The following excerpted article was published by researchers at the U.S. Centers for Disease Control & Prevention (CDC). We have, ourselves, italicized some of the more interesting findings. You can read the entire article by going to the link given. Please note the terms of use provisions given by the article.

The findings contained in the article demonstrate distinct metabolic changes on exercise challenge as a result of altered gene expression in Chronic Fatigue Syndrome (CFS) patients versus healthy controls.

Please note: The pilot study report excerpted below is based on an extremely small sample: 5 women with CFS and 5 female healthy controls. Therefore, a new study with a larger sample-size would have to be done to confirm these findings.

Moreover, the CFS subjects were selected according to the 1994 CDC CFS case definition. As we know, this definition is a very broad one that can lead to a confounding of research findings due to inclusion of subjects who may not have CFIDS.

We do, however, find the results interesting and hope they will be replicated in a larger study.

Toni Whistler, James F. Jones, Elizabeth R. Unger and Suzanne D. Vernon, "Exercise responsive genes measured in peripheral blood of women with Chronic Fatigue Syndrome and matched control subjects," *BMC Physiology* (2005) 5:5 doi:10.1186/1472-6793-5-5

The electronic version of this article is the complete one and can be found online at: http://www.biomedcentral.com/1472-6793/5/5

Abstract

Background

Chronic fatigue syndrome (CFS) is defined by debilitating fatigue that is exacerbated by physical or mental exertion. To search for markers of CFS-associated post-exertional fatigue, we measured peripheral blood gene expression profiles of women with CFS and matched controls before and after exercise challenge.

Results

Women with CFS and healthy, age-matched, sedentary controls were exercised on a stationary bicycle at 70% of their predicted maximum workload. Blood was obtained before and after the challenge, total RNA was extracted from mononuclear cells…We identified differences in gene expression among and between subject groups before and after exercise challenge and evaluated differences in terms of Gene Ontology categories.

Exercise-responsive genes differed between CFS patients and controls... Differences in ion transport and ion channel activity were evident at baseline and were exaggerated after exercise, as evidenced by greater numbers of differentially expressed genes in these molecular functions.

Conclusion

These results highlight the potential use of an exercise challenge combined with microarray gene expression analysis in identifying gene ontologies associated with CFS.

Background

In a state of health, physical exercise has a quantifiable effect on neuroendocrine, autonomic, and immune systems influencing metabolic and immune responses. However, in the initial phase of acute illness, there is an avoidance of physical stressors so energy can be dedicated to healing and a return to homeostasis. While physiologic disturbance in acute illness is transient, chronic illnesses, such as chronic fatigue syndrome (CFS), have prolonged

disturbances that have a debilitating effect both physiologically and psychologically. Consequently, activities that are physiologic stressors, such as physical exercise, exacerbate the symptoms that define CFS.

CFS is a complex, multifactorial illness whose etiology and pathophysiology remain unclear [1]. CFS is defined by a characteristic symptom complex in the absence of other medical or psychiatric conditions with similar clinical characteristics [2,3]. Subtle differences in hypothalamic-pituitary-adrenal axis function [4], immune system function [5], and psychological profiles [6] between CFS patients and controls have been reported; however, no consistent distinguishing difference or frank abnormality has been confirmed [7,8], and it remains unclear whether CFS represents a unique disease or a common illness response to a variety of insults.

Perhaps the greatest methodological problem with studying CFS is that many individuals identified in population studies have been sick for at least 5 years [9]. During this time, the illness waxes and wanes, making it difficult to identify biomarkers or define pathogenesis. Physical, mental, and emotional stress exacerbate CFS and result in case-defining post-exertional fatigue [2] with measurable physiologic differences [10]. Therefore, exercise challenge of people with CFS is an effective method for calibrating CFS subjects and thus increasing the likelihood of uniformly identifying biomarkers and/or physiologic abnormalities.

We used gene expression profiling of peripheral blood to evaluate differences between CFS subjects and sedentary healthy controls both before and following an exercise challenge. Overall, we found the gene expression profiles to be quite similar, and of importance, most differences were present prior to exercise challenge. These differences were in G protein-coupled receptor and ion transport and ion channel activity ontologies. The latter was exaggerated after exercise as evidenced by differential expression of a greater number of genes involved in these molecular functions. Differences were also evident in exercise response, including chromatin and nucleosome assembly, cytoplasmic vesicles, membrane transport and G-protein coupled receptor ontologies. These differences may help explain the symptoms of CFS.

Results

Exercise response genes were evaluated using a random variance test in a paired, class comparison analysis of control subjects before and after exercise, and 21 genes were identified

as being differentially expressed…

Since these 21 genes reflect a healthy subject's peripheral blood gene expression response to exercise challenge, we reasoned that the expression of these would be altered in CFS subjects… The response of 10 of the 21 genes was quite similar in terms of magnitude and direction for both CFS and control subjects… For the other 11 genes, the magnitude of the exercise change was considerably smaller in CFS subjects… than in control subjects… However, 5 genes classified in vesicle-mediated and protein-transport ontologies differed between CFS and control subjects…
…Exercise-related changes that were seen only in CFS subjects were related to G-protein-coupled receptor signaling (purple, Figure 2b).

Gene ontology comparison was also used to evaluate differences between control and CFS subjects before…and after…exercise. *Baseline differences between CFS subjects and controls that continued after exercise involved GO terms relating to ion transport…*
After exercise, these differences appear to be amplified, as evidenced by increased numbers of genes present in these GO categories and also by inclusion of more GO terms pertaining to ATPase transmembrane movement of ions… G-protein-coupled receptor binding… part of the broad functional category of signal transduction, differed between CFS subjects and controls prior to exercise.
This baseline difference between controls and CFS subjects was not significant after exercise. Interestingly, complement activation…was one of the exercise-induced differences between subjects and controls that was present only after challenge. Genes in most of the ontologies identified as different between CFS and control subjects had lower expression levels in CFS subjects.

Discussion

Gene expression profiling affords a unique opportunity to characterize CFS at a systems biology level. Changes in gene expression underlie many biologic processes and may provide insight into disease-specific gene expression and the response of genes to environmental stimuli. In *a proof-of-concept study, we found that CFS patients had different blood mononuclear cell gene expression patterns than non-fatigued controls*
… and that CFS is a heterogeneous illness as evidenced by different gene expression profiles for patients reporting gradual onset of their illness compared with those reporting sudden onset of illness…
In addition, differential display polymerase chain reaction on a small number of CFS and control subjects identified candidate biomarkers in the peripheral blood…

CFS is defined by a post-exertional fatigue that does not subside 24 hours following physical stress. In contrast, exercise in healthy, untrained people induces changes in cellular homeostasis in 1 to 4 hours and a return to basal levels within 24 hours, as measured in muscle… In contrast, 11 of the genes were unchanged in CFS subjects before and after exercise; with 5 being classified in a transport-related ontology. Because this difference in gene expression is so dramatic, *it implicates a fundamental perturbation in the biochemical activity of lymphocyte and monocyte peripheral blood fractions from CFS subjects compared with control subjects* that does not affect classical immunologic markers (i.e, CD45) that have been shown to be unaffected in CFS patients…
Rather, low expression of these genes may have subtle effects on immune function. Immune dysfunction has been inconsistently implicated in CFS pathogenesis…

Class comparison was used to identify these 21 differentially expressed genes, which indicated the possible disturbance of biologic pathways… To explore this possibility, we used the GO comparison that is based on the knowledge that gene expression levels are dependent variables in biological processes, cellular components, and molecular functions. In this way, multiple genes in the same category reinforce each other and enhance the power for identifying the significance of the category. The GO categories considered significantly different (p

It is evident that ion transport and ion channel activity segregate cases from controls and that exercise seems to intensify these differences. Several other conditions have been reported in which fluctuating fatigue occurs that are known to be caused by abnormal ion channels. These conditions include genetically determined channelopathies and acquired conditions such as neuromyotonia, myasthenic syndromes, multiple sclerosis, and polyneuropathies…
There are other transmembrane functions associated with differences between controls and CFS patients, including signal transducer activity through receptor binding/activity
… Signal transduction of transmembrane receptors occurs by a number of mechanisms, including structural changes, ion channels, and changes of transmembrane potentials. The G-protein-coupled receptors play an important role in the membrane trafficking machinery… The most obvious exercise-induced changes in CFS cases pertain to gene regulation at the point of chromatin structure; whether these changes reflect the differences seen in the mRNA transcripts relating to membrane trafficking differences between cases and controls has not yet been determined. One interesting correlate of this study was the finding that the complement pathway showed significant differences between CFS and control subjects after exercise. This has been reported previously in the analysis of these same exercise challenge-derived specimens. Sorensen et al.… measured levels of complement split products in the sera of these subjects and found differences between CFS and control subjects in C4a after exercise challenge. Complement activation was identified as an ontology that was significantly different between CFS and control subjects after exercise. The correlates on the data are interesting as their study measured protein levels (i.e., gene product levels) and this study measured the transcript levels…

The lack of statistical significance in the 3 other class comparison analyses performed (CFS cases compared before and after exercise, comparison of cases to controls at baseline, and the comparison of cases to controls 24 hours after exercise) reflects low experimental sensitivity, most likely due to a small number of subjects, rather than an absence of biological effect…

The next line of research will detail larger numbers of subjects in the expression arrays. The emphasis in such studies will be on developing a gene expression-based multivariate function, or predictor, that accurately predicts the class membership of a new sample on the basis of the expression levels of key genes. Class discovery tools will also be applied to CFS subjects' expression profiles in an attempt to further describe discrete subsets of this disease on the basis of gene expression as we have done for gradual and sudden onset of illness… *However, the methods used in this study will be applied to these data sets too, as these analytical tools will prove to be very helpful in defining the pathophysiology of CFS. It is hoped that this broader, more fully encompassing approach to CFS research will open many doors to the understanding of this syndrome and perhaps of fatigue and un-wellness in general.*