ELEVATION OF PLASMA TYROSINE AFTER
A SINGLE ORAL DOSE OF L-TYROSINE

Bruce S. Glaeser*, Eldad Melamed*,
John H. Growdon**, and Richard J. Wurtman*

*Laboratory of Neuroendocrine Regulation
Department of Nutrition and Food Science
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

**Department of Neurology
Tufts University Medical School
Boston, Massachusetts 02111

(Received in final form May 29, 1979)

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 (X ± SEM)
after the 100 mg/kg dose and to 203 ± 31.5 nmols/ml
after the 150 mg/kg dose (p ≤ 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 (X ± SEM) 2 hours after the 100
mg/kg dose (p < 0.001) and to 0.35 ± 0.05 2 hours after
the 150 mg/kg dose (p < 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

---

1These studies were 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 TW 02579-01). Dr. Growdon is the
George Cotzias Fellow of the American Parkinson's Disease Associa-
tion.

0024-3205/79/030265-07$02.00/0
Copyright (c) 1979 Pergamon Press Ltd
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 noradrenaline 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 Blom 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 $69 \pm 3.9$ mmols/ml ($\bar{X} \pm$ SEM); it rose to a peak concentration of $154 \pm 9.5$ mmols/ml 2 hours after ingestion of the 100 mg/kg dose of tyrosine ($p < 0.001$) 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 $203 \pm 31.5$ mmols/ml within 2 hours, and were still significantly elevated after 8 hours ($p < 0.001$).

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 $53 \pm 4.1$ mmols/ml ($\bar{X} \pm$ SEM) in group A, and $56 \pm 3.6$ mmols/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
Top panel: Plasma tyrosine concentrations after L-tyrosine administration (100 mg/kg [●] and 150 mg/kg [○]). Plasma tyrosine concentrations are given as nmols/ml (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 (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 (X ± SEM).
TABLE 1
Plasma Amino Acid Concentrations after L-Tyrosine Administration

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

Plasma amino acid concentrations are given in nmols/ml (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 to $704 \pm 29.2$ to $543 \pm 31.2$ nmols/ml ($p < 0.001$) after 4 hours, subsequently rising to $588 \pm 33.5$ ($p \leq 0.05$) after 6 hours, and to $609 \pm 34.2$ nmols/ml after 8 hours. In group B, the sum fell to $566 \pm 22.9$ ($p < 0.05$) after 4 hours and then rose to $675 \pm 24.4$ nmols/ml after 8 hours (Table 1). The tyrosine ratio increased markedly in both groups 2 hours after tyrosine administration (Fig. 2), rising from $0.10 \pm 0.02$ to $0.28 + 0.03$ in group A ($p < 0.001$) and to $0.35 + 0.05$ in group B ($p < 0.005$). 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 [○]). 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-distinguishable side effects. Furthermore, they did not significantly change blood pressure or pulse rate. Patients with hereditary tyrosinemia or persistent hyperphenylalaninemia 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).

Acknowledgements

We are grateful to Dr. W. Rand and Mr. Y. Ozaki for assistance in preparing the statistical analysis, and to the nursing staff of the MIT Clinical Research Center for their help and cooperation.

References


