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Salivary Cortisol Release and Hypothalamic Pituitary Adrenal Axis Feedback Sensitivity in Fibromyalgia Is Associated With Depression But Not With Pain

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Abstract: Results on hypothalamicpituitary-adrenal (HPA) axis function in fibromyalgia are heterogeneous and studies that integrate psychological and biological mechanisms in the search for pathways to fibromyalgia are rare. The goal of the study was to evaluate cortisol release and HPA axis feedback regulation in fibromyalgia and its association with psychopathology and pain. Beneath assessment of pain thresholds and self-report of pain, salivary free cortisol release over the day before and after intake of 0.5 mg of dexamethasone was measured in 21 female patients with fibromyalgia and 26 control women. Depression was assessed by questionnaires and clinical interview. We found reduced feedback sensitivity and slightly enhanced cortisol release in patients with fibromyalgia compared with healthy control subjects. Post hoc analyses showed that these effects are exclusively found in those patients, who also had major depressive disorder. Patients with fibromyalgia had lower pain pressure threshold, whereas heat pain thresholds were comparable with control subjects. Pain pressure and heat pain thresholds were not associated with cortisol release. On the other hand measurements of affective pain experience and depression were positively correlated with salivary cortisol over the day. Our results support the hypotheses that HPA axis related alterations are associated with affective disturbances, for example, depression, in patients with fibromyalgia.

***Perspective:** The presented data suggest depression to be an important factor in HPA axis–related dysfunction in fibromyalgia. This might be one explanation for equivocal findings in the literature.*

***Key words:** Fibromyalgia syndrome, HPA axis, salivary cortisol, pain, depression.*

Fibromyalgia is a common disorder, with a prevalence of 3.4% in the female population.[46] The syndrome is characterized by widespread and chronic musculoskeletal pain, increased sensitivity to palpation, fatigue, sleep disturbance, and morning stiffness.[46] Patients also frequently report elevated levels of depression, anxiety, and psychosocial stress.[44,45] The etiology of fibromyalgia remains unknown and findings regarding potential pathophysiological mechanisms are inconsistent. However, increasing evidence suggests an increased sensitivity to pain mediated by central nervous system, with deficiencies in the endogenous pain inhibitory control subjects.[9,11,14,23,36,38] However, increasing evidence suggests an increased sensitivity to pain mediated by central nervous system, with deficiencies in the endogenous pain inhibition. Adding to that, increased pain sensitivity has been found not only for one physical stressor, namely pressure, but also for electrical current, heat, and cold.[9,24,34] However, also diverging results have been reported.[7]

Because stress has been suggested to be one etiological factor in fibromyalgia, dysfunctions in hypothalamic-pituitary-adrenal (HPA) axis have been investigated intensively. Both hyperactivity and hypoactivity of the

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HPA axis have been reported. Increased basal cortisol levels have been observed,[5] whereas other studies reported decreased 24-hour urinary free cortisol and low morning cortisol release in fibromyalgia.[6,16,18] Normal 24-hour cortisol and diurnal patterns of ACTH and cortisol secretion have been reported as well.[1,25,26,28] Findings regarding alterations in diurnal variation, for example, flattened diurnal cycle, of cortisol secretion are also inconsistent.[5,6,20,27,37] Of note, reduced cortisol release in fibromyalgia is associated with depressive symptoms[17,18] and experiences of childhood trauma.[37]

Several studies have evaluated alterations in feedback regulation of the HPA axis using the standard (1 mg) dexamethasone (DEX) suppression test (DST), which is typically used to identify non-suppression of cortisol in the context of HPA axis hyperactivity and impaired feedback sensitivity, for example, in major depression.[4] Increased rates of non-suppressors among patients with fibromyalgia were reported in 2 studies,[10,27] but non-suppression was associated with depression. Several other studies reported lower rates of non-suppressors among patients with fibromyalgia compared with rates of non-suppressors among control subjects,[15,16,31] raising the possibility of increased negative feedback sensitivity in fibromyalgia. The standard DST almost completely suppresses cortisol secretion in healthy individuals. To identify increases in negative feedback sensitivity, the dose of DEX must be lowered to 0.5 mg. To our knowledge, only one study used the low dose DST in fibromyalgia, reporting enhanced cortisol suppression, whereas the suppression of ACTH was unaltered.[42]

In line with studies suggesting reduced adrenal output in fibromyalgia, reduced cortisol secretion has been observed in response to $ACTH_{1-24}$ stimulation,[3,19] although negative results have been reported as well.[16] In another study we found that fibromyalgia patients showed lower total cortisol release to a social stressor and also to exogenous ACTH, but normal free cortisol and ACTH levels compared with control subjects.[40] Interestingly, lower total cortisol but normal free cortisol concentrations in fibromyalgia has been reported before.[25]

The role of HPA axis functioning in FMS for the etiology of the disorder is still unclear. Further insights might be gained by studying the association of the putative HPA axis pathophysiology with fibromyalgia pain (spontaneous pain, pain sensitivity), the core symptom of fibromyalgia, and with psychopathological changes, namely depression. The aims of the present study were the assessment of HPA axis functions and their associations with FMS pain and depression. Investigating a sample of inpatients with fibromyalgia, we hypothesize a high amount of depressive symptoms in this sample, and, thus rather elevated cortisol levels and reduced feedback sensitivity than lowered cortisol release and enhanced feedback.

Materials and Methods

Participants

Patients with fibromyalgia were inpatients and were recruited at the "Medizinisch-Psychosomatische Klinik Bad Bramstedt." The clinic is oriented towards behavioral medicine and combines medical, psychotherapeutic and socially therapeutic measures. The female control subjects were recruited by means of local advertising. Patients were diagnosed by their physician according to criteria of the American College of Rheumatology.[46] All patients with fibromyalgia were diagnosed with widespread chronic musculoskeletal pain and increased sensitivity to palpation with no medical causes identified. Exclusion criteria were current eating disorders, alcohol or drug dependence, current or lifetime psychosis, and bipolar disorder. Women with additional medical illnesses that could explain pain symptoms were excluded. Included control subjects never had sought psychiatric or psychotherapeutic treatment and did not suffer from any current or lifetime DSM-IV Axis I disorder or medical illness. The protocol was approved by the ethics committee of the medical faculty of the University of Marburg, Germany; all subjects gave written informed consent.

Twenty-three women with fibromyalgia (FMS) and 26 healthy control subjects (HC) participated in the study. Two of the patients have to be excluded, one due to missing cortisol data and one because she forgot to take the DEX. Sociodemographic data are presented in Table 1. Although there was no significant difference between the groups with respect to age, FMS patients had a significantly higher body mass index. The 2 study groups differ also with respect to education. The patients were at the hospital for a 14.9-day average (SD, 16.7). As expected patients with fibromyalgia had higher scores on the complaint scale as well as on the pain experience scale and depression scale (see Table 1). Twelve patients and none of the control subjects took any medication. The other 9 patients took medications for several different complaints: hypothyroidism (n = 3), gastrointestinal symptoms (n = 3), hypertension (n = 4), and depression (n = 1).

Procedure

All patients with fibromyalgia underwent a part of a clinical interview (SCID-I) assessing major depression disorder using the section "affective disorders" only.[43] Depressive mood state was also measured using the Depression Scale (D-S)[49] and the Beck Depression Inventory (BDI).[2] The BDI consists of 21 items with a total score rage from 0 to 63. A score above 17 is interpreted as reflecting clinical relevant depression. All participants performed the D-S but only the patients also completed the BDI. Further the psychosomatic complaints were assessed by the Complaint Scale, the "Beschwerde Liste" (BL).[48] The BL consists of 24 Items which were scored on a 4-point Likert scale. Several predominantly somatic complaints are assessed, for example, breathlessness, weakness, breast pain, neck pain, nausea, irritability, perspiration, sleeplessness, fatigue, and dizziness. To assess the clinical (endogenous) pain, we used the Pain Experience Scale (PES, German: Schmerzempfingungsskala, SES,[12]), which is a scale derived from the McGill Pain Questionnaire. The questionnaire follows a multidimensional approach, assessing 2 components of pain, namely sensory (10 items)