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Hair and salivary cortisol in a cohort of women with chronic fatigue syndrome

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ABSTRACT

Hypocortisolism has been found in CFS patients in blood, urine, and saliva. It is unclear if hypocortisolism can also be demonstrated using long-term cortisol measurements, such as cortisol in hair. In addition, the interaction between the HPA axis and the immune system, both expected to play an important role in CFS, is unclear. The objective of the current study was to compare hair and salivary cortisol concentrations in a cohort of female CFS patients to those in healthy controls, and to test the effect of an interleukin-1 receptor antagonist (anakinra) on the HPA axis. Salivary cortisol concentrations of 107 CFS patients were compared to 59 healthy controls, with CFS patients showing a decreased cortisol awakening response (4.2 nmol/L ± 5.4 vs 6.1 nmol/L ± 6.3, $p = 0.036$). Total cortisol output during the day did not differ significantly in saliva, but there was a trend to lower hair cortisol in a subset of 46 patients compared to 46 controls (3.8 pg/mg ± 2.1 vs 4.3 pg/mg ± 1.8, $p = 0.062$). After four weeks of treatment with either daily anakinra (100 mg/day) or placebo, there was a slight decrease of hair cortisol concentrations in the anakinra group compared to an increase in the placebo group ($p = 0.022$). This study confirms the altered dynamics of the HPA axis in a group of CFS patients, and for the first time shows that this might also be present for long-term cortisol measures.

1. Introduction

Since the first publication by Demitrack and colleagues in 1991 (Demitrack et al., 1991), numerous studies have been performed investigating alterations of the hypothalamic-pituitary-adrenal (HPA) axis in patients with chronic fatigue syndrome (CFS). This interest is predominantly caused by the overlap of CFS symptoms with diseases characterized by hypocortisolism such as Addison's disease, where 95% of patients report fatigue at diagnosis (Erichsen et al., 2009). Several case definitions for CFS exist and, according to most of them, severe and persisting fatigue is its central feature (Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness, 2015). The Center for Disease Control (CDC) criteria for CFS are most often used in research and require that at least four out of eight accompanying symptoms have to be present in addition to fatigue (e.g., joint pain, concentration problems, unrefreshing sleep, and post-exertional malaise) (Reeves et al., 2003).

Studies investigating the relationship between levels of cortisol, the end product of the stress-responsive HPA axis, and CFS thus far have been summarized in a review by Papadopoulos and Cleare (Papadopoulos and Cleare, 2011). Despite the large heterogeneity between studies, it was concluded that there is substantial evidence for hypocortisolism in CFS. This was also described in a meta-analysis by Tak et al. (Tak et al., 2011), where a significantly decreased activity of the HPA axis was found, which was more frequent in studies predominantly including women. A potential mechanism underlying the pathophysiology of hypocortisolism in CFS appears to be an heightened negative feedback response (Jerjes et al., 2007), although it is unclear whether this is of etiological importance or rather a consequence of for example the use of medication (Tak et al., 2011), widespread pain (Riva et al., 2012), or illness duration (Fries et al., 2005).

Limitations of studies previously performed are the relatively small samples sizes and differences in the type of cortisol measurement. HPA axis deregulation can be manifested in disturbed short term dynamics of cortisol or alterations of the chronic cortisol secretion. Cortisol can be measured in various media, for example blood, saliva, urine, and hair.

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Saliva is usually depicted as the preferred method, as it offers insight into short term cortisol fluctuations (diurnal rhythm, response to a stimulus), which makes it a useful method to investigate the functional dynamics of the HPA axis. On the other hand, the hair cortisol concentration (HCC) offers information on long-term activity of the HPA axis (Stalder and Kirschbaum, 2012). An advantage of this measurement is that it is less influenced by situational factors, and may thus constitute a more stable measure (Stalder and Kirschbaum, 2012).

Another important issue when investigating the HPA axis is its interaction with other bodily systems, for example the immune system, where increased activity of the HPA axis has an inhibitory effect on the production of pro-inflammatory cytokines (Wolf et al., 2009). In the context of CFS this is of particular interest, as alterations of inflammatory activity have been described in CFS for many years (Roerink et al., 2015). It is suspected that increased activity of pro-inflammatory cytokines, for example interleukin-1 (IL-1) and tumor necrosis factor (TNF), lead to the experience of typical CFS symptoms often described as sickness behavior (Dantzer et al., 2008). The attention for this subject is reflected by the large quantity of studies measuring circulating cytokines in CFS (Blundell et al., 2015). In a complex illness, like CFS, it is likely that the interaction between the neuroendocrine system and the immune system is altered. A decreased inhibitory effect of dexamethasone on the immune system has already been established in adolescent CFS patients (Kavelaars et al., 2000), but in adults the opposite has been found (Visser et al., 2001). A decreased signaling at the level of the glucocorticoid receptor (GR) on immune cells can eventually lead to a low-grade inflammatory state (Raison and Miller, 2003). Understanding the interaction between these systems in CFS, might lead to more targeted intervention strategies.

To expand the knowledge on HPA axis alterations in CFS patients, the aim of the current study was two-fold. The first aim was to investigate both dynamic (saliva) and long-term (hair) cortisol outcome measures in a group of CFS patients as compared to controls, where it was expected to replicate earlier findings on salivary cortisol (i.e. lower dynamic and absolute cortisol output) and for the first time investigate if this can be found in HCC as well. The second aim was to investigate the interaction between the HPA axis and pro-inflammatory cytokines. Therefore, the effect of the interleukin-1 receptor antagonist (IL-1Ra) anakinra on salivary and hair cortisol as compared to placebo treatment was assessed. It was hypothesized that decreasing inflammation would lead to less fatigue in CFS, improving activity and physical functioning, eventually leading to normalization of cortisol.

2. Materials & methods

2.1. Patients

Patients included in the current study were participating in two separate trials that investigated the effect of two distinct interventions on fatigue severity, which were described in detail elsewhere (van Der Schaaf et al., 2015; Roerink et al., 2015). To avoid heterogeneity, both studies included only female CFS patients; the results on the behavioral effects of these therapies have been reported separately (Roerink et al., 2017). In the study by van der Schaaf et al. (van Der Schaaf et al., 2015), female patients, between 18 and 59 years old, were included when meeting the Centers for Disease Control and Prevention (CDC) consensus criteria for CFS (Fukuda et al., 1994). In this study, the effect of cognitive behavioral therapy (CBT) on neuronal processes was assessed ("CBT study"). Main exclusion criteria were the presence of a psychiatric disorder (e.g., depression, anxiety) evaluated using the Mini-International Neuropsychiatric Interview (M.I.N.I.), presence of a somatic disease that could explain severe fatigue, or the use of psychotropic medication. In the second study, inclusion and exclusion criteria were similar, and adult female patients were included when fulfilling the CDC criteria. In addition, patients were excluded when using any medication (with the exception of oral contraceptives and paracetamol). In both studies, patients were asked to be accompanied by a healthy female peer who served as a control at baseline. In the study by Roerink et al., patients were treated with either daily subcutaneous anakinra (100 mg/day) or placebo injection for a duration of four weeks ("anakinra study") (Roerink et al., 2015).

For the current analysis, additional exclusion criteria were use of corticosteroids in any application form, the presence of fever on the days of saliva collection, and not adhering to the saliva collection protocol, awakening after 10 a.m. For HCC, which was determined in patients participating in the anakinra study, samples were excluded when a patient had been sick or used antibiotics during the preceding month.

All patients provided written informed consent prior to participation, all study measures were conducted according to the declaration of Helsinki. Both studies were approved by the local ethics committee.

2.2. Questionnaires

In both studies patients and controls were asked to fill out web-based questionnaires on fatigue severity and accompanying symptoms at baseline. Fatigue was measured with the fatigue subscale of the Checklist Individual Strength (CIS), which is a validated questionnaire used frequently in CFS research (Vercoulen et al., 1994). The score can range between 0 and 56, with a score ≥ 35 reflecting severe fatigue (Wiborg et al., 2015).

Impairment as a consequence of fatigue was measured with the Sickness Impact Profile (SIP8 total score), a score ≥ 700 reflects severe disability (Jacobs et al., 1990). The presence of depressive symptoms was evaluated using the Becks Depression Inventory (BDI) primary care version (Beck et al., 1997). Scores ≥ 4 indicate the presence of clinically relevant levels of depressive symptoms. Only patients participating in the anakinra study were asked to complete a visual analog scale (VAS) on pain severity, with a range between 0 (no pain) and 10 (worst pain ever).

In addition to the questionnaires, the following information was collected from all patients: age, height, weight, duration of symptoms, use of medication, and menopausal state.

2.3. Saliva cortisol

Participants were instructed to collect saliva on two consecutive working days using the passive drool method by using Salicap® devices (IBL, Hamburg, Germany) consisting of a collection tube and a straw. Thirty minutes before collection, patients were asked to refrain from eating, drinking, and taking medication. During the day, four saliva samples were collected; at awakening, 30 min after awakening ($\pm$ 15 min), at noon (between 11 a.m. and 1.15 p.m.), and in the evening (between 7 p.m. and 9.30 p.m.). Participants were asked to note date and exact time of sampling on the label of the respective Salicap® tube. Participants were instructed to store samples in their home freezer before bringing them to the hospital (after several days-weeks). At the hospital, all samples were stored at least at a temperature of -20 °C until analysis. Salivary cortisol concentrations were determined by using commercially available enzyme-linked immunosorbent assays (ELISA; IBL, Hamburg, Germany). After completion of therapy in the anakinra study, the collection procedure was repeated.

2.4. Hair sampling

Participants in the anakinra study provided hair samples for determination of HCC at baseline (patients and controls) and after treatment (patients only)*. Small hair strands were taken by the research physician from the posterior vertex region, from the area closest to the scalp. As the average hair growth rate is 1 cm/month (Wennig, 2000), cortisol was measured in 1 cm before and after treatment to evaluate the effect of the intervention. All hair samples were kept at room