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Individual day-to-day variations in plasma amino acid levels in healthy persons

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Summary. Fasting plasma levels of the large neutral amino acids (LNAA; L-forms) and L-tryptophan (TRP) ratios were determined in thirteen healthy volunteers (7 males, 6 females) on five consecutive mornings, and the same procedure was repeated for each individual three months later. We found characteristic overall ranges for the parameters studied, and, in addition to certain differences between the sexes, considerable inter- and intraindividual daily variations. Although the individuals showed statistically identifiable mean levels that, in the majority of subjects, were maintained over a period of three months, it is concluded that the degree of intraindividual variability does not allow us to regard a single value as "characteristic" for a given individual. This should be borne in mind in particular in follow-up studies of plasma LNAA in patients with, for example, depressive disorders.

Keywords: Amino acids – Plasma – Tryptophan – Large neutral amino acids – Variability – Variation coefficient – Affective disorders

Introduction

As precursors of monoamine neurotransmitters in the central nervous system (CNS), plasma amino acids have attracted considerable attention in psychiatry for more than two decades (Birkmayer et al., 1968; Coppen et al., 1972). This applies in particular to L-tryptophan (TRP), the precursor of the indolamine serotonin (5-hydroxytryptamine, 5-HT), which occurs in plasma in free and albumin-bound form (McMenamy and Oncley, 1958).

TRP crosses the blood-brain barrier and enters the CNS with the aid of a carrier system it shares with the other large neutral amino acids (LNAA): L-phenylalanine (PHE), L-tyrosine (TYR), L-valine (VAL), L-leucine (LEU), and L-isoleucine (ILEU) (Fernstrom and Wurtman, 1972). Thus, the tryptophan ratio

(TRP ratio, i.e., the plasma level of free or total TRP, divided by the sum of the concentrations of the five competing amino acids) determines the amount of this amino acid, in relation to the others, penetrating the blood-brain-barrier (Fernstrom and Wurtman, 1972; Fernstrom et al., 1976; Knott and Curzon, 1972).

There is good evidence that depressive disorders are caused by a dysfunction of the serotonergic nerve impulse transmission in limbic and cortical CNS areas (Coppen, 1967). This impairment can be explained inter alia by a reduction in the supply of TRP from the peripheral blood. Numerous studies have shown changes in TRP plasma levels (free and total) and TRP ratio in depressed patients. More recent investigations (Cowen et al., 1989; Maes et al., 1987) appear to suggest that, in depressives, total TRP levels and total TRP ratios are lower than in controls, but results remain equivocal (DeMyer et al., 1981; Dunlop et al., 1983; Møller et al., 1983).

Most of these findings are based on interindividual means calculated from single individual values. When differences were found, depressed patients ranged approximately one-third below control means (Coppen et al., 1972; Cowen et al., 1989; DeMyer et al., 1981; Joseph et al., 1984; Møller et al., 1976, 1986). Although this was frequently significant on statistical analysis, the question remains whether differences of this order are within the physiological range of intraindividual variability. In fact, Liappis et al. found a substantial degree of variation of plasma amino acid levels over a period of 4 weeks, but this group did not consider TRP (Liappis, 1985).

We therefore investigated the longitudinal intraindividual variability of morning fasting levels of plasma LNAA, in particular TRP, in healthy individuals on normal nutrition in order to obtain a reference for future studies on pathological conditions. Another point of interest was the range of variation of LNAA plasma levels and TRP ratios.

Methods

Individuals

Seven males (mean age 33 years, SD 9.6, range 26–53 years) and six females (mean age 37 years, SD 8.7, range 27–49 years) were investigated, after giving informed consent. All were members of our clinical staff and had no somatic or psychiatric disorders. Their body mass index was within the normal range and they were neither on drugs nor on a special diet. None of the women was pregnant or took contraceptives. Food intake was not standardized.

Sampling schedule and procedure

Blood samples were taken between 7 and 7.30 a.m. on five consecutive days. At this time, each individual had had about 8 hours of sleep, fasted for at least ten hours, and had avoided any major physical exertion. Between 97 and 103 days after the first series, blood was again obtained from each person on five consecutive days under identical conditions. Blood sampling was performed between February and June for the first and between May and September for the second series within the same year.

Blood was drawn from the cubital vein with a 10 ml EDTA syringe and centrifuged immediately for 10 minutes at 3000 g. Supernatants were divided into two 2 ml aliquots each and immediately deep frozen at −80°C. Previous comparative studies in our laboratory had shown that the TRP content of plasma samples not deproteinized prior to deep freezing

remained unchanged for 13 months, while in samples deproteinized immediately by sulfosalicylic acid, TRP was degraded considerably (unpublished data). Each pair of plasma samples was analyzed for free/total TRP and the other LNAA within 4 weeks.

Chemical assays

Total TRP: Samples were deproteinized by mixing (1:1, v/v) with perchloric acid (14%) and centrifugation. The supernatant was applied directly to the HPLC system. Separation was performed on reversed-phase columns (Nucleosil 7 C 18; length of columns: 150 mm, inside diameter: 4.6 mm; Marchery-Nagel, D-5160 Düren, FRG) using 0.1 % citic acid 0.1 % with 20 % methanol as eluent.

Free TRP: Samples were deproteinized by ultrafiltration through an MPS-1 membrane filter (molecular cut-off level: 30,000 daltons; AMICON, Danvers, MA, USA) and were then applied directly to the HPLC column.

Fluorescence detection (excitation: 289 nm, emission: 353 nm) largely eliminates other constituents of plasma. The coefficient of variation of this method for free and total TRP is 1.5 ($n = 5$).

VAL, LEU, ILEU, PHE and *TYR* were measured by cation exchange chromatography with ninhydrine derivatization (Moore and Stein, 1951, with modifications), after deproteinization with sulfosalicylic acid. We used an automatic Biotronic analyzer, model 5001 (Puchheim, FRG) in which the amino acids are separated in a lithium citrate buffer system with varying proportions of methanol over a 7 μm CK 10 F exchange resin (Mitsubishi, Japan). Photometric detection was effected simultaneously at 440 and 570 nm. The coefficient of variation is 2 ($n = 5$).

All determinations were conducted in compliance with the Principles of Good Laboratory Practice of the Organization for Economical Cooperation and Development (OECD).

Statistics

Differences of two means were tested by the two-tailed Student's t-test for independent samples. One-way analysis of variance (ANOVA) was used for testing the variation of more than two means. The quotient eta-square estimates the fraction of explained variance (Kerlinger, 1964). Coefficients of variation (CV) were used as a numerical measure of the variability of the chemical parameters tested (Bortz, 1985). Statistics and graphics were processed on a personal computer using the SPSS PC V 3.0 package.

Results

Personal data (sex and age), means and standard deviations of LNAA and TRP ratios are shown in Table 1 for each of the 13 individuals tested. Table 1 also gives the overall CV for each person. Three males (Nos. 1, 3 and 7) and one female (No. 10) appear to regulate the LNAA mean levels more closely than the other subjects, as is indicated by their lower CV. No substantial differences can be found between younger and older individuals.

Table 2 shows the means and standard deviations for the LNAA, as also ratios. Significant sex differences in means were found for total TRP, LEU, ILEU and free TRP ratio ($p < 0.01$). The CV of the LNAA have similar ranges, except for ILEU and TYR (higher in females, $p < 0.05$) and free TRP in both sexes. The high CV of free TRP contrast with the relatively low CV of total TRP; the same applies to free versus total TRP ratios.

Interindividual differences of mean plasma levels were tested by analysis of variance (ANOVA; Table 3). Differences are highly significant with respect to

Table 1. Numbers and data of persons, means ± standard deviations ($\bar{x} \pm SD$) of the large neutral amino acid (LNAA) plasma levels (μmol/l) and of the tryptophan ratios

No.	Subjects sex	age	Total tryptophan $\bar{x} \pm SD$	Free tryptophan $\bar{x} \pm SD$	Valine $\bar{x} \pm SD$	Leucine $\bar{x} \pm SD$	Isoleucine $\bar{x} \pm SD$
1	male	26	48.9 ± 6.4	5.4 ± 1.5	269 ± 23	158 ± 8	86 ± 5
2	male	26	55.4 ± 4.0	4.4 ± .7	242 ± 36	147 ± 17	81 ± 12
3	male	29	48.7 ± 4.5	4.7 ± .9	196 ± 24	105 ± 9	63 ± 6
4	male	29	52.8 ± 6.2	4.5 ± .7	239 ± 50	139 ± 26	77 ± 14
5	male	30	45.2 ± 5.3	5.7 ± .9	196 ± 27	131 ± 20	73 ± 13
6	male	38	51.7 ± 7.5	5.7 ± 2.6	276 ± 23	146 ± 11	80 ± 14
7	male	53	44.9 ± 2.7	3.5 ± .5	214 ± 27	110 ± 11	58 ± 6
8	female	27	38.7 ± 4.4	5.0 ± 1.1	175 ± 24	103 ± 12	60 ± 13
9	female	28	52.2 ± 7.8	4.9 ± .8	212 ± 30	121 ± 14	59 ± 11
10	female	38	37.2 ± 1.6	4.4 ± .6	232 ± 33	122 ± 13	61 ± 9
11	female	39	41.5 ± 3.9	5.0 ± 1.0	214 ± 29	103 ± 14	65 ± 8
12	female	42	53.9 ± 8.4	6.0 ± 1.3	223 ± 36	118 ± 20	69 ± 11
13	female	49	48.1 ± 8.2	5.7 ± 1.8	257 ± 24	144 ± 17	77 ± 18

No.	Subjects sex	age	Phenylalanine $\bar{x} \pm SD$	Tyrosine $\bar{x} \pm SD$	Total tryptophan ratio $\bar{x} \pm SD$	Free tryptophan ratio $\bar{x} \pm SD$	Mean CV of all LNAA
1	male	26	68 ± 4	81 ± 6	.0742 ± .0112	.0082 ± .0025	.11
2	male	26	61 ± 9	64 ± 11	.0943 ± .0140	.0075 ± .0020	.14
3	male	29	52 ± 4	56 ± 5	.1037 ± .0113	.0099 ± .0016	.11
4	male	29	55 ± 9	58 ± 10	.0957 ± .0207	.0082 ± .0017	.17
5	male	30	62 ± 7	65 ± 7	.0863 ± .0083	.0109 ± .0012	.14
6	male	38	61 ± 9	68 ± 7	.0823 ± .0123	.0089 ± .0040	.17
7	male	53	51 ± 6	50 ± 6	.0941 ± .0112	.0073 ± .0012	.11
8	female	27	49 ± 7	50 ± 16	.0894 ± .0146	.0117 ± .0030	.18
9	female	28	55 ± 6	71 ± 10	.1014 ± .0149	.0095 ± .0021	.14
10	female	38	61 ± 5	61 ± 8	.0700 ± .0084	.0082 ± .0016	.12
11	female	39	55 ± 5	68 ± 7	.0826 ± .0080	.0100 ± .0028	.13
12	female	42	61 ± 6	56 ± 8	.1025 ± .0112	.0114 ± .0020	.16
13	female	49	56 ± 7	64 ± 10	.0808 ± .0120	.0096 ± .0026	.17

The tryptophan ratio is the level of total or free tryptophan divided by the sum of the other LNAA levels. – The mean of all LNAA coefficients of variation (*CV*) of each individual, calculated from the means and standard deviations, is given at the far right as a measure of the "strictness" of the global plasma LNAA regulation of an individual

Table 2. Means ± standard deviations and mean coefficients of variation of all LNAA measurements and tryptophan ratios (cf. legend to Table 1), calculated for males and females separately

Amino acids (μmol/l)	$\bar{x} \pm SD$		Coefficients of mean variations (CV)	
	Males	Females	Males	Females
Tryptophan				
total	49.8 ± 7.1	46.9** ± 10.4	0.12	0.12
free	4.9 ± 1.5	5.3 ± 1.6	0.22	0.22
Valine	232 ± 40	219 ± 44	0.13	0.14
Leucine	134 ± 23	118** ± 24	0.12	0.13
Isoleucine	73 ± 13	65** ± 14	0.14	0.18*
Phenylalanine	58 ± 9	57 ± 9	0.12	0.11
Tyrosine	63 ± 12	64 ± 19	0.12	0.17*
Total			0.14	0.15
Tryptophan ratios				
total	0.090 ± 0.015	0.091 ± 0.022	0.1945	0.1741
free	0.008 ± 0.002	0.010** ± 0.003	0.3773	0.3072

Significant differences of means between the sexes are marked by one asterisk (*, $p < 0.05$) or two asterisks (**, $p < 0.01$), respectively

Table 3. Differences between the means of the amino acid plasma levels of all individuals as tested by analysis of variance and expressed by p (probability error). The percentages of interindividual variation contributing to the total (i.e. inter-plus intraindividual) variation of each amino acid are expressed by the quotient eta-square

Amino acid	p	Eta square (%)
Total tryptophan	<0.001	50.2
Free tryptophan	<0.001	28.0
Valine	<0.001	45.1
Leucine	<0.001	54.3
Isoleucine	<0.001	41.2
Phenylalanine	<0.001	38.1
Tyrosine	<0.001	44.2

all LNAA. The quotient eta-square was used to distinguish between inter- and intraindividual variations, expressed as percentages of the global variability of each LNAA. The extremes are LEU (54.3 % of estimated interindividual, i.e. largest intraindividual variation) and total TRP (50.2 %) as also, at the other end of the scale, free TRP (28 %).

Finally, means and standard deviations of the first and second series of LNAA determinations and TRP ratios were calculated separately for each

Table 4. Probabilities of error of differences in means between the first and second series of determinations given for each individual

Subject No.	Total tryptophan	Free tryptophan	Valine	Leucine	Isoleucine	Phenylalanine	Tyrosine	Total tryptophan ratio	Free tryptophan ratio
1			*		**	*			
2		*					*		*
3	*		*				*	**	
4			*	*	*				
5		**							*
6			*				*	*	
7				*	*				
8	**	**	*	**					**
9					*				
10	*	*							
11			*	*	**	*	**		*
12									
13			*						

Significant intraindividual differences are indicated by one asterisk (*, $p < 0.05$) or two asterisks (**, $p < 0.01$), respectively. For definition of tryptophan ratio (total and free), see legend to Table 1

individual (Table 4). Application of the t-test revealed that 82 of the 117 pairs of intraindividual means (70.1 %) differed nonsignificantly. With respect to consistency, the extremes were PHE and total TRP ratio (significant deviations in two individuals) and VAL (seven individuals).

Discussion

Our results show that morning plasma LNAA levels after overnight fasting are subject to considerable daily variations in each individual. The mean levels correspond well with findings based on single measurements in larger populations, with respect both to LNAA concentrations (Akamatsou et al., 1975; Armstrong and Stave, 1973; Liappis, 1972; Oepen and Oepen, 1965) and TRP ratios (Branchey et al., 1984; DeMyer et al., 1981).

In the case of some LNAA, females show lower levels than males. This is in good accordance with most reports (Armstrong and Stave, 1973; Liappis, 1972; Milsom et al., 1979; Møller et al., 1986; Thomas et al., 1986). Scriver et al. (1985), however, failed to find significant sex differences in any fasting amino acid level. As for total TRP, Armstrong and Stave (1973) found a significant sex difference, while in the population of Troll et al. (1978) mean levels were almost identical in men and women.

Studies of the correlation of plasma amino acid levels and age found that subjects over 65 years, in particular men, had significantly lower TRP concentrations than younger subjects (Møller et al., 1976; Phipps and Powell, 1985; Thomas et al., 1986). In our sample, the oldest male (53 years) showed a tendency towards lower LNAA mean values.

As indicated by differences in the CV, some individuals appear to regulate LNAA levels more closely than others, males more so than females. Most amino acids, including the LNAA, tend to decrease during the luteal phase (Craft and Wise, 1969; Hrboticky et al., 1989; Landau and Lugibihl, 1967), although these changes may not reach significance (Cox and Calame, 1978; Soupart, 1960). We did not consider the menstrual phase in this study, nor has this been done in the majority of psychiatric studies on plasma LNAA, but the issue deserves attention in future investigations.

Total TRP and PHE were subject to the most consistent regulation (smallest CV), and showed the greatest conformity between the sexes. Both findings are interesting in view of the fact that these amino acids are the neurotransmitter precursors in the CNS. Our CV are in good accordance with those reported by Liappis (1985) who in young males found CV of about 10 % for the LNAA (TRP was not studied). Free TRP had the highest CV, which may indicate that, with respect to homeostasis, total TRP levels in plasma have greater importance for TRP influx into the brain than the free form (Fernstrom et al., 1976).

As demonstrated by ANOVA, there are differences in means for all LNAA and TRP ratios that clearly distinguish individuals from one another, thus underscoring the concept of a "private" plasma phenotype (Scriver et al., 1985). Total TRP is subject to relatively close regulation in the individual person. Nevertheless, on account of large intraindividual variability, a single plasma

LNAA value in an individual cannot be considered a measure of that person's characteristic or "mean" level.

Comparing – for each parameter and person – the means and standard deviations found in the first sequence of determinations with those obtained three months later revealed relatively good consistency for total TRP, total TRP ratio and the catecholamine precursor PHE. With respect to perennial oscillations of TRP (Wirz-Justice and Richter, 1979; Swade and Coppen, 1980), Sarrias et al. (1989) found a remarkable consistency of total TRP levels over a 14-month period, in contrast to other plasma indole compounds.

It may be concluded from our results that fasting mean levels of LNAA depend not only on the chosen population, but also on the day of sampling, even when done at the same clock time. This finding appears to be relevant in particular in follow-up studies when plasma LNAA levels are compared in the same subject before and after treatment.

Studies similar to the present one may help clarify the physiological variability of plasma LNAA as a basis for studying clinical populations. Other means of establishing reliable plasma amino acid characteristics are a 24 hour profile (Candito et al., 1990; Dam et al., 1984; Eriksson et al., 1989; Melatino et al., 1982) or an oral loading test (Møller, 1985; Russ et al., 1990) that allows us to examine altered pharmacokinetics and clearances. By standardizing food intake before and during the study (DeMyer et al., 1981), changes in amino acid metabolism inherent in the disease may also become apparent. If, however, mood is influenced by the composition of amino acids ingested, artificial changes in nutrition may have an involuntary effect on the clinical parameter under investigation, e.g. the current severity of the affective disorder (Maes et al., 1987).

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