

# Heterogeneity of serum tryptophan concentration and availability to the brain in patients with the chronic fatigue syndrome

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## Abstract

We assessed the serotonin status of patients with the chronic fatigue syndrome (CFS). Tryptophan (Trp) availability to the brain, expressed as the ratio of concentration of serum Trp to the sum of those of its five competitors (CAA), and other parameters of Trp disposition were compared in 23 patients with the CFS and 42 healthy controls. The serum [free Trp]/[CAA] ratio was 43% higher in CFS patients, due to a 48% higher [free Trp]. [Total Trp] was also significantly higher (by 19%) in CFS patients, and, although the [total Trp]/[CAA] ratio did not differ significantly between the control and patient groups, the difference became significant when the results were co-varied with age and gender. [CAA] was not significantly different between groups, but was significantly lower in females, compared to males, of the CFS patient

group. We have established normal ranges for Trp disposition parameters and propose criteria for defining the serotonin-biosynthetic status in humans. We have provisionally identified two subgroups of CFS patients, one with normal serotonin and the other with a high serotonin status. The relevance of our findings to, and their implications for, the pharmacological and other therapies of the chronic fatigue syndrome are discussed.

## Keywords

amino acids, chronic fatigue syndrome, selective serotonin re-uptake inhibitors, serotonin function, tryptophan, tryptophan availability to the brain

## Introduction

The chronic fatigue syndrome (CFS) is a persistent and debilitating condition associated with a variety of somatic and psychological symptoms (Sharpe *et al.*, 1991; Fukuda *et al.*, 1994). Although the central serotonin (5-hydroxytryptamine or 5-HT) status of patients with the CFS has been investigated, a clear consensus has not been established. Some studies suggested that central serotonergic activity is increased (Bakheit *et al.*, 1992; Cleare *et al.*, 1995) in the CFS, whereas others showed activity to be normal (Bearn and Wessley, 1994; Yatham *et al.*, 1995). One possible explanation is heterogeneity within the CFS population. Determining the serotonergic status of an individual with the CFS may prove important, as patients with normal, or an excess of, serotonergic transmission are unlikely to benefit from, whereas those with a

serotonin deficiency may be usefully treated using, serotonin-modifying agents, particularly if depression is also present. A better understanding of the serotonin status in individuals with the CFS could also provide a more rational basis for the use of other therapies in this syndrome, such as exercise, which exerts significant effects on serotonin metabolism (see the 'Discussion' section).

To identify the serotonin status of patients with the CFS in a general clinical non-research setting, a simple approach is needed without the specialized neuroendocrine challenge tests. One such approach is to assess the serotonin-biosynthetic status through determination of availability to the brain of the serotonin precursor amino acid tryptophan (Trp) in the circulation. Because the rate-limiting enzyme of the serotonin-biosynthetic pathway, Trp hydroxylase, is unsaturated with its Trp substrate, brain Trp concentration is the most important single metabolic determinant of

the rate of serotonin synthesis (Fernstrom and Wurtman, 1971; Carlsson and Lindqvist, 1978; Curzon, 1979). Consequently, peripheral factors influencing circulating Trp availability to the brain play important roles in central serotonin synthesis. These include, at the primary level of control, activity of the major Trp-degrading enzyme, liver Trp pyrrolase (Badawy, 1977) and, at the secondary, but more immediate, level Trp binding to albumin (Curzon and Knott, 1974; Curzon, 1979) and extent of competition with Trp for entry into the brain mainly from five other amino acids (valine, leucine, isoleucine, phenylalanine and tyrosine), known collectively as the competing amino acids (CAA) (Fernstrom and Wurtman, 1971). The most accurate predictor of brain Trp, and hence 5-HT, changes is therefore the ratio of concentrations of serum Trp to the sum of those of its five competitors, i.e. the  $[Trp]/[CAA]$  ratio, which is now widely used to assess the central serotonin-biosynthetic status. Using a modified ratio, that of  $[Trp]$  to the sum of only the first three of the above five competitors, it has been shown (Castell *et al.*, 1999) that patients with the CFS have a high free (i.e. non-albumin-bound)  $[Trp]/[CAA]$  ratio. In the present study, we report a detailed examination of Trp metabolism and disposition in 23 CFS patients and establish the heterogeneity of the serotonin status in, and discuss its implications for the treatment of, this condition.

## Subjects and methods

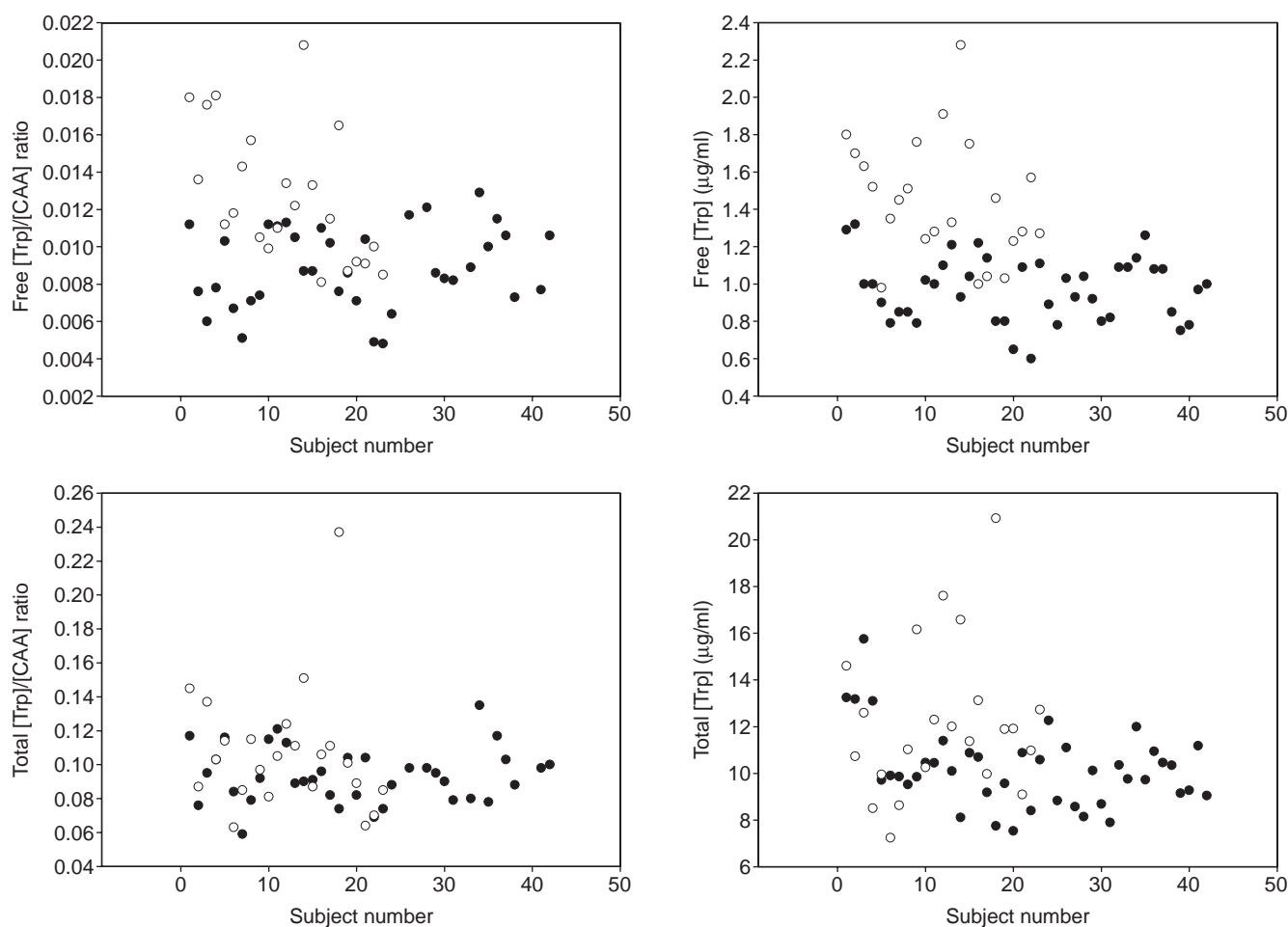
### *Subjects and study design*

This was an open prospective study of 23 patients with the chronic fatigue syndrome (CFS) attending the outpatient Fatigue Clinic at the University Hospital of Wales, Cardiff, UK. The subjects were studied between 6 July 1998 and 19 February 2001. The mean age ( $\pm$ SD) of the 23 patients was  $41.0 \pm 8.9$  years (range: 21–55 years). Of the 23 subjects, nine were males and 14 were females, and the mean ages ( $\pm$ SD) of these two subgroups were  $37.1 \pm 10.7$  and  $43.4 \pm 6.8$  years respectively (ranges were 21–55 for males and 27–55 for females). The 17% higher mean age for the female subgroup was not statistically significant ( $p = 0.1$ , one-way analysis of variance). The subjects were diagnosed according to, and fulfilled, the criteria for the CFS (Fukuda *et al.*, 1994). Other diagnoses were excluded by examination, routine blood tests and past medical history. Major depression, except for melancholic depression, is not an exclusion criterion for the CFS; only one subject had depression, without melancholia, so they were not excluded. Screening for depression was performed using the Hospital Anxiety and Depression Scale, with the slowed-down question deleted and a cut-off of 11. Because only one subject had depression, in the statistical analysis of the results, depression was not co-varied. Most of the subjects arrived at the clinic fasting and gave their consent for venesection after a full explanation of the reasons for the study, which was approved by our local (Bro-Taff) Health Authority's relevant Ethics Committee. Of the 23 CFS patients, 15 fasted overnight (at least 10 h), whereas the remaining eight had only light breakfasts (mainly toast). Of these eight, six subjects had serum glucose levels of 88–110 mg/dl, i.e. within the

fasting normal range; the other two had higher levels. Of these eight subjects, six also had normal Trp/CAA ratios, whereas the remaining two had a low and a high ratio respectively, despite having normal glucose levels. From these data and analysis of variance of the results obtained from fasting and non-fasting CFS patients as separate subgroups (see the 'Results' section), we conclude that, in our experiments, overall, the light breakfast exerted no significant effects on parameters of tryptophan metabolism and disposition or availability to the brain in these eight subjects. Of these 23 CFS patients, only four were receiving medication: two on temazepam (patients nos 11 and 15), one on hormone-replacement therapy (patient no. 1) and one on sertraline 50 mg (patient no. 8). However, the results from these four subjects, all of whom were in the fasting state, gave no indication or trend suggesting any differences from the group as a whole (see the scatter plots in Fig. 1). The control group consisted of 42 healthy volunteers from among the Whitchurch Hospital medical and nursing staff and science and medical students in Cardiff, who also gave informed consent to participate in tryptophan-related research projects, also approved by the relevant local Ethics Committee. All subjects in the control group fasted overnight before providing their blood samples. The mean age ( $\pm$ SD) of the 42 control subjects was  $27.8 \pm 7.3$  years. The mean ages of the 16 females and 26 males constituting this control group were  $28.4 \pm 10.0$  and  $27.4 \pm 5.2$  years respectively, with no significant differences ( $P = 0.67$ ; one-way ANOVA). It is clear from these values and those for the CFS patient group described above that, although there were no significant gender differences in age within either the control or the CFS group, the latter group as a whole was significantly older than the control group ( $p < 0.0001$ ; one-way ANOVA).

### *Laboratory procedures*

A venous-blood sample (15–20 ml) was obtained from an antecubital vein from each subject between 10.00 AM and 12.30 PM, from which serum was isolated within 2 h. A 1 ml portion of serum was ultrafiltered immediately after isolation, using the Amicon Micropartition MPS-1 assembly (Amicon Ltd, Upper Mill, Stonehouse, Gloucestershire, GL10 2BJ, UK) by centrifugation in a bench centrifuge at 2000g for 20–30 min at room temperature. Both the ultrafiltrate and its parent serum were then frozen at  $-40^\circ\text{C}$  until analysis of the various parameters described below, within 1–3 days. Serum free and total  $[Trp]$  were determined by a modification (Bloxam and Warren, 1974) of a fluorimetric method (Denckla and Dewey, 1967), as described previously (Badawy and Evans, 1976). Albumin (Doumas and Biggs, 1972), the physiological binder of Trp, non-esterified fatty acids (NEFA) (Mikac-Dević *et al.*, 1973), the physiological displacers of albumin-bound Trp, glucose (Slein, 1963), which can influence Trp entry into the brain through insulin (and also to confirm fasting) and kynurenine (Joseph and Risby, 1963), an index of hepatic Trp oxidation by Trp pyrrolase, were all determined by standard procedures. Routine clinical laboratory procedures were used to determine the serum concentrations of cortisol (the physiological inducer of hepatic Trp pyrrolase) (by radioimmunoassay at the Department of Medical Biochemistry, University Hospital of Wales, Cardiff) and



**Figure 1** Scatter plots of parameters of the serotonin status in controls and in patients with the chronic fatigue syndrome (CFS). Free and total [Trp] and the [Trp]/[CAA] ratios were determined as described in the 'subjects and methods' section in 23 CFS patients (○) and 37–42 control subjects (●)

amino acids (by autoanalyser at the Institute of Medical Genetics, University of Wales College of Medicine, Cardiff). From the latter, the [Trp]/[CAA] ratios were determined to assess Trp entry into the brain and, hence, central serotonin synthesis.

### Statistical procedures

Statistics and graphics were performed using Stat-100 (Biosoft, Cambridge, UK), SPlus-6 (Insightful, Basingstoke, UK) and Sigma Plot 2001 (Statistical Solutions, Cork, Ireland). One- and two-way analysis of variance (ANOVA) was performed, with gender, condition and grouped age as factors. Age correlations were investigated using simple linear regression and Spearman's Rank correlation. To avoid spurious significances due to multiple testing, all data were fit simultaneously to a linear model, with gender and condition as factors and age as a continuous variable. Fitted models were subjected to stepwise regression analysis to

eliminate unimportant predictors. All tests were two-tailed, and a probability of  $\leq 0.05$  was taken as significant.

### Results

#### *Comparisons of parameters of tryptophan metabolism and disposition in the CFS patient and control groups*

The various parameters of Trp metabolism and disposition and related metabolic processes in sera of patients with the chronic fatigue syndrome (CFS) and control subjects are shown in Table 1. The mean serum free and total Trp concentrations were significantly higher in the CFS patient, compared to the control, group. The elevation was greater in free (48%), than in total (19%), [Trp]. As a result of these different elevations, the percentage free serum Trp, an expression of Trp binding to albumin, was 24% higher in

CFS patients, compared to controls. This latter value is close to that (26%) in the difference between CFS patients and controls in the levels of NEFA, the physiological displacers of albumin-bound Trp, which were higher in the patient group. Albumin concentration itself was, however, also higher in CFS patients, but only slightly (by 6%), if significantly. Serum glucose concentration was also moderately (14%) higher in CFS patients, compared to controls. By contrast, no significant differences in serum cortisol or kynurenine concentrations were observed between CFS patients and controls, though data for these two parameters in the control group were derived only from males and females respectively.

The results in Table 1 also show parameters of Trp availability to the brain. The serum [free Trp]/[CAA] ratio in the CFS patient group was significantly higher (by 43%) than that of the control group. The serum [total Trp]/[CAA] ratio was moderately (14%) higher in the CFS patient group, though this difference did not reach statistical significance. The sum of the five Trp competitors, i.e. the [CAA], was not significantly different between the two study groups.

### Role of gender and age

When both the CFS patient and control group results in Table 1 were analysed by gender, no significant gender differences were detected in the control group. By contrast, the only significant differences observed in the CFS patient group were a lower (16%;  $p < 0.0396$ ) [CAA] and a higher (58%;  $p < 0.01$ ) [kynurenine] in females, compared to males.

To examine the potential role of age in the Trp changes, linear regression and/or Spearman's Rank correlation analyses were performed on the Trp parameters in Table 1 which showed significant group differences. No significant correlations with age were observed for free serum or total serum [Trp], or the free or total

serum [Trp]/[CAA] ratio in either controls or CFS patients (data not shown).

Because of the age difference between the control and CFS patient groups and as a significantly lower [CAA] was observed in female, compared to male, CFS patients, the results of the Trp parameters in Table 1 determining the serotonin-biosynthetic status were further subjected to linear modelling, with gender, age and condition as predictors of parameter levels. No significant effects of gender or age were found ( $p > 0.27$ ), whereas the effects of the condition on the Trp parameters (except the [total Trp]/[CAA] ratio) were highly significant ( $p \leq 0.0052$ ).

### Lack of effect of light breakfast on parameters of tryptophan metabolism and disposition

As eight out of the 23 CFS patients consumed a light breakfast (mainly toast and tea), the results from these subjects were analysed separately from those of the 15 fasting subjects. One-way ANOVA with replicate measures revealed a modest (19%) but significant ( $p = 0.04$ ) difference between fasting and non-fasting subjects (means  $\pm$  SD for 15 fasting and eight non-fasting subjects respectively) only for serum [free Trp] ( $1.55 \pm 0.32$  vs  $1.26 \pm 0.26$ ), a not unexpected finding, since fasting is known to increase this parameter (Curzon and Knott, 1974). No significant differences between fasting and non-fasting CFS patients were, however, observed in any of the following serum parameters: [total Trp] ( $11.99 \pm 3.10$  vs  $12.53 \pm 3.62$ ;  $p = 0.71$ ), [CAA] ( $577 \pm 128$  vs  $572 \pm 97$ ;  $p = 0.92$ ), [free Trp]/[CAA] ratio ( $0.0136 \pm 0.0037$  vs  $0.0111 \pm 0.0029$ ;  $p = 0.10$ ), [total Trp]/[CAA] ratio ( $0.1041 \pm 0.0268$  vs  $0.1132 \pm 0.0524$ ;  $p = 0.58$ ), [albumin] ( $48.9 \pm 3.7$  vs  $52.1 \pm 3.5$ ;  $p = 0.06$ ), [non-esterified fatty acids] ( $0.54 \pm 0.28$  vs  $0.52 \pm 0.15$ ;  $p = 0.88$ ), [glucose] ( $126 \pm 32$  vs  $112 \pm 28$ ;  $p = 0.34$ ).

**Table 1** Parameters of tryptophan metabolism and disposition in controls and in patients with the chronic fatigue syndrome

Parameter	Control group	Chronic fatigue patients	Significance* ( $p$ )
Free [Trp] ( $\mu\text{g/mL}$ )	$0.97 \pm 0.17$	$1.45 \pm 0.32$	0.0000
Total [Trp] ( $\mu\text{g/mL}$ )	$10.19 \pm 1.66$	$12.18 \pm 3.22$	0.0016
Free Trp (%)	$9.62 \pm 1.51$	$11.90 \pm 3.14$	0.0000
NEFA (mM)	$0.42 \pm 0.14$	$0.53 \pm 0.24$	0.0192
Albumin (g/L)	$46.7 \pm 3.8$	$49.7 \pm 3.9$	0.0016
Glucose (mg/dL)	$106 \pm 10$	$121 \pm 31$	0.0058
Cortisol (nM)	$367 \pm 145$	$362 \pm 125$	ns
Kynurenine ( $\mu\text{g/mL}$ )	$0.50 \pm 0.08$	$0.52 \pm 0.20$	ns
[CAA] ( $\mu\text{M}$ )	$556 \pm 110$	$575 \pm 116$	ns
[Free Trp]/[CAA] ratio	$0.0089 \pm 0.0021$	$0.0127 \pm 0.0036$	0.0000
[Total Trp]/[CAA] ratio	$0.094 \pm 0.016$	$0.107 \pm 0.037$	0.0562**

Values are means  $\pm$  SD for 23 subjects in the chronic fatigue group, except for kynurenine ( $n = 22$ ) and cortisol ( $n = 18$ ), and for 42 subjects in the control group, except for [CAA] and the [Trp/CAA] ratios ( $n = 37$ ), cortisol ( $n = 22$ , males only) and kynurenine ( $n = 16$ , females only). ns, denotes not significant. \*ANOVA with replicated measures followed by Duncan's multiple comparison test. \*\*The [total Trp]/[CAA] ratio differences became highly significant ( $p < 0.0000$ ) following two-way ANOVAs with age and gender as covariates.

### Identification of two subgroups of CFS patients by their serotonin status

We observed wide individual differences in the Trp parameters, which determine the serotonin status in both the 23 CFS patients and the 42 control subjects, as illustrated in the scatter plots shown in Fig. 1. We should like to suggest here criteria for the serotonin status, from which ranges of control values could be established. A normal serotonin status must be defined primarily in terms of normal serum free and total [Trp]/[CAA] ratios and, preferably but not essentially, also normal free and total [Trp]. By contrast, a high or a low serotonin status should be associated with at least one high or one low [Trp]/[CAA] ratio respectively, and also, preferably but not essentially, at least one high or one low [Trp] respectively. From the mean values of these four parameters in the 42 control subjects shown in Table 1 and applying cut-off values of  $\pm 2$  SDs, we propose that abnormal values should lie outside the following normal ranges (in  $\mu\text{g/ml}$  or  $\mu\text{M}$ , or as ratios): free serum [Trp] (0.64–1.32  $\mu\text{g/ml}$ , or 3–6  $\mu\text{M}$ ); total serum [Trp] (7.13–13.51  $\mu\text{g/ml}$ , or 35–66  $\mu\text{M}$ ); free serum [Trp]/[CAA] ratio (0.0047–0.0131); total serum [Trp]/[CAA] ratio (0.062–0.126).

Applying these criteria, and in comparison with the control group, we found (Table 2) that, of the 23 CFS patients, 13 had a normal, whereas ten had a high, serotonin status. Comparison of the mean values ( $\pm$ SD) between the normal serotonin and the high serotonin subgroups revealed significant differences in three of the four parameters, namely the two essential ones (the [Trp]/[CAA] ratios) and also the free serum [Trp] (Table 2). Of the 13 subjects constituting the normal serotonin subgroup, 12 had normal values of all four parameters; the thirteenth had normal ratios, but high free and total [Trp]. Of the ten subjects in the high serotonin subgroup, four showed higher values of all four parameters, whereas the remaining six subjects all had a high free [Trp]/[CAA] ratio, with five having also a high free [Trp] and the sixth high free and total [Trp].

## Discussion

The results of this study show that, as a group, patients with the chronic fatigue syndrome (CFS) have an increased availability to the brain of the serotonin precursor tryptophan, as expressed by the serum [free Trp]/[CAA] ratio (Table 1), and may thus generally appear to exhibit a central serotonin excess. This was the con-

clusion of a previous study (Castell *et al.*, 1999) with ten CFS patients, in which an elevated ratio of [free Trp] to the sum of three of the five circulating Trp competitors was demonstrated. An increase in the [Trp]/[CAA] ratio could be caused by an increase in [Trp], a decrease in [CAA] or both. As the results in Table 1 of the present work show, [CAA] was not different between controls and CFS patients. The above higher [free Trp]/[CAA] ratio in CFS patients is therefore due solely to the higher serum [free Trp]. The latter is mainly due to a higher circulating concentration of the physiological displacers of albumin-bound Trp, namely non-esterified fatty acids (NEFA), as the elevation of the latter (26%) was similar in magnitude to that (24%) in the percentage free serum Trp, an expression of Trp binding to albumin (Table 1). If the increase in [free Trp] was accompanied by either no change, or even a decrease, in [total Trp], then Trp displacement by NEFA would be the only mechanism involved (Curzon and Knott, 1974; Badawy, 1977). However, as serum [total Trp] was also increased (though less strongly, by only 19%), an additional mechanism must also be operating, namely that of a lower liver Trp pyrrolase activity (Badawy, 1977) in CFS patients. The mechanism(s) of such a possible decrease requires investigation. One possible mechanism is that of a low circulating concentration of the major glucocorticoid inducer of Trp pyrrolase, cortisol. However, although serum cortisol values determined at a single time point in the small CFS sample of the present study were not lower than those in the control group, evidence for hypocortisolaemia in the CFS has been demonstrated in studies measuring 24 h urinary free cortisol levels (Cleare *et al.*, 2001) and dexamethasone suppression over 2 days (Gaab *et al.*, 2002).

As the CFS patients were significantly older than the controls, we explored whether age was a confounder of the above results. No significant age correlations were obtained for any of the parameters listed in Table 1. Similarly, no significant gender differences were observed, except for a lower [CAA] and a higher [kynurenine] in females, compared to males, of the CFS patient group. Future studies with larger numbers of subjects will therefore need to consider these gender-specific differences. Two-way ANOVAs with gender or age as covariates, however, showed highly significant group differences ( $p < 0.0000$ ) in all four Trp parameters involved in determining the serotonin status.

Trp availability to the brain was not, however, increased in all 23 patients with the CFS. From the scatter-plots in Fig. 1, which show wide individual variations in Trp disposition parameters in both the control and CFS patient groups, we have established

**Table 2** Provisional classification of patients with the chronic fatigue syndrome into two subgroups with a normal and a high serotonin status

Parameter of serotonin status	Normal serotonin subgroup ( $n = 13$ )	High serotonin subgroup ( $n = 10$ )	Significance* ( $p$ )
Free [Trp]/[CAA] ratio	0.0101 $\pm$ 0.0013	0.0161 $\pm$ 0.0025	0.0000
Total [Trp]/[CAA] ratio	0.092 $\pm$ 0.018	0.127 $\pm$ 0.046	0.0195
Free [Trp] ( $\mu\text{g/ml}$ )	1.26 $\pm$ 0.22	1.71 $\pm$ 0.25	0.0002
Total [Trp] ( $\mu\text{g/ml}$ )	10.66 $\pm$ 3.56	13.25 $\pm$ 4.08	0.1189

\*ANOVA with replicated measures followed by Duncan's multiple comparison test.

criteria for assessing the serotonin-biosynthetic status based on new, if provisional, normal ranges (see the 'Results' section), and propose that CFS patients could be divided into two subgroups; one with a normal and the other with a high serotonin status (see Table 2). Future studies with larger numbers will test the validity of this proposed classification. Our proposed heterogeneity of the serotonin status in the CFS is, however, supported by the contradictory results of previous neuroendocrine and related studies (Bakheit *et al.*, 1992; Bearn and Wessley, 1994; Cleare *et al.*, 1995; Yatham *et al.*, 1995) suggesting that not all CFS patients have enhanced serotonergic function. Also, although we recognize that increased serotonin synthesis is not always synonymous with enhanced serotonin function, it is unlikely that CFS subjects who synthesize more serotonin will have impaired serotonin metabolism, as there is currently no evidence for decreased serotonin turnover in this condition. Such subjects should therefore be expected to have increased serotonin turnover and release, parameters usually associated with enhanced serotonin function.

If the present results are confirmed, our proposals should have important implications for the pharmacotherapy of the CFS. Serotonin-modifying and other antidepressants are prescribed to CFS patients to treat depression (if present), pain and/or fatigue. However, CFS patients with serotonin excess should not be exposed to, and are unlikely to benefit from, serotonin-modifying antidepressants, particularly selective serotonin-re-uptake inhibitors (SSRIs), to avoid a potential excessive serotonin hyperactivity. Similarly, in view of the well known Trp-SSRI interaction, the latter should not be prescribed to CFS patients with high Trp levels or increased availability to the brain. By contrast, as suggested by a meta-analysis of previous pharmacological trials (O'Malley *et al.*, 1999) and a survey of psychiatrists (Hickie *et al.*, 1999), tricyclic antidepressants have a greater likelihood of efficacy than SSRIs, are preferred by patients with chronic pain, and have superior antinociceptive properties in fibromyalgia (McQuay *et al.*, 1996). Also, our clinical impression suggests that tricyclic antidepressants improve sleep disturbances in, and are better tolerated than SSRIs by, CFS patients.

A high level of brain serotonin may also be important in relation to other therapies, which influence this indolylamine, such as exercise and diet. Exercise is a recognized therapy of the CFS (McCully *et al.*, 1996), but it is also known to increase serum [free Trp] and the [free Trp]/[CAA] ratio in normal subjects (Newsholme *et al.*, 1991) by a mechanism involving NEFA-mediated release of serum albumin-bound Trp. In CFS patients, however, exercise fails to increase Trp availability to the brain (Castell *et al.*, 1999). In this latter study, only one exercise session was conducted, and it is therefore important to establish if a repeated exercise programme in CFS patients is associated with normalization of the above Trp response and whether such a potential normalization is related to, or indeed predictive of, therapy outcome. Food can also have profound effects on Trp disposition, with carbohydrate increasing (Madras *et al.*, 1973), and protein decreasing (Møller, 1985), brain [Trp] and hence serotonin synthesis and turnover. If our results are confirmed, CFS patients with excess serotonin could be advised to avoid eating carbohydrate-rich foods

and targeted to adjunctive nutritional strategies aimed at reducing their high central serotonin levels.

The present results suggest that further research on the serotonin status of patients with the CFS should yield important information for the appropriate management of, and advice and ultimately a better service provision to sufferers from, this condition, in accord with the aims of recent recommendations (Clark *et al.*, 2002).

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