Psychoneuroendocrinology (2013) 38, 2983—2995

Available online at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/psyneuen

Differing leukocyte gene expression profiles associated with fatigue in patients with prostate cancer versus chronic fatigue syndrome

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Received 8 March 2013; received in revised form 22 August 2013; accepted 27 August 2013

KEYWORDS
Prostate cancer;
Chronic fatigue syndrome;
Fatigue;
qPCR;
Gene expression;
Purinergic;
GABA-receptor modulator;
Cytokine

Summary
Background: Androgen deprivation therapy (ADT) often worsens fatigue in patients with prostate cancer, producing symptoms similar to chronic fatigue syndrome (CFS). Comparing expression (mRNA) of many fatigue-related genes in patients with ADT-treated prostate cancer versus with CFS versus healthy controls, and correlating mRNA with fatigue severity may clarify the differing pathways underlying fatigue in these conditions.
Methods: Quantitative real-time PCR was performed on leukocytes from 30 fatigued, ADT-treated prostate cancer patients (PCF), 39 patients with CFS and 22 controls aged 40—79, together with ratings of fatigue and pain severity. 46 genes from these pathways were included: (1) adrenergic/monoamine/neuropeptides, (2) immune, (3) metabolite-detecting, (4) mitochondrial/energy, (5) transcription factors.
Results: PCF patients showed higher expression than controls or CFS of 2 immune transcription genes (NR3C1 and TLR4), chemokine CXCR4, and mitochondrial gene SOD2. They showed lower expression of 2 vasodilation-related genes (ADRB2 and VIPR2), 2 cytokines (TNF and LTA), and 2

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0306-4530/$ — see front matter
http://dx.doi.org/10.1016/j.psyneuen.2013.08.008

metabolite-detecting receptors (ASIC3 and P2RX7). CFS patients showed higher P2RX7 and lower HSPA2 versus controls and PCF. Correlations with fatigue severity were similar in PCF and CFS for only DBI, the GABA-A receptor modulator ($r = -0.50$, $p < 0.005$ and $r = -0.34$, $p < 0.05$). Purinergic P2RY1 was correlated only with PCF fatigue and pain severity ($r = +0.43$ and $+0.59$, $p = 0.025$ and $p = 0.001$).

Conclusions: PCF patients differed from controls and CFS in mean expression of 10 genes from all 5 pathways. Correlations with fatigue severity implicated DBI for both patient groups and P2RY1 for PCF only. These pathways may provide new targets for interventions to reduce fatigue.

With 98% of prostate cancer patients surviving for 5 years or more after diagnosis and initial treatment, it is increasingly important to determine the physiological pathways underlying symptoms that affect quality of life (QOL) in these survivors, and to improve medical management of these symptoms. One symptom with a powerful impact on QOL is cancer-related fatigue (CRF), defined by the National Comprehensive Cancer Network as a persistent subjective sense of tiredness that interferes with daily functioning, is not proportional to activities, is not fully relieved by rest, and results in a chronic state of exhaustion. CRF is reported to seriously affect QOL in over 40% of prostate cancer patients treated with androgen deprivation therapy (ADT) (Escalante and Manzullo, 2009; Storer et al., 2012). ADT with leuprolide and related drugs is the current treatment of choice to improve survival for metastatic prostate cancer patients, who often use ADT for many months or years. ADT is also used, with lower doses and shorter treatment periods, for localized prostate cancer.

It is clear that the initiating causes of fatigue in ADT-treated prostate cancer patients are primarily the cancer itself and the treatments for that cancer; however, the specific fatigue-related neurological, energy metabolism and immune pathways that are functionally altered by these causal factors and may enhance daily fatigue in ADT-treated prostate cancer have not been established. Jager et al. (2008) has proposed that pro-inflammatory changes in immune function, anemia, and altered activity of the hypothalamic-pituitary-adrenal (HPA) and serotonergic systems may individually or interactively contribute to this excess fatigue. Similarly, Ryan et al. (2007) hypothesized that: ''In any individual, the etiology of CRF probably involves the dysregulation of several physiological and biochemical systems . . . 5-HT neurotransmitter dysregulation, vagal afferent activation, alterations in muscle and ATP metabolism, hypothalamic-pituitary-adrenal axis dysfunction, circadian rhythm disruption, and cytokine dysregulation.'' If these specific dysregulated pathways are identified, targeted treatments to alleviate this CRF may be developed.

One approach that has been used to examine pathways associated with fatigue in breast cancer and during interferon-alpha treatment in chronic hepatitis, as well as in other disorders such as chronic fatigue syndrome (CFS) and multiple sclerosis (MS), is to examine peripheral blood cell gene expression (mRNA) of multiple fatigue-related genes (Kerr, 2008; Light et al., 2009, 2012; Bower et al., 2011a,b; Felger et al., 2012; White et al., 2012). This method is efficient by allowing many physiological targets to be examined from a single blood sample, and the mRNA reflects both genetic (inherited) and environmental influences. Because environmental influences vary across individuals and over time in the same individual, the latter is either a strength or a vulnerability depending upon whether stability is a significant concern. For CFS, studies attempting to use such gene expression as a stable and reproducible diagnostic biomarker have been unable to replicate a consistent profile of differences from controls, due in part to the heterogeneity of the syndrome and to month-to-month variations in status (Kerr, 2008; Galbraith et al., 2011; Frampton et al., 2011). The less challenging objective in the current study was to use leukocyte gene expression to identify potentially dysregulated pathways linked to pathological fatigue in ADT-treated prostate cancer or CFS. For this objective, the same pattern of differential effects need not be present in all or even the majority of these patients but possibly only in subgroups whose levels influence group means. Of specific interest in this regard are the patients whose current fatigue level is more severe.

Many fatigue-related symptoms reported by ADT-treated prostate cancer patients overlap with those reported by patients with CFS, including earlier fatigue onset and decreased performance during exercise, low energy, disturbed sleep, muscle weakness, and increased ''mental fog'', and immune-related symptoms like feelings of unwellness (Jager et al., 2008; Saylor et al., 2009; Storer et al., 2012). Other symptoms seem specific to the syndrome of CFS, including post-exertional malaise, widespread muscle and joint pain with no evidence of injury, and orthostatic intolerance (Fukuda et al., 1994; Saiki et al., 2008; White et al., 2012). Thus, it is plausible that debilitating daily fatigue in these two chronic conditions may involve both shared and different physiological pathways.

In the present study, we used 46 genes representing 5 general pathways: (1) adrenergic, monoamine and peptides; (2) immune response and inflammation; (3) sensory ion channel receptors responding to adenosine triphosphate (ATP) and other metabolites of muscle activity; (4) mitochondrial and other genes involved in lipid/energy metabolism; and (5) transcription and growth factors (see Table 1). Among these are genes that were over-expressed during our prior studies of post-exertional fatigue in CFS: both sensory (ASIC3, P2RX4, TRPV1) and adrenergic receptors (ADRA2A, ADRA2C, ADRB1, ADRB2) and cytokines IL6, IL10, TNF (formerly TNFα) and LTA (formerly TNFβ). Because of the importance of ATP in muscle activity, we included other purinergic ion-channel ATP-receptors, P2RX1 and P2RX7, and G protein coupled purinergic receptors P2RY1 and P2RY2, as well as another subtype of the acid-sensing family, ASIC1, and another transient vanilloid receptor, TRPV4. Based on prior research (Saiki et al., 2008; Hsiao et al., 2013), we also included genes with