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Depression, evening salivary cortisol and inflammation in chronic fatigue syndrome: A psychoneuroendocrinological structural regression model

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ABSTRACT

Introduction: Chronic Fatigue Syndrome (CFS) is a poorly understood illness that is characterized by diverse somatic symptoms, hypothalamic pituitary adrenal (HPA) axis dysfunction and heightened inflammatory indicators. These symptoms are often exacerbated and accompanied by psychological distress states and depression. Since depression is known to be associated with HPA axis dysfunction and greater inflammation, a psychoneuroendocrinological (PNE) model of inflammation was examined in persons diagnosed with CFS in order to uncover underlying biopsychosocial mechanisms in this poorly understood chronic illness.

Methods: Baseline data were drawn from two randomized controlled trials testing the efficacy of different forms of psychosocial intervention, and included psychological questionnaires, di-urnal salivary cortisol, and blood samples. Data were analyzed with structural equation modeling (SEM).

Results: The sample (N = 242) was mostly middle-aged (M_{age} = 49.36 ± 10.9, range = 20–73 years), Caucasian (70.1%), female (84.6%), highly educated (88.6% completed some college, college, or graduate program), and depressed (CES-D M = 23.87 ± 12.02, range 2–57). The SEM supporting a psychoneuroendocrinological model of immune dysregulation in CFS fit the data χ^2 (12) = 17.725, p = 0.1243, RMSEA = 0.043, CFI = 0.935, SRMR = 0.036. Depression was directly related to evening salivary cortisol and inflammation, such that higher evening cortisol predicted greater depressive symptoms (β = 0.215, p < 0.01) and higher pro-inflammatory cytokines (interleukin-2 [IL-2], IL-6, and tumor necrosis factor-alpha [TNF-α] levels (β = 0.185, p < 0.05), when controlling for covariates.

Discussion: Results highlight the role of depression, cortisol and inflammation in possible biological mechanisms involved in the pathophysiology of CFS. Time-lagged, longitudinal analyses are needed to fully explore these relationships.

1. Introduction

Chronic fatigue syndrome (CFS) is a chronic unremitting condition with an estimated worldwide prevalence of 0.8–3.5% (Bhui et al., 2011), and is overrepresented among women (Klimas and Koneru, 2007). The disorder is a mysterious and debilitating inflammatory illness with no known etiology or cure. CFS symptoms include debilitating fatigue, post-exertional malaise, sore throat, and unrefreshing sleep, among other varied somatic symptoms (Fukuda et al., 1994). Research has revealed physiological manifestations of the disease, such as dysregulated cortisol awakening response (CAR) and cytokine expression imbalance, which are both shown to be associated with psychological distress in otherwise healthy individuals and those suffering from similar disorders such as fibromyalgia (Marques et al., 2009; Menzies et al., 2013a; Powell et al., 2013; Sutcigil et al., 2007; Vreeburg et al., 2013). However, there is less known about how cortisol relates to inflammatory cytokine levels in this patient population.

Cortisol dysregulation has been shown in CFS (Nater et al., 2008), which is significant because chronically dysregulated cortisol can result in poorer inflammatory control (Cohen et al., 2012). Periods of

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increased perceived stress or depression can have deleterious effects on immune functioning (Anderson et al., 2014; Silverman and Sternberg, 2012; Wright et al., 2015). The concept of allostatic load, which was put forth by McEwen and colleagues (McEwen, 2000) may be relevant here (Arroll, 2013). One of the concepts in allostatic load is the idea that cortisol is immunosuppressive under short term, acute conditions. However, with chronic increased cortisol secretion, the cells and tissues of the body become less responsive to cortisol (i.e., glucocorticoid resistance, GR) (Cohen et al., 2012; Marques et al., 2009; McEwen, 2000). Once glucocorticoid resistance occurs, immune cells are less responsive to the immunosuppressive actions of cortisol; therefore, pro-inflammatory cytokine production is relatively uninhibited (Cohen et al., 2012; Marques et al., 2009; McEwen, 2000; Silverman and Sternberg, 2012).

Hypothalamic pituitary adrenal (HPA) axis functioning can be evaluated in many ways. The cortisol awakening response (CAR) either with respect to baseline or increased levels (area under the curve with respect to ground [AUCg] and increase [AUCi], respectively), cortisol diurnal slope, and evening cortisol levels are all indicators of HPA functioning and have been implicated in chronic stress and depression (Herbert, 2013; Hsiao et al., 2010; Powell et al., 2013). Given the putative role of inflammatory signaling in CFS (Broderick et al., 2010; Fletcher et al., 2009; Jason et al., 2011; Klimas and Koneru, 2007; Morris et al., 2016b; Peterson et al., 2015), it is important to evaluate the effect of HPA functioning on inflammatory markers in CFS patients, yet little work exists, especially using structural modeling techniques.

Because links between psychological adversity and neuroimmune processes (i.e. glucocorticoid resistance and inflammation) have been established in many conditions (Cohen et al., 2012; Marques et al., 2009; Pace et al., 2007), it is important to consider the role of psychological distress states such as depression in CFS (Jason et al., 2011). CFS is commonly comorbid with depression. In a study comparing CFS, fibromyalgia and irritable bowel syndrome, CFS sufferers experienced more mood and anxiety disorders (ORs = 2.00–4.08 and 1.63–2.32, respectively) than the other groups (Janssens et al., 2015). The interaction of HPA dysregulation, depression, and inflammation may account for the debilitating fatigue and somatic symptoms of CFS/ME by way of sickness behavior processes (Dantzer et al., 2008; Maes, 2011). There is evidence that HPA dysregulation predicts depression and inflammation, and that depression itself is also directly linked to inflammation; however, a model simultaneously examining the direct and indirect effects of depression on cortisol variables and inflammation has not yet been tested in the CFS population using statistical approaches such as structural equation modeling (SEM) (Maes, 2011; Menzies et al., 2013b; Morris et al., 2016a). Analytical approaches such as SEM are particularly useful for simultaneously estimating indirect and direct effects of factors that are possibly involved in the dysregulation of homeostatic systems evident in this heterogeneous disorder. The present study aims to test a psychoneuroendocrinological model in this patient population to examine the inter-relationships among depressive symptoms and multiple indicators of HPA axis function and inflammation.

2. Methods

2.1. Participants

Participants in this study were participating in one of two trials evaluating the effects of psychosocial interventions. Baseline data using in this analysis were derived from the women who participated in the trials. Recruitment procedures for one of these trials are described elsewhere, and reflect the procedures used in the second trial (Hall et al., 2014; Lattie et al., 2012). All participants received a physician-determined CFS diagnosis, as defined by the CDC criteria (Fukuda et al., 1994). Recruitment methods included physician referral, support groups, CFS conferences and advertisements in CFS-related websites. Participants were eligible if they were fluent in English, and were between the ages of 21 and 75 years.

Potential participants were excluded from the study if they met criteria for schizophrenia, bipolar disorder, substance abuse, or if they were actively suicidal, as assessed by a brief screening measure adapted from the Structured Clinical Interview for the DSM-IV (First et al., 1997). Participants were also excluded if they showed markedly diminished cognitive capabilities, as evidenced by making four or more errors on the Short Portable Mental Status Questionnaire (Pfeiffer, 1975). Presence of another condition (e.g. AIDS, lupus, rheumatoid arthritis) that might influence biological processes associated with CFS symptomatology, or taking medications that would modulate immune or neuroendocrine functioning excluded participants from the study. Potential participants were also excluded from the study if they were suffering from untreated obstructive sleep apnea (OSA). A total of approximately 220 screened participants were excluded from the two studies.

Participants who met criteria signed an informed consent form and were administered a battery of self-report measures. Salivary cortisol samples were collected for two consecutive weekdays, and a blood sample was drawn by a certified phlebotomist, all within a span of 10 days. After completing these assessments participants were compensated with $50.

2.2. Center for Epidemiologic Studies Depression Scale (CES-D)

The CES-D (Radloff, 1977) is a 20-item measure that assesses depressive symptomatology over the past week. Participants were asked questions such as “I felt sad” and responded on a 4 point scale ranging from “Rarely or none of the time (< 1 day)” to “Most or All of the Time (5–7 days).” A score of 16 or above indicates clinically significant depressive symptoms. The reliability coefficient for the CES-D is 0.85 in the general population, 0.90 in an in-patient psychiatric population (Radloff, 1977), and 0.88 in a chronically ill population of HIV patients (Gay et al., 2016).

2.3. Salivary cortisol

We provided the participants with 8 Salivette® tubes, as described previously (Hall et al., 2014; Lattie et al., 2012). Participants provided saliva samples from two consecutive weekdays, on which they were asked to take a sample at awakening, 30 min after awakening, at 4 pm and at 9 pm. Participants were instructed to abstain from eating or drinking before and between the first two samples each day, and to avoid eating a large meal an hour before the afternoon and evening samples. Participants were also asked to avoid alcohol for at least 12 h prior to sample collection and to avoid vigorous exercise on sample collection days. Following the collection of samples, participants were instructed to freeze the Salivette® tubes in their home freezers in order to keep the salivary cortisol stable until it was retrieved by a member of the study staff or mailed back to the lab. Once received, saliva samples were frozen at − 20 °C until enough samples were accumulated to be assayed in batches. On the day of the assay, saliva samples were thawed, vortexed and centrifuged at 1500 RPM for 15 min. Samples were then assayed using the Salimetrics high sensitivity ELISA kit (State College, PA). The present study only focused on awakening and 30 minutes post awakening to calculate the AUC values. In addition evening (9 pm) averaged cortisol values were computed separately. Area under the curve with respect to ground (AUCg) and increase (AUCi) were also calculated (Powell et al., 2013). AUC values were used to approximate the cortisol awakening response (CAR), while evening cortisol was analyzed separately.

2.4. Circulating pro-inflammatory cytokines

Blood was centrifuged and plasma stored at − 80 °C within 4 h of