Brain 5-HT$_{1A}$ Receptor Binding in Chronic Fatigue Syndrome Measured Using Positron Emission Tomography and [^{11}C]WAY-100635

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Background: *Research from neuroendocrine challenge and other indirect studies has suggested increased central 5-HT function in chronic fatigue syndrome (CFS) and increased 5-HT$_{1A}$ receptor sensitivity. We assessed brain 5-HT$_{1A}$ receptor binding potential directly using the specific radioligand [^{11}C]WAY-100635 and positron emission tomography (PET).*

Methods: *We selected 10 patients from a tertiary referral clinic who fulfilled the CDC consensus criteria for CFS. To assemble a homogenous group and avoid confounding effects, we enrolled only subjects who were completely medication-free and did not have current comorbid psychiatric illness. We also scanned 10 healthy control subjects.*

Results: *There was a widespread reduction in 5-HT$_{1A}$ receptor binding potential in CFS relative to control subjects. This was particularly marked in the hippocampus bilaterally, where a 23% reduction was observed.*

Conclusions: *There is evidence of decreased 5-HT$_{1A}$ receptor number or affinity in CFS. This may be a primary feature of CFS, related to the underlying pathophysiology, or a finding secondary to other processes, such as previous depression, other biological changes or the behavioral consequences of CFS.*

Key Words: Chronic fatigue syndrome, 5-HT$_{1A}$ receptor binding potential, serotonin, myalgic encephalomyelitis

Chronic fatigue syndrome (CFS) is an operationally defined syndrome in which prolonged, disabling, and medically unexplained fatigue is the primary complaint (Fukuda et al 1994; Sharpe et al 1991). The development and persistence of CFS is related to a number of biopsychosocial factors that are likely to be heterogeneous in nature (Wessely et al 1998). Nevertheless, research attempting to delineate possible neurochemical and, in particular, serotonergic dysfunction has developed over the last decade.

Early studies in humans suggested that normal fatigue after exercise is associated with a rise in plasma tryptophan, the amino-acid precursor of 5-HT, and a reduction in other amino acids (Blomstrand et al 1988). The effect of a rise in blood tryptophan is to increase levels of tryptophan entering the brain, and, because the rate-limiting enzyme in 5-HT synthesis is nonsaturated, increase brain 5-HT production. Thus, it was hypothesized that increased brain 5-HT levels could be at least partly responsible for the subjective feeling of fatigue (Blomstrand et al 1988). Further support for this hypothesis came from studies showing that healthy subjects who were administered a tryptophan load complained of fatigue, mental slowness and lack of vigor (Cleare 1998).

Following this, there have been a number of studies attempting indirectly to assess brain serotonergic function in CFS itself, and several intriguing findings have emerged. Initially, Demitrack et al (1992) found increased levels of 5-HIAA, the breakdown product of 5-HT, in the cerebrospinal fluid (CSF) and plasma of CFS patients, suggesting increased central turnover of 5-HT in the brain. The link between these measures and brain 5-HT metabolism is unclear, however; most of the 5-HT in plasma can be shown to be of gut origin, whereas a large proportion of that in the CSF comes from the spinal cord rather than the brain. Results from neuroendocrine challenge studies have provided additional information. Two studies using the selective 5-HT-releasing drug D-fenfluramine found increased prolactin responses in CFS patients compared with control subjects, suggesting increased neurotransmission across serotonergic pathways, though a study using the less selective D,L-fenfluramine failed to confirm this (Cleare 1998). Two studies have assessed 5-HT$_{1A}$ receptor function directly using challenge with the 5-HT$_{1A}$ agonist buspirone. Increased prolactin responses were found in both studies in CFS compared with control subjects (Bakheit et al 1992; Sharpe et al 1996), suggesting increased sensitivity of 5-HT$_{1A}$ receptors, although Sharpe and colleagues suggested that the dopaminergic effects of buspirone may have been responsible for this effect given the absence of an increased growth hormone response in their study. Dinan et al (1997) used the more specific 5-HT$_{1A}$ agonist ipsapirone; while they found reduced corticotropin (ACTH) and normal cortisol responses compared with control subjects, this measure could have been confounded by the generally reduced magnitude of ACTH and cortisol responses to a variety of challenges in CFS (Cleare 2003), and growth hormone and prolactin were not measured.

In summary, then, there is some evidence that increased 5-HT production may contribute to normal fatigue and that in CFS there is increased turnover of 5-HT and increased serotonergic synaptic transmission. The evidence specifically supporting up-regulation of 5-HT$_{1A}$ receptors is weaker. Nevertheless, there is much evidence of involvement of this receptor in depression (Maes and Meltzer 1995; Sargent et al 2000), a condition with some overlapping symptoms but possibly a contrasting serotonergic profile (Cleare et al 1995). Furthermore, the 5-HT$_{1A}$ receptor appears to be powerfully regulated by the hypothalmic-

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Table 1. Details of Subjects

	CFS Subjects (n = 10)	Control Subjects (n = 10)
Age Range (years)	35–56	30–56
Age Mean ± SD (years)	46.5 ± 5.9	40.7 ± 10
Gender (Male/Female)	8/2	9/1
Weight (kg)	82.0 ± 14.4	86.1 ± 10
Illness Duration (years)	3.1 ± 2.0	—
Fatigue Questionnaire Score (max = 33)	27.4 ± 1.0	—
GHQ-12 Score (max = 36)	18.6 ± 7.1	—
BDI Score (max = 63)	11.1 ± 6.8	—
Spielberger Trait Anxiety Score (max = 80)	40.9 ± 10.9	—
Spielberger State Anxiety Score (max = 80)	34.6 ± 10.1	—
Disability Score (WSAS; max = 40)	27.3 ± 5.0	—
Past Psychiatric History	6/10	0/10
Past Use of Antidepressants	10/10	0/10
Activity Injected (MBq)	355 ± 22	307 ± 46
Specific Activity (MBq/μmol)	87416	156936
Weight of Unlabeled WAY-100635 (μg)	3.2 ± 3.1	1.1 ± .6
Weight of WAY 100634 (μg)	3.0 ± 2.8	5.0 ± 4.4

BDI, Beck Depression Inventory; CFS, chronic fatigue syndrome; GHQ-12, General Health Questionnaire, 12-item; WSAS, Work and Social Adjustment Questionnaire.

pituitary-adrenal (HPA) axis (Chaouloff 1993). Because there is evidence to suggest a mild hypocortisolemic state in CFS (Cleare 2003), it might be expected that this would be associated with 5-HT_{1A} receptor changes. Thus, given the preliminary neuroendocrine evidence of 5-HT_{1A} receptor upregulation, the overlap with depression and the link with the HPA axis, we felt it was necessary to assess more directly the status of 5-HT_{1A} receptors in CFS. We did this by measuring 5-HT_{1A} receptor binding potential using PET and the selective 5-HT_{1A} receptor ligand WAY-100635. To avoid confounding effects of other conditions that can affect brain serotonergic function, we attempted to recruit CFS patients without a current comorbid psychiatric diagnosis. Although the previous evidence as reviewed earlier was not entirely consistent, we hypothesized that we would find evidence of enhanced 5-HT_{1A} receptor binding in CFS.

Methods and Materials

Subjects

Ten patients (eight men and two women) with chronic fatigue syndrome were recruited from an established CFS referral clinic at King's College Hospital, London (Table 1). All clinic attenders were assessed using a thorough semistructured examination (Sharpe et al 1997a) at initial consultation to evaluate CFS and the presence of additional psychiatric disorder. Patients were included if they fulfilled both international consensus criteria for CFS (i.e., the Oxford criteria; Sharpe et al 1991) and the more restrictive CDC criteria (Fukuda et al 1994). These criteria exclude patients with a past or current diagnosis of psychotic, melancholic or bipolar depression; psychosis; dementia; or eating disorder. No subjects had alcohol or substance abuse for 2 years before the onset of symptoms or any time thereafter. All patients had received a thorough medical screening to exclude an underlying organic cause, including physical examination and relevant investigation, with a minimum of urinalysis, full blood count, urea and electrolytes, thyroid function tests, liver function tests, and erythrocyte sedimentation rate. The absence of comorbid psychiatric disorder in included patients was confirmed by using the Structured Clinical Interview for DSM-IV, performed by a psychiatrist (AJC). Patients filled in several self-rating questionnaires, including the 12-item General Health Questionnaire (GHQ), Likert scored; the Work and Social Adjustment Scale (WSAS) as a measure of disability; the 11-item Chalder fatigue scale; the Beck Depression Inventory (BDI); and the Spielberger State-Trait Anxiety Inventory.

Exclusion criteria were the presence of any current comorbid psychiatric disorder according to DSM-IV criteria; the presence of comorbid fibromyalgia according to the consensus criteria of the American College of Rheumatology (Wolfe et al 1990); significant abnormalities on screening investigations; illness duration greater than 100 months; use of prescribed medication in the 2 months before study entry; and an inability to attend hospital for scanning.

Ten healthy volunteers were used as a control group and received contemporaneous [^{11}C]WAY-100635 PET scans (Table 1). There were no significant differences with the Student *t* test in any of the demographic or PET related (specific activity of radioligands, weight of unlabeled WAY-100635 or its precursor WAY-100634) variables, with the exception of the amount of activity injected, which was moderately (16%) but significantly higher in CFS patients than in control subjects. Healthy volunteers were screened clinically for medical and psychiatric disorders by a psychiatrist performing a routine clinical interview and the Structured Clinical Interview for DSM-IV. Details of all subjects including psychometric assessment results are shown in Table 1. Results of the assessment of lifetime psychiatric diagnosis found that 6 of the 10 CFS patients, but none of the control subjects, had a previous history of major depression.

Both patients and control subjects were scanned within the same time period (February 1999–December 2000). All were right-handed. All subjects gave informed written consent to the study, which was approved by the local ethics committees (Hammersmith Hospital and Maudsley Hospital), and permission was obtained from the Administration of Radioactive Substances Advisory Committee of the United Kingdom.

PET Scanning Protocol

PET scans were performed on an ECAT 935B PET camera (CTI, Knoxville, Tennessee) at the Medical Research Council Cyclotron Unit, Hammersmith Hospital, London. This scanner acquires 31 planes of data with an axial field of view of 10.5 cm. Subjects were positioned in the scanner, parallel to the orbitomeatal line, so as to include the cerebellum and the brainstem in the field of view.

[Carbonyl-11C]WAY-100635 was prepared at the Medical Research Council Cyclotron Unit (McCarron et al 1996) and passed standard quality control before being injected into the subjects. A 10-min transmission scan was acquired in two-dimensional mode for correction of tissue attenuation. Subjects received an average of 340 MBq of [^{11}C]WAY-100635 injected intravenously over 30 sec. Dynamic PET data were acquired in three-dimensional mode for 90 min after injection (Gunn et al 1998). The emission data were attenuation and scatter corrected (Grootoonk et al 1996) and reconstructed using a reprojection algorithm (Kinahan and Rogers 1989).

Kinetic Modeling of [^{11}C]WAY-100635 Emission Data

Quantitative tracer kinetic modeling was performed using a simplified reference tissue compartmental model, with the cere-