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Cortisol secretion and fatigue: Associations in a community based cohort

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Summary The association between fatigue and reduced activity in the hypothalamo-pituitary—adrenal (HPA) axis has been described. However the temporal association between fatigue and HPA activity is under debate. We examine whether alterations in cortisol secretion play a role in the development of fatigue or whether changes occur later as a consequence of fatigue in a longitudinal cohort study of 4299 community dwelling adults (mean age 61). Cortisol secretion was measured from saliva samples collected waking, waking + 0.5, 2.5, 8, 12 h and bedtime at phase 7 (2003—2004) of the Whitehall II study. Fatigue was measured at phase 6 (2001), phase 7 and phase 8 (2006) of the Whitehall II study. Three elements of secretion were examined: waking cortisol, the cortisol awakening response and diurnal slope in cortisol secretion. Fatigue was determined using the vitality sub-scale of the Short Form-36. A wide variety of co-variates were measured. We find that fatigue measured at phase 6 was not associated with cortisol secretion at phase 7. At phase 7, low waking cortisol levels and a flat slope in diurnal cortisol secretion were associated with fatigue independently of co-variates. In participants low or free of fatigue at phase 7 low waking cortisol and flatter slope in cortisol secretion were associated with new-onset fatigue at phase 8 (for example, odds ratio for lowest vs. highest tertile of waking cortisol 1.50; 95% confidence intervals, 1.08, 2.09 after adjusting for all co-variates). In conclusion, we find that low waking salivary cortisol and a flat slope in cortisol secretion is associated with fatigue. Cortisol is also associated with future onset of fatigue suggesting that changes in cortisol secretion are etiologic or occur early in the genesis of fatigue.

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1. Introduction

Fatigue is a symptom of Addison's disease, or primary adrenal failure, suggesting that diminished adrenal steroid production is linked with fatigue (Werbel and Ober, 1993). A number of clinical and case—control studies on post-traumatic stress disorder, chronic fatigue syndrome (CFS) and fibromyalgia, which all feature fatigue as a symptom suggest that these syndromes have low levels of the adrenal corticosteroid cortisol (Fries et al., 2005; Van Den Eede et al., 2007; Nater et al., 2008). These findings are not apparent in all studies (Crofford et al., 2004; Di Giorgio et al., 2005). Diurnal cortisol release is typically characterized by high levels upon waking, an increase of some 50—60% in cortisol concentration following awakening (called the cortisol awakening response or CAR), and a subsequent decline over the remainder of the day, reaching a low point or nadir around midnight. Studies that fail to show diminished cortisol secretion in association with fatigue have generally measured morning or serum cortisol which is not analysed in relation to waking (Crofford et al., 2004; Di Giorgio et al., 2005). Recent evidence from 77 patients suggests that mild hypocortisolism found in CFS can be reversed by cognitive behavioral therapy (Roberts et al., 2009).

Research on non-clinical populations suggests cortisol to be associated with concepts close to fatigue, such as burnout and vital exhaustion (Appels, 1990; Melamed et al., 2006; Ter Wolbeek et al., 2007). Evidence of the direction of the association between diminished cortisol secretion and fatigue is limited. Thus, it is unclear whether alterations in cortisol secretion play a role in the development of fatigue or whether changes in cortisol develop later as a consequence of co-morbidities associated with fatigue and related syndromes (Wessely et al., 1995; Candy et al., 2003; Cleare, 2003). For example, fatigue in burnout, which is a concept used in a work-related context, may have a different aetiology to fatigue associated with vital exhaustion which is a health related concept. In these cases changes in cortisol may be related to the syndromes rather than fatigue per se.

A recent study of 77 apparently healthy participants found cortisol secretion to be associated with fatigue assessed by the 'vitality' sub-scale of the Short Form-36 scale, a measure of health related quality of life (Lindeberg et al., 2008). These data, in which low cortisol at waking and flattened decline (slope) in diurnal cortisol secretion was associated with exhaustion, suggest that the association of cortisol with fatigue may be apparent in non-patient populations before the onset of overt disease. The etiology of hypocortisolism is unclear and may represent an adaptation or response to chronic stress (McEwen, 1998; Fries et al., 2005). The etiology of flattened diurnal slopes in cortisol secretion is unclear. Flattened slopes in cortisol are reportedly predictive of mortality in cancer patients (Sephton et al., 2000).

A short term longitudinal study, conducted over the course of several days, provides initial evidence that low morning cortisol may precede fatigue symptoms in non-patient populations (Adam et al., 2006). In this study, fatigue assessed the day before was not associated with diminished cortisol secretion the next morning, but low morning cortisol secretion was associated with increased fatigue later in the same day (Adam et al., 2006). However, the status of cortisol as a long term predictor of future or persistent fatigue symptom reporting has not been described in community dwelling populations.

In this longitudinal epidemiological study of over 4000 participants, we examine cortisol secretion from saliva samples collected across one single day and fatigue, assessed by score in the vitality sub-scale of the SF-36 approximately 2.5 years before, concurrently with and 2.5 years after cortisol assessment. We address two questions: first, is fatigue an independent predictor of future derangements in cortisol secretion in a community dwelling population? Secondly, does cortisol secretion predict future fatigue? We also examine the role of persistent fatigue in these associations and take into account a wide variety of potential confounding factors, including depressive symptoms, sleep disturbance and use of medication.

2. Methods

2.1. Study population

The Whitehall II study was originally recruited as an occupational cohort and was designed to examine the mechanisms by which social position impacts health. The cohort was initially recruited between 1985 and 1988 (phase 1) from 20 London based civil service departments, 10,308 people participated (response 73%). The cohort was predominantly male (66% men) and participants were aged between 39 and 55 at baseline. Eight phases of the study have been completed, details of the cohort profile have been reported elsewhere (Marmot and Brunner, 2005). This study used data from phase 6 (2001), phase 7 (2002—2004) when cortisol was measured and phase 8 (2006). The number of participants at phase 7 was 6941; of these 6484 (93.4%) had a clinical assessment, the collection of saliva samples was instigated part way through phase 7 and of those eligible for cortisol assessment 4609 (90.1%) returned samples. In analyses reported here, fewer participants were in the lowest employment grades compared to the baseline population of the study, however this difference was small. Ethical approval for the Whitehall II study was obtained from the University College London Medical School committee on the ethics of human research.

2.2. Saliva collection and cortisol analysis

The protocol for saliva collection has been described previously (Badrick et al., 2007). Briefly, participants that agreed, were requested to provide six saliva samples over the course of a normal weekday at waking, waking + 30 min, waking + 2.5 h, waking + 8 h, waking + 12 h and bedtime. Participants were instructed to record the time of sample collection in an instruction booklet (the 'logbook') to record information on wake time and stressful events on the day of sampling. The salivettes and logbook were then returned via post. Salivette devices were centrifuged at 3000 rpm for 5 min resulting in a clear supernatant of low viscosity. Salivary cortisol levels were measured using a commercial immunoassay with chemiluminescence detection (CLIA, IBL-Hamburg, Hamburg, Germany). The lower concentration limit of this assay is 0.44 nmol/l; intra- and interassay coefficients of variance were below 8%. Any sample over 50 nmol/l was repeated.