Corticotropin releasing factor in urine—A possible biochemical marker of fibromyalgia
Responses to massage and guided relaxation
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Abstract
The purpose of this preliminary study was to evaluate the relationship between a possible biochemical marker of stress, 24-h urinary concentrations of Corticotropin Releasing Factor-Like Immunoreactivity (CRF-LI), and ratings of stress-related symptoms like depression and anxiety, as well as to evaluate pain and emotional reactions in patients with fibromyalgia (FM). Another purpose was to study the effects of massage and guided relaxation, with respect to change in the same variables. Urine sampling and ratings were performed before treatments, after and 1 month after completed treatments. Concentrations of CRF-LI was analysed with radioimmunoassay technique. For the assessment of depression, anxiety and pain the CPRS-A questionnaire was used and for rated pain and emotional reactions the NHP questionnaire was used. The 24-h urinary concentration of the CRF-LI was found to be related to depression, mood and inability to take initiative. After treatment the urinary CRF-LI concentrations and the rated levels of pain and emotional reactions were found to have decreased. In conclusion, the 24-h urinary CRF-LI concentration may be used as a biochemical marker of stress-related symptoms such as depression in patients with FM and possibly also other conditions characterized by chronic pain. Therapies such as massage and guided relaxation may be tried for the amelioration of pain and stress but further studies are required.

Keywords: CPRS-A; CRF; Depression; Fibromyalgia; Guided relaxation; Massage; NHP; Stress

Fibromyalgia (FM) is a widespread chronic pain condition [35] of unknown origin [24,25] with a suggested abnormal processing of nerve impulses in the central nervous system (CNS) [16] that can be characterized by generalized allodynia/hyperalgesia [15,18]. Beside the pain, FM is also associated with stress-related symptoms [27] like depression [12], and anxiety [32]. Aberrant functions of the sympathetic nervous system [26] and, the hypothalamic-pituitary-adrenal (HPA) axis [23] or its negative feedback loop [8,24] have been discussed as plausible causes of the stress-related symptoms in FM.

Corticotropin releasing factor, CRF, synthesized in the hypothalamic paraventricular nuclei and widely spread in the CNS, is known as a key physiological mediator of the endocrine, autonomic, and behavioural responses to stress [2–4]. Elevated plasma and cerebrospinal fluid (CSF) concentrations of CRF have been found in patients with FM [27] and, in patients with post-traumatic stress disorder [6]. It has therefore been suggested that hyperactive CRF neurons play a role in the nociceptive and psychological mechanisms in FM [7,23,24,27]. The central autonomic control of stress is complex and not possible to assess by a single test so a variety of techniques have been tried out [26]. CRF concentration is usually measured in CSF, which is a procedure that may be stressful. A possible alternative for analysis of CRF concentration could be urinary sampling. Furthermore, by analyzing 24-h urinary samples, the influence of diurnal variation could be diminished.

Conventional medicine has generally been reported as ineffective in the treatment of FM [19] and stepwise rehabilita-
tion programs have been recommended [13,21]. Despite lack of strong evidence for the use of non-pharmacological inter-ventions in FM [28], different modes of sensory stimulation like massage, relaxation therapies and acupuncture have gained increasing popularity. Massage has been reported to reduce pain, depression and anxiety in patients with FM [1,5,9]. Hypotheti-cally, stimulation of mechanical receptors in the skin and deeper tissues during massage or psychologically induced interventions may alter the functions of limbic structures of the brain, lead-ing to a reduction in pain and stress-like symptoms changes that possibly are reflected in reduced concentrations of Corticotropin Releasing Factor-Like Immunoreactivity, CRF-LI, in 24-h urine samples.

The aim of this study was to examine the measured concen-trations of 24-h urinary CRF-LI and their possible relationship to rated stress-related symptoms like depression and anxiety as well as to evaluate rated pain and emotional reactions in patients with fibromyalgia. A secondary aim was to evaluate the changes in assessed variables in response to a treatment period of mas-sage and guided relaxation.

Patients fulfilling the criteria for fibromyalgia according to the American College of Rheumatology (ACR) [35], and enrolled in an outpatient fibromyalgia course at the Rehabili-tation Medicine Clinic at Karolinska University Hospital were invited to participate. All the patients were medically exam-ined and a kidney function test was included in the examination. The patients were asked not to start any new interventions but were allowed to continue ongoing treatment and medication. The patients were asked not to start any new treatments during massage or psychologically induced interventions and/or prone position. Soft standardized music at low volume was mixed, measured, and a sample of 50 mL was stored containing labels with treatment allocation were the means for the randomization procedure. Hence, the level of emotional reaction is scored from 0 to 9. Heart rate frequency and blood pressure were measured before every treatment by radial pulse palpation and by using a standard cuff technique in the patients after they had been lying down for 10 min.

Twelve treatments of either massage or guided relaxation, lasting for 30 min each, were given twice weekly for 6 weeks. During the treatments the patients were lying down in a back and/or prone position. Soft standardized music at low volume was used in order to mute stressful feelings and background. The massage treatment was applied to different body areas (feet and legs 18 min, hands and arms 8 min, face 4 min) and consisted of the standardized massage techniques stroking (effleurage), kneading (petrissage), friction, and shaking—all performed in a slow rate of approximately 1 Hz. The hand pressure was always maintained.

The urine samples were collected in plastic boxes, containing 6 M hydrochloric acid, during 24 h. The individual total urine volume was mixed, measured, and a sample of 50 mL was stored containing labels with treatment allocation were the means for the randomization procedure. Hence, the level of emotional reaction is scored from 0 to 9. Heart rate frequency and blood pressure were measured before every treatment by radial pulse palpation and by using a standard cuff technique in the patients after they had been lying down for 10 min.

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adjusted according to the patients’ preference. Massage lotion (CCN, Stockholm, Sweden) or massage oil (Rolf Kullgren AB, Stockholm, Sweden) was used to diminish friction of the skin-to-skin contact during massage treatment. The patients assigned to relaxation therapy were personally guided into progressive relaxation according to Jacobsen [20].

The mean and S.D. was used to describe age. The median and range was used to calculate the duration of fibromyalgia and self-rated outcome variables. The distribution of datasets and relation between variables were described as plots. A possible relation between the CRF-LI concentrations and the ratings of the perceived psychological problems, anxiety, and depression.

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The levels of change in the variables assessed by the CPRS-A and NHP were described by square contingency tables and evaluation of the systematic changes reflects the treatment efficacy on the entire group. Strong evidences of additional individual changes, high RV values, indicate that individually designed interventions would be preferable. For more information, see [31]. A two-side p-value less than 0.05 was regarded as significant.

The mean age of the participating women were, n = 19, was 50.7 (S.D. 9.7) years and the median duration time of fibromyalgia was 14 (range, 3–42) years. Demographic data and clinical characteristics are shown in Table 1. Ten of the patients were randomized to massage and nine to guided relaxation. Two of the patients assigned to the relaxation exercises at by themselves at home. The remaining 16 patients were included in the analysis of rated variables regarding treatment effects. Two of the patients assigned to the guided relaxation failed to deliver their urine samples. Due to small number of individuals, the guided relaxation group was excluded from analysis of the treatment effects.

Fig. 1a–c show the observed relationships between the urinary CRF-LI concentrations and rated levels of depression, anxiety, and ability to take an initiative. The software package SYSSRAN 1.0 for Matlab 6 was used to calculate the measures of RV and, their corresponding 95% confidence intervals. Moreover, STATISTICA 7.0 was used.

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Fig. 1. (a–c) Relationship between 24-h urinary CRF-LI concentrations and rated depression (a), mood (b), and ability to take initiative (c) according to the CPRS-A questionnaire. One urine sample was excluded from analysis due to undetectable activity, n = 18.

In the massage group, the median changes in CRF-LI concentrations after treatments was 0.51 pmol/L (n = 10, T = 3.00; p = 0.01) and 0.61 pmol/L (n = 7, T = 5.00; p = 0.13), 1 month after completed treatments, Fig. 2.

As evident from the pairs of observations in Fig. 3a, 10 of 16 women (seven massage) rated their perceived pain and ache lower after treatments and 8 of 16 women (five massage) 1 month after completed treatments, Fig. 3b. The non-zero RP value Rp −0.64 (95% CI −0.94 to −0.34) indicate that the observed decrease in pain and ache after massage is a systematic group change, p = 0.02, though an individual variation was present RV −0.33 (95% CI 0.00−0.80). Corresponding results in the small guided relaxation group, n = 6, were RP −0.28 (95% CI −0.33 to −0.25) and RP −0.28 (95% CI −0.33 to −0.33). Additional individual variations were also here present, RV 0.06 (95% CI 0.00−0.25) and RV 0.22 (95% CI 0.00−0.06), respectively.

After the treatment period, less indications of pain according to the NHP questionnaire were reported in 4 (one massage) of 16 women and 1 month after completed treatment in 6 (four massage) of 16 women, RP −0.28 (95% CI −0.53 to −0.03). Also, fewer indications of emotional reaction were reported after...
treatment, in 9 (six massage) of 16 women RP $-0.24$ (95% CI $-0.43$ to $-0.05$), $p=0.04$, and in 7 (six massage) 1 month after completed treatments, RP $-0.40$ (95% CI $-0.76$ to $-0.04$), $p=0.13$. The additional individual variations in change were negligible for pain, RV 0.00 (95% CI 0.00–0.05) after treatment, but pronounced regarding emotional reactions 1 month after completed treatments, RV 0.46 (0.00–1.00).

No changes were seen in either treatment group after the treatment period in the measured heart rate frequency (mean change; massage -4 beats/min; guided relaxation 4 beats/min), and systolic blood pressure (mean change; massage 1.86 mmHg; guided relaxation 5.83 mmHg).

In this study a 24-h urine sampling procedure was chosen to allow quantification of CRF-LI concentration representing stress level and the function of the HPA-axis across the diurnal cycle. The relationship found between the 24-h urine CRF-LI concentrations and the rated level of depression, mood and, ability to take initiative may indicate that urinary CRF-LI concentration could be used as a biochemical marker of perceived stress-related symptoms, like depression, in patients suffering from fibromyalgia. Possibly it could also serve as a biochemical marker for other painful conditions than fibromyalgia since depression may be an integral part of long-lasting pain [22].

Despite the limited number of individuals some interesting evidences of treatment effects were found. After 6 weeks of massage treatments twice a week, the 24-h urinary concentrations of CRF-LI were decreased as were the rated pain and emotional reaction. In the group receiving guided relaxation a similar pattern of emotional reactions was seen.

The effects of massage were sustained for 1 month after but with larger individual variations suggesting that long-term effects of improvement may be obtained. This finding is supported by a recent study reporting amelioration of pain, depression and anxiety 3 months after a treatment period of Swedish massage [33]. Also, in a study by Hanley and collaborators [17], a decrease of stress was seen in response to treatments of massage or listening to a relaxation tape. It has been suggested that anti-depressants induce an increase of glucocorticoid receptors in the HPA-axis resulting in a re-establishment of the function of the HPA-system [4] but the mechanism for massage and relaxation therapies affecting the stress-related symptoms needs further research.

Variability of the results, such as overlapping of the CRF-LI concentration compared to the positions on the CPRS-A rating scale, could be due to various factors such as that patients diagnosed as suffering from fibromyalgia are a heterogeneous group [11]. Distinct subgroups of patients with fibromyalgia have been identified by assessing pressure pain thresholds, mood and cognitive factors [11,14]. The existence of subgroups in fibromyalgia is also supported by Thieme et al. [32] who reported varying proportions of co morbid anxiety and depression dependent on psychosocial characteristics of the patients. In the present results the responses to treatment demonstrated individual variations confirmed by the measure of RV. This may indicate that individual responses should be taken into consideration for instance in determining number of treatments for optimal results. Possibly sensory stimulation techniques may influence subgroups of fibromyalgia affected by the presence of depression differently.

Interestingly, Finset and collaborators [10], suggest that depression may serve as a predictive factor for treatment response. Beside the low number of participating patients, the possible contribution of different stages of the hormonal cycle as well as postmenopausal effects has not been taken into consideration.

In conclusion, the 24-h urinary CRF-LI concentration may be used as a biochemical marker of stress-related symptoms like depression in patients with FM and possibly also other conditions characterized by chronic pain. Therapies such as massage and guided relaxation may be tried for the amelioration of pain and stress but further studies are required.

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References