand. J. Lab. Invest. *28*, 49—55 (1971).

Maas, J. W.: Biogenic amines and depression—biochemical and pharmacological separation of two types of depression. Arch. Gen. Psychiatry *32*, 1357—1361 (1975).

Mendels, J., Stinnett, J. L., Burns, D., Frazer, A.: Amine precursors and depression. Arch. Gen. Psychiatry *32*, 22—30 (1975).

Scally, M. C., Ulus, I., Wurtman, R. J.: Brain tyrosine level controls striatal dopamine synthesis in haloperidol-treated rats. J. Neural Transm. *41*, 1—6 (1977).

Waalkes, T. P., Udenfriend, S.: A fluorimetric method for estimation of tyrosine in plasma and tissues. J. Lab. Clin. Med. *50*, 733—736 (1957).

Wurtman, R. J.: Diurnal rhythms in mammalian protein metabolism. In: Mammalian Protein Metabolism (*Munro, H. N.*, ed.), Vol. 4, pp. 445 to 479. New York: Academic Press. 1970.

Wurtman, R. J., Larin, F., Mostafapour, S., Fernstrom, J. D.: Brain catechol synthesis: control by brain tyrosine concentration. Science *185*, 183 to 184 (1974).

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Printed in Austria