

Relative increase in choline in the occipital cortex in chronic fatigue syndrome

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Objective: To test the hypothesis that chronic fatigue syndrome (CFS) is associated with altered cerebral metabolites in the frontal and occipital cortices.

Method: Cerebral proton magnetic resonance spectroscopy (^1H MRS) was carried out in eight CFS patients and eight age- and sex-matched healthy control subjects. Spectra were obtained from $20 \times 20 \times 20 \text{ mm}^3$ voxels in the dominant motor and occipital cortices using a point-resolved spectroscopy pulse sequence.

Results: The mean ratio of choline (Cho) to creatine (Cr) in the occipital cortex in CFS (0.97) was significantly higher than in the controls (0.76; $P = 0.008$). No other metabolite ratios were significantly different between the two groups in either the frontal or occipital cortex. In addition, there was a loss of the normal spatial variation of Cho in CFS.

Conclusion: Our results suggest that there may be an abnormality of phospholipid metabolism in the brain in CFS.

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Introduction

Recent work has shown that simple reaction times are longer in patients with chronic fatigue syndrome (CFS) than in controls, despite electrophysiological indices of corticospinal excitability and inhibition being within the normal range (1, 2). There is strong evidence that simple reaction time indexes the functioning of both the frontal and occipital lobes (3–5). Furthermore, CFS patients have significantly lower cortical to cerebellar regional cerebral blood flow ratios throughout multiple brain regions, particularly in the frontal and occipitoparietal lobes (6). Based on these findings, we hypothesized that such patients have altered cerebral metabolites in the frontal and occipital cortices.

Aims of the study

Our aim was to test our hypothesis by carrying out the first investigation of cerebral metabolites in the frontal and occipital cortices in CFS using proton magnetic resonance spectroscopy (^1H MRS).

Material and methods

Eight patients with CFS (mean age = 42.7 years, $\text{SD} = 8.4$ years; six females and two males) were compared with eight healthy normal controls (mean age = 40.1 years, $\text{SD} = 8.8$ years; four males and four females) with no known medical or psychiatric disorder. The patients were diagnosed according to the criteria of Fukuda et al. (7) and were investigated by a general physician and a psychiatrist to exclude any other medical or psychiatric disorder. None of the patients fulfilled the DSM-IV or ICD-10 criteria for a psychiatric disorder. All the patients and controls were of similar socio-economic and educational status and all were right-handed. None were on medications which might affect metabolites measured using cerebral ^1H MRS. After complete description of the study to the subjects, written informed consent was obtained.

^1H MRS data were obtained using a 1.5 T Marconi Eclipse system (Marconi Medical Systems, Cleveland, OH, USA) and a birdcage quadrature head coil. Spectra were obtained from $20 \times 20 \times 20 \text{ mm}^3$ voxels in the dominant (left) motor and occipital cortices using a point-resolved

spectroscopy (PRESS) pulse sequence. A repetition time of 1500 ms, echo time of 135 ms and 128 data collections were used.

Peak areas for the *N*-acetylaspartate (NAA), choline (Cho) and creatine (Cr) resonances were calculated using a proprietary Marconi (formerly Picker) software package (Marconi Medical Systems, Cleveland, OH, USA) and the ratios NAA:Cho, NAA:Cr and Cho:Cr of the two groups were compared.

The study was carried out according to the Declaration of Helsinki. The patients and control subjects were given both verbal and written details of the study and gave written informed consent. The study was approved by the relevant ethics committees.

Results

The two groups did not differ significantly with respect to sex (Fisher’s exact probability test, $P > 0.6$) or age ($t = 1.72$, $df = 14$, $P = 0.11$ (two-tailed)).

The cortical metabolite ratios are shown in Table 1. It can be seen that regional differences in NAA:Cho and Cho:Cr that occurred in the controls was not present in the patients.

There were no significant differences in Cho levels between the males and females in the control group. In the motor cortex, the mean Cho:Cr ratio was 1.15 (SD = 0.11) in the male controls and 0.89 (SD = 0.29) in the female controls ($t = 1.66$, $df = 6$, $P = 0.15$ (two-tailed)). In the occipital cortex, the mean Cho:Cr ratio was 0.71 (SD = 0.16) in the male controls and 0.80 (SD = 0.04) in the female controls ($t = 1.00$, $df = 6$, $P = 0.35$ (two-tailed)).

A rearrangement of the data in Table 1 to analyze group differences is shown in Table 2. It can be seen that in the occipital cortex the mean Cho:Cr ratio was significantly higher in the patients than in the controls. No other metabolite

Table 1. Regional comparisons of metabolite ratios between the motor cortex and occipital cortex in patient and control groups

Metabolite ratio (SD)	Motor cortex	Occipital cortex	<i>t</i>	df	<i>P</i> (two-tailed)
CFS patients					
NAA:Cr	1.88 (0.21)	1.94 (0.19)	0.532	7	0.61
NAA:Cho	1.85 (0.25)	2.03 (0.24)	1.86	7	0.11
Cho:Cr	1.02 (0.07)	0.97 (0.15)	1.51	7	0.17
Normal controls					
NAA:Cr	1.92 (0.38)	1.86 (0.58)	0.317	7	0.76
NAA:Cho	2.00 (0.11)	2.43 (0.11)	3.34	7	0.01
Cho:Cr	1.02 (0.10)	0.76 (0.14)	2.69	7	0.03

Table 2. Comparison of metabolite ratios between the patient and control groups

Metabolite ratio (SD)	CFS patients	Normal controls	<i>t</i>	df	<i>P</i> (two-tailed)
Motor cortex					
NAA:Cr	1.88 (0.21)	1.92 (0.38)	0.228	14	0.82
NAA:Cho	1.85 (0.25)	2.00 (0.11)	0.600	14	0.56
Cho:Cr	1.02 (0.07)	1.02 (0.10)	0.035	14	0.97
Occipital cortex					
NAA:Cr	1.94 (0.19)	1.86 (0.58)	0.390*	8.51*	0.71
NAA:Cho	2.03 (0.24)	2.43 (0.11)	2.00	14	0.07
Cho:Cr	0.97 (0.15)	0.76 (0.14)	3.11	14	0.008

*Unequal variances.

ratios were significantly different between the two groups in either the frontal or occipital cortex.

Discussion

First, the mean Cho:Cr ratio was significantly higher in the chronic fatigue patients than in the controls in the occipital cortex. Second, in the normal controls, but not in the patients, NAA to Cho and Cho to Cr (but not NAA to Cr) differed between the motor and occipital cortices. Since cerebral Cr levels tend to be relatively stable, the results of this first study of CFS using ¹H MRS suggest that Cho is significantly increased in the occipital cortex in this disorder, and that there is a difference in relative Cho levels between the motor and occipital cortex in the controls. The latter finding is consistent with previous reports of spatial variation of Cho levels in normal subjects (8).

Increased Cho levels are associated with abnormal membrane phospholipid metabolism, specifically relating to phospholipid head groups (9). Hence our findings of increased Cho levels in the occipital cortex and of a loss of the normal spatial Cho variation in the patients suggest that there may be an abnormality of phospholipid metabolism in the brain in CFS.

It should be noted that while ratios to Cr are frequently reported in the literature, these ratios have limitations. The peak contains both phosphocreatine and Cr which sometimes differ between psychiatric groups. (For this reason, some groups report absolute levels based on the water signal.)

These results add weight to the recently reported perfusion studies (6) suggesting that pathophysiological changes in CFS may occur in the occipital cortex.

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