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Lower Serum L-Tryptophan Availability in Depression as a Marker of a More Generalized Disorder in Protein Metabolism

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Recently, it has been reported that major and melancholic depression are accompanied by a lower availability of total L-tryptophan (L-TRP) to the brain and by significant changes in electrophoretically separated protein fractions, such as albumin and α_2-globulin. The aim of this study was to examine the relationships between serum L-TRP availability and total serum protein, albumin, and α_2-globulin in 42 depressed and 24 normal subjects. In depressed and normal subjects, alone and together, there were significant and positive correlations between serum L-TRP and total serum protein or albumin concentrations. In the depressed subjects, but not in normal controls, there were significant inverse relationships between the L-TRP/competing amino acid ratio and the α_2-globulin fraction. Serum L-TRP and albumin were significantly lower in melancholic subjects than in normal and minor depressed subjects. Depressed subjects had a significantly lower L-TRP/competing amino acid ratio and significantly higher serum α_2-globulin than normal controls. Total serum protein was significantly lower in major depressed subjects than in normal controls. The results suggest that lower L-TRP availability to the brain in depression is related to lower serum albumin and to increased α_2-globulin fraction, which are both hallmarks of the acute phase response in depression. The results further corroborate the hypothesis that lowered L-TRP availability in depression is related to the acute phase response in that illness.

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KEY WORDS: *Acute phase proteins; Electrophoresis; Serotonin; L-tryptophan; Albumin*

There is now evidence that major depression is accompanied by disorders in the peripheral and central metabolism of serotonin (5-HT) and by an acute phase response. One on the most consistently reported abnormal findings in serotonergic metabolism in major depression is a reduced availability of L-tryptophan (L-TRP) to the brain (DeMyer et al. 1981; Maes et al. 1990a; Cowen et al. 1989). Thus, serum L-TRP as well as the ratio of L-TRP to the sum of amino acids known to compete for the same cerebral uptake mechanisms (competing amino acids, e.g., tyrosine, valine, leucine, isoleucine, phenylalanine) is lower in major depressed subjects than in normal controls (review: Maes and Meltzer 1995). The relevance of these findings for the pathophysiology of major depression is underscored by recent reports that in normal and depressed subjects, acute lowering of plasma L-TRP may cause an acute lowering of mood or rapid clinically significant return of depressive symp-

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toms, respectively (Young et al. 1985; Delgado et al. 1990; Heninger et al. 1992).

There are now several reports that major depression is accompanied by an acute phase response, as demonstrated by higher plasma levels of positive acute phase proteins, such as haptoglobin, α_1-antitrypsin, and ceruloplasmin, increased concentrations of the electrophoretically separated serum α_2-globulin fraction, and lower concentrations of negative acute phase proteins, such as albumin and transferrin (Maes et al. 1991, 1992a,b, 1993, 1994a; Joyce et al. 1992; Song et al. 1994; Sluzewska et al. 1995b). Moreover, an acute phase response has also been observed in the olfactory bulbectomized rat model of depression (Arnold and Meyerson 1990; Song and Leonard 1994). We have argued that the acute phase response in major depression is related to an increased production of interleukin-6 (IL-6) in major depression (Maes et al. 1993; Sluzewska et al. 1995a,b). Indeed, IL-6 is a pleiotropic cytokine, which is mainly produced by activated cells of the monocyte/macrophage lineage and is a major mediator of the acute phase response in humans (Mackiewicz et al. 1988; Hirano 1991). This hypothesis is underscored by the significant relationships between IL-6 secretion and acute phase proteins, such as haptoglobin and C-reactive (positive) and transferrin (negative) (Maes et al. 1993; Sluzewska et al. 1995b).

Recently, it has been hypothesized that the reduced L-TRP availability to the brain in depression may be related to the acute phase response in that illness (Maes et al. 1993, 1994b). Indeed, highly significant relationships were found between plasma L-TRP availability and plasma haptoglobin (negative), transferrin (positive), and IL-6 production by peripheral blood mononuclear cells (negative) (Maes et al. 1993). Some factors that may explain the reduced L-TRP availability during an acute phase response are (1) peripheral amino acids are used for leukocyte activity and synthesis of acute phase proteins (Blackburn et al. 1979; Moldawer et al. 1987; Hasselgren et al. 1988; Heinrich et al. 1990; Wolvekamp and Marquet 1990), and (2) indoleamine 2,3 dioxygenase (IDO), a major L-TRP catabolizing enzyme, may be induced during the acute phase response (Takikawa et al. 1984, Brown et al. 1989; Moroni et al. 1991). The latter hypothesis is underscored by the significant inverse relationship between lower plasma L-TRP and increased neopterin concentrations in major depression (Maes et al. 1994b). Indeed, it is known that IDO and GTP hydroxylase, which stimulates the synthesis of neopterin in activated monocytes/macrophages, are induced simultaneously during an acute phase response (Fuchs et al. 1990, 1991).

Another possible explanation for the inverse relationship between lower L-TRP availability and indices of the acute phase response in depression revolves around the binding of L-TRP to albumin, which is an acute phase reactant. Under normal conditions, L-TRP circulates in the blood with a minor fraction free, whereas 70% to 90% of L-TRP is loosely bound to serum albumin (Rao 1987; Curzon and Sarna 1984; Fernstrom 1984; Yuwiler et al. 1977; McMenamy and Oncley 1958). This explains that the availability of circulating L-TRP is generally influenced by its binding to albumin (Curzon and Knott 1975). Moreover, the extraction of plasma L-TRP by the brain is, in part, related to competition of the brain transport site with plasma albumin, that is, it is proposed that the blood-brain barrier (BBB) transport site of L-TRP and its competing amino acids strips off albumin as it passes through the brain capillaries (Pardridge 1979; Smith et al. 1990). Therefore, the influx of L-TRP into the brain depends on plasma concentrations of all L-TRP, that is, free and/or total L-TRP, as well as on the concentrations of albumin and the competing amino acids (Pardridge 1979; Yuwiler et al. 1977). Thus, reduced serum albumin concentrations in major depression (Maes et al. 1991; Song et al. 1994), could be accompanied by lower total L-TRP concentrations and, consequently, by a lowered extraction of L-TRP by the brain.

The aim of the present study was to examine the relationships between plasma availability of L-TRP to the brain and the serum concentrations of albumin, total serum protein, and the α_2-globulin fraction. A positive correlation between L-TRP availability and serum albumin or total serum protein and a negative correlation between L-TRP availability and the elecrophoretically separated α_2-globulin fraction would be expected, if the hypothesis that lowered L-TRP availability is related to the acute phase response is correct.

SUBJECTS

In this study, 66 subjects participated, 24 healthy controls and 42 depressed inpatients, and were admitted to the psychiatric ward of the University Hospital of Antwerp between October 1992 and April 1994. The depressed patients were categorized according to DSM-III-R criteria (APA 1987) using the Structured Clinical Interview for DSM-III-R, version 1989 (SCID) (Spitzer et al. 1990) into: (1) dysthymic disorder (300.40) or adjustment disorder with depressed mood (309.00), labeled as minor depression, (2) major depression without melancholia or simple major depression (296.X2), and (3) major depression with melancholia (296.X3). The Hamilton Depression Rating Scale (HAM-D), 17-item version, was used in order to measure the severity of depression (Hamilton 1967). The SCID and HDRS were scored by the same author (i.e., AvG) ±8 days after hospital admission of patients.

Patients with other axis 1 diagnoses beside depression, such as substance use disorder (1/2 year previous to admission), organic mental disorder, and schizophrenia, were excluded from these studies. We have

Table 1. Demographic Data of the 66 Subjects in This Study

Diagnostic Groups	Index	Men/Women Ratio	Age (years) Mean ± SD	HDRS[b] Mean ± SD	AD	Drug State (yes/no)[a] BZ1	NL	BZ2
Healthy controls	HC	11/13	41.1 ± 13.5	–	–	–	–	–
Minor Depression	md	4/8	42.8 ± 11.9	16.2 ± 3.6	1/11	4/8	3/9	3/9
Simple major depression	MD−M	3/18	48.7 ± 14.3	21.6 ± 3.8	3/18	12/9	3/18	8/13
Melancholia	MD+M	3/6	58.7 ± 14.0	23.7 ± 1.7	4/5	3/6	1/8	2/7
ANOVA or χ^2-test		3.9	3.6	14.6	2.7	1.2	0.2	0.3
df		3	3/58	2/39	2	2	2	2
p		0.3	0.02	$<10^{-4}$	0.3	0.5	0.9	0.9

[a]Drug state: use of antidepressants (AD), benzodiazepines (BZ1), or low-dosage antipsychotic agents (NL) the month prior to the 8-day washout period, or use of benzodiazepines (BZ2) during the study period.
[b]HDRS: Hamilton Depression Rating Scale, 17-item version.

excluded patients who were on lithium, monoamine oxidase inhibitors, (MAOI), antipsychotic dosages of neuroleptics and anticonvulsants or barbiturates, and patients who underwent electroconvulsive therapy (ECT) the year previous to hospital admission. The drug state of the patients before the eight-day washout period is listed in Table 1. Eight depressed patients have been treated with antidepressants, that is, maprotiline, clomipramine, amitriptyline; 19 subjects had been taking benzodiazepines, whereas seven patients were treated with a low dosage of typical neuroleptics, for example, equivalent of haloperidol <0.5 mg/day. These drugs were discontinued upon admission, and, subsequently, these subjects underwent a washout period of eight days. The authors administered a low dosage of benzodiazepines to 13 patients (equivalent of ≤25 mg di-K-chlorazepate) in the case of severe agitation, anxiety, sleep disorders, or suicidal ideation. Inclusion criteria for normal controls and depressed subjects included normal blood tests such as liver function tests (e.g., SGPT, SGOT, and GGT), hematologic measures (e.g., hematocrit), electrolytes, and renal function tests (e.g., urea and creatinine). All patients had a normal radiograph of lungs and heart, electrocardiogram, and electroencephalogram. Subjects were on a low monoamine diet for three days prior to the blood samplings.

Normal volunteers were free of any medication during at least one month previous to blood sampling. All were free of medical and psychiatric illnesses. They were screened and excluded for present, past history, and family history of psychiatric disorder by means of a semistructured clinical interview based on the SCID. None had ever been taking psychotropic drugs or was a regular drinker. They had raw scores <32 on the Zung Depression and Anxiety Scales and <9 on the Beck Depression Inventory. All subjects were free of drugs known to interfere with endocrine or immune functions. All subjects were free of chronic illnesses known to affect the endocrine or immune status (e.g., diabetes, infections) and of acute infectious or allergic reactions for at least 2 weeks prior to the study.

METHODS

Fasting blood was sampled at 8:00 A.M., 8 days after hospital admission for the assay of serum L-TRP, the competing amino acids, valine, leucine, phenylalanine, isoleucine, and tyrosine, total serum protein, albumin, and the α_2 globulin fraction. Amino acids were determined by means of a HPLC method as previously described by us (Maes et al. 1990c). The ratio of L-TRP to the sum of the five competing amino acids was computed. Total serum protein was assayed by means of the Kodak Ektachem Analyzer (Kodak, Vilvoorde, Belgium). The interassay and intraassay coefficients of variation (expressed as a percentage, CV%) obtained in our laboratory were 2.16% and 0.83%, respectively. Serum protein electrophoresis has been carried out by means of the Beckman Paragon SPE agarose system (Analis, Namur, Belgium) with densitometric quantitation of the protein fractions. The interassay and intraassay CV values for the percentages of albumin were 3.05% and 0.63%, and for α_2 globulin 7.05% and 3.64%, respectively.

STATISTICS

Normality of distribution has been ascertained by means of the Kolmogorov-Smimov test. Relationships between variables have been ascertained by means of Pearson's product-moment or Spearman's rank-order correlation coefficients, multiple regression, or path analysis. The independence of classification systems has been checked with the analysis of contingence (χ^2 test). Mean group differences have been assessed with

the analysis of variance (ANOVA) or covariance (ANCOVA). Multiple post-hoc comparisons between group means were checked with Fisher's least significant difference (LSD).

RESULTS

Demographic Data

Table 1 lists the demographic data of the 66 subjects in this study. There were no significant differences in men: women ratio between the four study groups. There were no significant differences in age among minor, simple major, and normal subjects. Patients with melancholia were somewhat older than the other groups (LSD at p = .05). The HAM-D ratings were significantly different among the three groups and increased from minor to simple major to melancholic depression. Correlation analyses pooled over the four diagnostic groups showed significant correlations between age and α_2-globulin concentrations (r = 0.35, p = .005), percentage of α_2-globulin (r = 0.44, p = .0005), albumin concentrations (r = −0.35, p = .005), percentage of albumin (r = −0.30, p = .01) and the L-TRP/competing amino acid ratio (r = −0.31, p = .01). There were no significant correlations between age and total serum protein (r = −0.18, p = .1) and serum L-TRP (r = −0.09, p = .5). There were no significant differences between men and women (results of ANOVAs, factorial design with diagnostic groups and gender as factors) in L-TRP (F = 2.9, p = .09), L-TRP/competing amino acid ratio (F = 0.2, p = .7), total serum protein (F = 0.2, p = .7), the percentage (F = 3.1, p = .01) or concentration (F = 2.5, p = .1) of α_2-globulin, and percentage (F = 0.1, p = .7) or concentration of albumin (F = 0.04, p = .8). In any case, we have adjusted subsequent statistical tests for possible age and gender effects through multiple regression analyses with age and gender as additional explanatory variables.

There were no significant relationships between the L-TRP or protein data and the drug state of the depressed patients, for instance, either use of benzodiazepines, antidepressants, or neuroleptics the month prior to the washout period or use of benzodiazepines during the study period. For example, the multiple regression of serum L-TRP concentrations on the four drug state variables was nonsignificant (F = 0.2, df = 4/37, p = .9); none of the drug state variables was significant in this regression equation, for instance, use of antidepressants (F = 0.4, p = .5), benzodiazepines (F = 0.2, p = .7) or neuroleptics (F = 0.4, p = .5) before the washout period, or use of benzodiazepines during the study span (F = 0.00, p = .9). The multiple regression of the L-TRP/competing amino acid ratio on the four drug state variables was nonsignificant (F = 2.0, df = 4/37, p = .1). Therefore, we have no evidence that the drug state of the patients has a major effect on our results.

L-TRP, Proteins, and DSM-III-R Classification

Table 2 lists the measurements of L-TRP, L-TRP/competing amino acids ratio, total serum protein, and protein fractions. Serum L-TRP was significantly lower in melancholic subjects compared to normal subjects and minor depressed subjects, whereas simple major depressed subjects occupied an intermediate position. Age (F = 0.1, p = .7) and gender (F = 2.4, p = .1) were not significant in the multiple regression analysis; diagnostic classification explained 20.7% of the variance in the L-TRP data. The L-TRP/competing amino acid ratio was significantly lower in depressed subjects than in normal controls, whereas melancholic subjects had the lowest ratio. Age (F = 9.1, p = .004) and diagnostic classification (F = 9.0, p = .004) explained 28.1% of the variance in the L-TRP/competing amino acid ratio; gender was not significant in this regression analysis. Total serum protein was significantly lower in major depressed patients than in normal controls and minor depressed subjects. The effects of diagnostic classification remained

Table 2. Measurements of Serum L-Tryptophan (L-TRP), L-TRP/Competing Amino Acids (CAA) Ratio, Total Serum Protein (TSP), Albumin and α_2 Globulin Fraction in 66 Subjects[a]

Index[b]	L-TRP 10^{-6} mole/L	L-TRP/CAA ×100	TSP g/L	Albumin %	Albumin g/L	α_2 globulin %	α_2 globulin g/L
HC	76.4 ± 11.2	10.96 ± 1.26	73.6 ± 3.4	63.0 ± 2.6	46.4 ± 2.7	8.3 ± 1.1	6.1 ± 0.8
md	74.7 ± 17.4	9.66 ± 1.90[2]	73.1 ± 7.3	65.4 ± 3.3	47.7 ± 4.6	9.5 ± 1.1[5]	6.9 ± 1.0[6]
MD−M	69.5 ± 12.2	9.74 ± 1.80[2]	70.1 ± 5.6[3]	64.6 ± 3.1	45.2 ± 3.8	9.5 ± 1.4[5]	6.6 ± 1.0
MD+M	57.7 ± 6.7[1]	8.50 ± 1.02[2]	68.3 ± 4.8[3]	62.1 ± 3.2	42.4 ± 4.0[4]	10.2 ± 1.7[5]	6.9 ± 1.0[6]
ANOVAs F	5.4	5.4	3.3	3.1	4.1	5.9	3.1
df	3/62	3/62	3/62	3/62	3/62	3/62	3/62
p	0.003	0.003	0.02	0.03	0.01	0.002	0.03

[a] All results are expressed as mean (±SD).
[1, 3, 4] Significantly different from HC or md; [2, 5, 6] Significantly different from HC (all results of Fisher's LSD at p = .05).
[b] HC/md/MD±M: for explanation see Table 1.

significant (F = 5.0, p = .03) after considering the effects of age (F = 2.4, p = .1) and gender (F = 0.1, p = .8). Serum albumin was significantly lower in melancholic subjects than in normal controls and minor depressed subjects. After considering the effects of age (F = 7.3, p = .009) and gender (F = 0.00, p = .99), the effects of diagnostic classification (F = 4.1, p = .04) remained significant. Serum α_2-globulin was significantly higher in depressed subjects than in normal controls (percentage as well as concentration). After considering the effects of age (F = 13.6, p = .0008) and gender (F = 2.7, p = .1), the effects of diagnostic classification (F = 8.3, p = .006) were still significant.

No significant Spearman's rank order correlation coefficients were found between serum L-TRP and anorexia (r = −0.29, p = .06) and weight loss (r = −0.20, p = .2). No significant Spearman's rank-order correlation coefficients were found between the L-TRP/competing amino acid ratio and either anorexia (r = 0.17, p = .3) or weight loss (r = 0.17, p = .3). There was a significant and positive relationship between anorexia and weight loss (r = 0.66, $p < 10^{-4}$). There were no significant relationships between anorexia or weight loss, on the one hand, and total serum protein, albumin, or α_2-globulin (percentage or concentration), on the other.

Relationships Between L-TRP and Proteins

Table 3 shows the relationships between L-TRP or L-TRP/competing amino acid ratio and total serum protein or protein fractions in depressed subjects and normal controls, alone and together. In normal and depressed subjects and in all patients together, a highly significant and positive relationship was found between L-TRP and total serum protein. There were highly significant and positive relationships between serum L-TRP and serum albumin. In depressed subjects and in the study group as a whole—but not in normal volunteers—there were highly significant and inverse relationships between the α_2-protein fraction (either percentage or concentration) and availability of L-TRP (either L-TRP or the ratio). There was a significant and negative correlation between serum albumin and the percentage of α_2-globulin fraction (r = −0.53, $p < 10^{-4}$). There was a highly significant correlation between total serum protein and albumin (r = 0.83, $p < 10^{-4}$), but not between total serum protein and α_2-globulin fraction (r = 0.10, p = .6).

Results of Path Analysis

In order to examine the complex interrelationships between L-TRP availability and total serum protein, albumin, α_2-globulin, and other explanatory variables such as age, gender, and DSM-III-R classification, a causal model was tested by means of path analysis. In that model, L-TRP/competing amino acid ratio and L-TRP were considered the dependent variables (or the effects), whereas albumin and α_2-globulin were considered to be direct causes (i.e., explanatory variables) of the variability in L-TRP availability. Finally, age, gender, and DSM-III-R classification were considered causes (explanatory variables) for each of the previous variables, that is L-TRP/competing amino acid ratio, L-TRP, albumin, and α_2-globulin. Gender, (i.e., man = 1, woman = 0) and DSM-III-R classification (healthy controls = 0, depressed subjects = 1) were entered as dummy variables. Thus, this model allows to examine the causal relationships between protein fractions and L-TRP availability taking into account the effects of age, gender, and DSM-III-R classification.

Figure 1 shows the final path model, that is, after omitting nonsignificant paths, for instance, from age to serum albumin and L-TRP and from gender to serum albumin and L-TRP. We found that 55% of the variance in the L-TRP/competing amino acid ratio was explained by serum L-TRP, gender, α_2-globulin fraction (percentage) and age (F = 18.6, df = 4/61, $p < 10^{-4}$). Thus, the significant correlation between L-TRP/competing amino acid ratio and α_2-globulin fraction found in the total study group (see Table 3), holds after considering the effects of gender, age, and serum L-TRP levels. 30.8% of the variance in L-TRP was explained by the regression on serum albumin and DSM-III-R classification (F = 6.8, df = 4/

Table 3. Relationships among Serum L-Tryptophan (L-TRP), L-TRP/Competing Amino Acids (CAA) Ratio, Total Serum Protein (TSP), Albumin (Alb), and α_2 Globulin Fractions

Relationships	Total Study Group (n = 66)	Depressed Subjects (n = 42)	Normal Subjects (n = 24)
TSP and L-TRP	0.56(<10^{-4})	0.54(0.0004)	0.49(0.01)
TSP and L-TRP/CAA	0.25(0.04).	0.12(0.5)	0.31(0.1)
Alb and L-TRP	0.46(0.0003)	0.46(0.003)	0.42(0.04)
Alb and L-TRP/CAA	0.32(0.008)	0.24(0.1)	0.55(0.006)
α_2% and L-TRP	−0.33(0.007)	−0.26(0.09)	−0.17(0.6)
α_2% and L-TRP/CAA	−0.44(0.0004)	−0.40(0.009)	−0.08(0.7)
α_2 and L-TRP	−0.05(0.7)	0.07(0.6)	0.00(0.9)
α_2 and L-TRP/CAA	−0.34(0.005)	−0.32(0.04)	0.03(0.9)

Listed are Pearson's product moment correlation coefficients (with exact p-value).

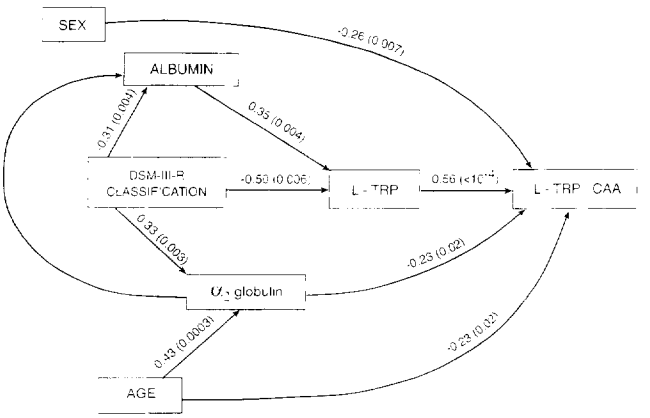

Figure 1. Results of path analysis. Shown is the final (overidentified) model, after exclusion of nonsignificant paths and nonsignificant variables. Listed are the path coefficients with exact p-value between brackets.

61, p = .0003). Thus, the significant correlation between L-TRP and albumin (see Table 3) holds after considering the effects of DSM-III-R classification, whereas age and gender did not affect this relationship. Of the variance in serum albumin, 37.1% was explained by α_2-globulin fraction and DSM-III-R classification (F = 18.6, df = 3/62, p = .00001). Of the variance in α_2-globulin, 36.5% was explained by age and DSM-III-R grouping combined (F = 18.2, df = 2/63, p = .00001).

DISCUSSION

The major findings of this study are that: (1) the availability of L-TRP to the brain is significantly lower in depressed and, particularly in melancholic patients compared to normal controls; (2) the availability of L-TRP is significantly and positively related to total serum protein and serum albumin and inversely to serum α_2-globulin fraction; and (3) lower L-TRP availability in depression may, in part, be explained by lower total serum protein or albumin concentrations or by an increase in the α_2-globulin fraction. The results will now be discussed.

In accordance with several other reports, this study found lower L-TRP availability in depressed subjects and, in particular, in melancholic subjects compared with normal controls (Maes et al. 1990a; Cowen et al. 1989; Moller et al. 1986). A major finding of this study is the significant positive relationship between serum L-TRP and total serum protein or serum albumin in normal controls as well as in depressed subjects. The positive relationship between serum total L-TRP and albumin concentrations may be explained by the fact that 70% to 90% of L-TRP is bound to serum albumin (McMenamy and Oncley 1958). Thus, serum albumin concentrations appear to constitute a major determinant of serum L-TRP concentrations in normal persons as well as in depressed subjects. Consequently, the decrease in serum albumin concentrations observed in depression may have caused lower serum total L-TRP concentrations because less L-TRP is bound to albumin. Moreover, as the path analysis showed that lower L-TRP in depression is, in part, determined (statistically) by lower serum albumin, it may be suggested that lower serum L-TRP in depression is secondary to lowered serum albumin in that illness. This may be of relevance for the influx of L-TRP into the brain, as the brain sees all the plasma L-TRP instead of only the free component (Pardridge 1979). Indeed, the BBB transport site of L-TRP strips off albumin as it passes through the brain capillaries (Pardridge 1979; Smith et al. 1990). As there is evidence that serum L-TRP availability is related to brain L-TRP contents and the metabolism of 5-HT in cerebro (Moir and Eccleston 1968; Maes and Meltzer 1995), lower serum albumin in depression may play a role in alterations in the central serotonergic metabolism in the brain of depressed subjects.

There was also a statistically highly significant positive correlation between total serum protein and serum L-TRP in normal subjects as well as in depressed patients. These findings are in accordance with one of our previous reports, showing significant positive within-subject or time-relationships between both factors in 26 normal volunteers who had monthly blood samplings during one calendar year (Maes et al. 1995). Because the variance in total serum protein is greatly determined (69% of the variance) by the variance in serum albumin, it may be suggested that the relationship between total serum protein and serum L-TRP is, in part, determined by that between albumin and L-TRP.

However, path analysis showed that part of the variance in serum L-TRP could be determined by the combined effects of lower serum albumin and DSM-III-R classification. These findings suggest that depression-related phenomena, other than the effects of albumin, may determine lower L-TRP availability in that illness. These phenomena may involve the following: (1) increased L-TRP catabolism through induction of liver pyrrolase by increased glucocorticoid activity in major depression (Maes et al. 1990b; Morgan and Badawy 1989) or (2) increased catabolism of L-TRP through induction of IDO by increased interferon-γ secretion in major depression (Maes et al. 1994b).

A second major finding of this study is the significant inverse relationship between the L-TRP/competing amino acid ratio and serum α_2-globulin fraction (either percentage or concentration) in depressed patients, but not in normal controls. Path analysis showed that an important part of the variance in the L-TRP/competing amino acid ratio was explained by the combined effects of serum α_2-globulin fraction and serum L-TRP, which, in turn, was partly determined by serum albu-

min. Thus, it appears that the relationship between the α_2-globulin fraction and the L-TRP/competing amino acid ratio reflects changes in the relative distribution of total L-TRP versus the competing amino acids. These findings corroborate one of our previous studies, reporting a significant inverse relationship in depressed patients between plasma haptoglobin, which migrates in the α_2-globulin zone (Putnam 1984a,b) and L-TRP availability (Maes et al. 1993).

As summarized previously, there is now some evidence that major depression is accompanied by an acute phase response. The decrease in total serum protein and serum albumin and the increase in α_2-globulin in depression or melancholia further underscore this theory. Indeed, albumin is one of the negative acute phase proteins, which has been shown to be reduced in depression (Swartz 1990; Maes et al. 1991; Song et al. 1994) and in the olfactory bulbectomized rat model of depression (Song and Leonard 1994), whereas positive acute phase proteins, such as haptoglobin and ceruloplasmin, are known to migrate in the α_2 zone (Ritzmann and Daniels 1976; Putnam 1984a,b). Thus, the present study shows that the lower availability of total L-TRP to the brain in depression is related to indicants of the acute phase response in that illness. These findings corroborate our previous report that there is a highly significant positive correlation in depression between L-TRP availability and production of IL-6, the key mediator of the acute phase response in human (Castell et al. 1989; Prowse and Baumann 1989; Heinrich et al. 1990; Mayer et al. 1991). Therefore, it is a reasonable theory that lower L-TRP availability in depression reflects, in part, the acute phase response in that illness.

It could be argued that malnutrition accompanying the anorexia or weight loss of depression may be related to reduced total serum protein, serum albumin, and L-TRP availability. However, in the present study, no significant relationships were found between L-TRP availability to the brain, serum L-TRP, or the L-TRP/competing amino acid ratio, and anorexia or weight loss. Moreover, this study showed that lower serum L-TRP as well as lower serum albumin were significantly and negatively related to increased α_2-globulin, another electrophoretically separated serum protein fraction, which indicates the presence of an acute phase response in depression. In this respect, Fleck (1989) has suggested that reductions in negative acute phase proteins, such as albumin and, consequently, total serum protein, may not be assumed to reflect a primary malnutrition when there is evidence for an acute phase response. Moreover, no nutritional disorders indicating protein loss due to malnutrition could be found in depression (Maes et al. 1991). Finally, the role of dietary effects on the control of L-TRP availability to the brain is rather small (review: Curzon 1990). Thus, fasting for up to 5 days had little effect on plasma L-TRP concentrations in the rat (Curzon 1990). It was found that plasma competing amino acid concentrations were unaffected by breakfast in freely feeding adults (Scriver et al. 1985; Milson et al. 1979). The L-TRP/competing amino acid ratio altered only moderately, if at all, in subjects given meals of considerably different composition (Ashley et al. 1982, 1985). Physiologically relevant differences in protein intake do not induce alterations in the L-TRP/competing amino acid ratio (Fernstrom et al. 1987). Thus, there is no evidence that lower L-TRP availability to the brain is determined by malnutrition due to the anorexia or weight loss occurring in depression.

In conclusion, this study showed that the reduced availability of L-TRP to the brain is related to lower albumin and, consequently, total serum protein concentrations and to α_2-globulin fraction. These findings suggest that lowered L-TRP availability to the brain may be secondary to the acute phase response in depression.

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