ORIGINAL ARTICLE

Role of dehydroepiandrosterone and cortisol in nociceptive sensitivity to thermal pain in anorexia nervosa and healthy women

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Abstract

OBJECTIVES: Anorexia nervosa (AN) patients represent a natural model of relationship between changed hormonal level and pain perception due to lower level of sex hormones and consistently described increased pain threshold. As the adrenal stress steroid hormones (cortisol and DHEA) are known to be also changed in AN (and share a common precursor), our study was aimed to analyze the association between these hormones and pain perception in AN patients and control healthy women.

METHODS: The pain threshold latencies to radiant heat stimuli were measured in 20 DSM-IV diagnosed patients with AN and in 21 healthy women. Blood samples were collected in the morning hours and analyses of the plasma levels of dehydroepiandrosterone (DHEA), its conjugated sulfate ester (DHEA-S) and cortisol were implemented.

RESULTS: Thermal pain threshold was higher in AN than in healthy women and correlated negatively with the level of DHEA and positively with cortisol/DHEA(S) ratio. No significant correlation between thermal pain and hormones was found in healthy women. If both groups were pooled together, the rest pain threshold correlated negatively with DHEA-S ($r=-0.42$, $p=0.008$).

CONCLUSION: We showed for the first time that sensitivity to thermal pain in women is dependent on DHEA-S and on cortisol/DHEA(S) ratio in patients with AN.

INTRODUCTION

Elevation of pain threshold in individuals with eating disorders is a consistent yet unexplained finding (Lautenbacher *et al.* 1991; de Zwaan *et al.* 1996; Papežová *et al.* 2005). Malnutrition and long-term starvation brings about a number of hormonal changes in female patients with eating disorders. As a consequence of chronic stress, anorectic patients have increased levels of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and cortisol (Licinio *et al.* 1996), while the values of 17-beta estradiol tend to be lower (Monteleone *et al.* 2001).

Dehydroepiandrosterone (DHEA) is another hormone regulated by ACTH in pituitary-adrenal

axis. In AN patients, the plasma levels of DHEA and DHEA-S were found to be significantly higher than in healthy controls (Monteleone *et al.* 2001), although anorectic patients did not differ from healthy women in DHEA/cortisol or DHEA-S/cortisol ratios (Monteleone *et al.* 2001).

There are several publications focused on association between DHEA(S) levels and pain in patients with fibromyalgia (Dessein *et al.* 1999), chronic migraine (Patacchioli *et al.* 2006) and neck, shoulder and back pain (Schell *et al.* 2007), however, no such study was done in relation with pain sensitivity either in healthy subject or in patients with psychiatric diagnoses. Due to decreased pain perception and changed hormonal levels in patient with AN, they represent a suitable model for studying relationships between pain perception and hormones.

The purpose of the present study was to examine to what extent the perception of pain in anorexia patients and healthy women depends on the DHEA(S), cortisol and their ratio.

As DHEA(S) is considered to be an excitatory neurosteroid (Wolf and Kirschbaum 1999; Maninger *et al.* 2009), we hypothesized that those subjects with increased DHEA(S) levels will have lower thermal nociceptive threshold in comparison with subjects with decreased DHEA(S) levels.

Cortisol/DHEA-S ratio is considered to be an inverse marker of psycho-physical well-being (Patacchioli *et al.* 2006). Alternatively, DHEA-S/cortisol ratio may index the degree to which and individual is buffered against the negative effects of stress (Morgan III *et al.* 2004). Therefore, we expected an increased pain threshold in patients with higher cortisol/DHEA-S ratio as a result of intensively perceived stress.

PATIENTS AND METHODS

The study sample consisted of 20 female patients hospitalized at Special Unit for Eating Disorders in Department of Psychiatry of the 1st Faculty of Medicine of Charles University (Prague) with DSM IV diagnosis of AN. All patients signed the informed consent formed approved by the Ethical Committee of the University Hospital.

All patients (6 of binge/purging type and 14 of restrictive type, age: 24.8±4.6 years, weight: 42.4±5.9 kg, height: 167.1±5.9 cm, BMI: 15.1±1.3 kg.m^{-2}, length of disease: 4.8±2.9 years) were taking hormonal replacement therapy. Seven patients were medication free, 13 patients were taking antidepressants or anxiolytics. There were no differences found between the two diagnostic subgroups of AN patients in any of the investigated parameters, and therefore we analyzed the group as a whole.

The tests of nociception were carried out during morning hours. Pain threshold latencies for thermal stimuli were measured using the Analgesia meter (IITC Life Science USA Model 33), which applies radiant heat to an area of 1 cm^2. Participants were asked to put their finger on the aperture and to withdraw, when they started to feel pain. The time from start of the radiant heat to the finger withdrawal was measured as thermal pain threshold latency. The pain threshold was measured three times at the dorsal aspect of the index, middle and ring fingers of the dominant hand (all participants were right-handed). An average of the three measurements was used in the analysis.

Blood samples were taken in a standard way in the morning hours and the samples were sent for a laboratory assessment of the levels of DHEA, DHEA-S and cortisol. For the expression of the cortisol/DHEA molar ratio we used conversion coefficient 3.47 (conversion from μg/l to nmol/l) (Wagner 2001).

The control sample consisted of 21 age matched healthy women without either eating disorders or endocrine disorders. They underwent the same procedure as the AN patients.

Statistical analysis

Differences between groups were analyzed by Student's t-test and relationship between nociceptive tests and hormonal levels were assessed using Pearson's correlation.

Pharmacologically treated patients did not differ in any variable from non-treated group as well as restrictive patients did not differ from binge/purging, therefore these factors were ignored in statistical analyses.

RESULTS

Table 1 shows demographic data and summarizes the results in AN patients and healthy controls.

Thermal pain threshold was significantly higher in patients in comparison with controls (p=0.037).

Levels of DHEA did not differ in the patient group compared to the controls (p=0.49), and also levels of DHEA-S in patients were not different from controls (p=0.43). Basal cortisol levels were also similar in both groups (p=0.86), and consequently the cortisol/DHEA molar ratio and cortisol/DHEA-S ratio did not differ between patients and controls (p=0.3 and p=0.97, respectively).

The relationship between DHEA(S), cortisol and cortisol/DHEA(S) ratio and the thermal pain threshold is summarized in a correlation matrix (Table 2.)

In AN patients, thermal pain threshold correlated negatively with DHEA (r=–0.53, p=0.017) and positively with cortisol/DHEA (r=0.76, p<0.001) (Figure 1) and cortisol/DHEA-S (r=0.54, p=0.024). Correlation with DHEA-S was marginally significant (r=–0.44, p=0.06).

In healthy women, only DHEA-S correlated negatively with thermal pain threshold but it did not reach statistical significance (r=–0.40, p=0.079).

Similar regression parameters and slopes of regression line made possible to pool the data of both groups together. Then, the rest pain threshold negatively correlated with DHEA-S (r=–0.42, p=0.008) (Figure 2).

DISCUSSION

In our study, DHEA and DHEA-S correlated negatively with thermal pain threshold in AN patients. A modulation effect of DHEA-S was similar in AN and controls. According to our knowledge this is the first study which analyzes the relationship between DHEA and nociception in humans.

Tab. 1. Comparison of patients with anorexia nervosa and healthy women (mean ± SD).

	Anorexia nervosa N=20	Healthy controls N=21	t-value	p-value
Age (years)	24.8±4.6	25.5±3.3	–0.58	0.56
Weight (kg)	42.4±5.9	62.6±8.4	–8.90	0.000
Height (cm)	167.1±5.9	169.1±7.3	–0.96	0.34
BMI ($kg.m^{-2}$)	15.1±1.3	22.0±3.1	–9.00	0.000
Duration of the illness (years)	4.8±2.9	---		
Thermal pain threshold (s)	6.0±1.6	5.0±1.3	2.16	0.037
DHEA (mg/l) RR: 1.0–12.9 µg/l	9.5±6.4	8.2±5.1	0.70	0.49
DHEA-S (mmol/l) RR: 2.4–14.5 µmol/l	4.2±2.4	4.5±3.4	–0.79	0.43
Cortisol (nmol/l) RR: 118–618 nmol/l	860±275	869±318	–0.18	0.86
Cortisol/DHEA	34.9±25.5	44.9±29.9	–1.06	0.30
Cortisol/DHEA-S	0.27±0.16	0.27±0.17	–0.03	0.97

RR - reference range

DHEA has a character of neurosteroid. As an allosteric modulator DHEA influences positively the activity of NMDA and sigma receptors (type I) and modulates negatively GABA A receptors (Akwa & Baulieu 2000; Mellon & Griffin 2002). Due to its impact on inhibitory and excitatory processes it can change the excitability of the central nervous system.

Several animal studies showed that acute application of DHEA-S should have either hyperalgesic (Uchida *et al.* 2003) or pronociceptive effect, whereas chronic application of DHEA and its metabolites can elevate nociceptive threshold in neuropathic and control rats (Kibaly *et al.* 2008). In mice, intra-thecal DHEA-S injection dose-dependently decreased the nociceptive threshold to mechanical stimulation but DHEA was without any effect on mechanical sensitivity (Yoon *et al.* 2009).

Study of De Roo (De Roo *et al.* 2003) showed that DHEA affects ionotropic P2X receptors activated by ATP. P2X receptors are expressed in peripheral nociceptors and in central endings of nonmyelinated sensory fibers. Increased level or increased local production of DHEA can sensitize these nociceptors by ATP or can facilitate release of glutamate from sensory

Tab. 2. Pearson's correlation coefficients between hormones and thermal pain threshold

	Anorexia nervosa	Healthy controls	Whole sample
DHEA	–0.53*	0.16	–0.22
DHEA-S	–0.44	–0.40	–0.42**
Cortisol	0.15	–0.28	–0.08
Cortisol/DHEA-S	0.54*	–0.05	0.23
Cortisol/DHEA	0.76**	–0.20	0.21

* $p<0.05$; ** $p<0.01$

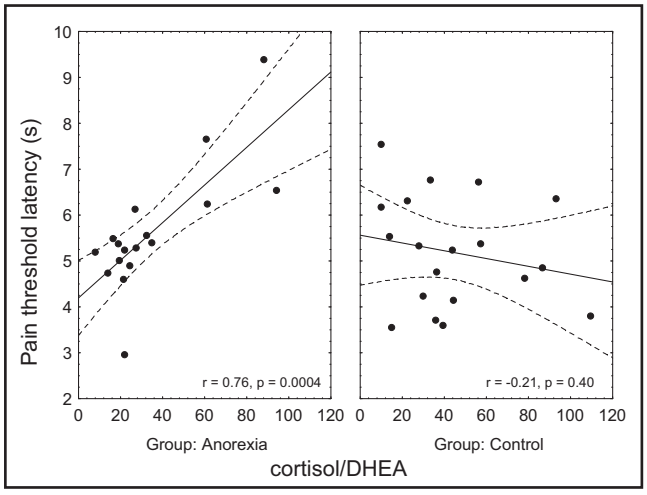

Fig. 1. Correlation between cortisol/DHEA ratio and pain threshold latency in anorexia and healthy women.

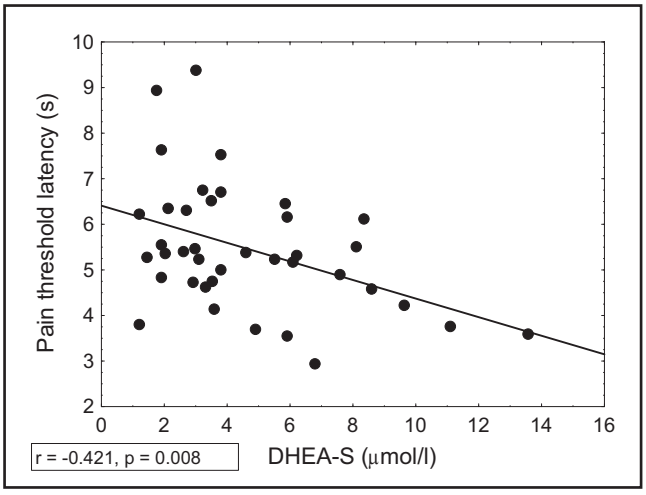

Fig. 2. Correlation between DHEA-S and pain threshold latency in both groups analyzed together.

endings in the dorsal horn of the spinal cord. However, under physiological conditions, the role of P2X receptors for pain perception is relatively small.

As we measured sensitivity to thermal pain, the more important finding is that DHEA(S) is able to modulate activity of TRPV1 channel which is activated by temperature. In vitro study of dorsal root ganglion neurons, however, showed an inhibitory action of DHEA on the capsaicin-induced current (Chen *et al.* 2004) which is contradictory to our results.

Several clinical studies used DHEA as an outcome predictor of pain intensity and disability in patients with acute or chronic pain. In patients with acute low back pain, DHEA-S was found to be a significant predictor of disability six months after the beginning of pain. Lower level of DHEA-S predicted a worse state (Hasselhorn *et al.* 2001) and in women with fibromyalgia DHEA-S correlated negatively with pain intensity (Dessein *et al.* 1999).

The cortisol/DHEA(S) ratios proved to be another significant predictor of pain. We found that high levels of cortisol together with a low level of DHEA predicted elevated pain threshold in patients with anorexia. The increased cortisol/DHEA ratio is the consequence either of the lowered production of DHEA with relatively normal cortisol values or, on the other hand, of increased production of cortisol and normal levels of DHEA. In both cases the homeostatic regulation of the stress axis is impaired, which may be accompanied also by changed nociception. Similar findings were published by Grillon *et al.* (2006), who demonstrated that cortisol and DHEA-S are involved if fear conditioning. The subjects with high cortisol/DHEA-S ratio exhibited increased fear-potentiated startle to conditioned stimuli, increased ratings of arousal and negative valence compared to subjects with low ratio.

Besides eating disorders, an increased ratio of cortisol to DHEA was found in non-medicated depressive patients, where it correlated positively with the length of depressive period (Young *et al.* 2002) and in hospitalized schizophrenic patients, where it correlated positively with the duration of the disease (Ritsner *et al.* 2004). Lowered sensitivity to pain described in eating disorders is frequently observed in patients with different psychiatric diagnoses (Lautenbacher & Krieg 1994; Blumensohn *et al.* 2002).

Increased cortisol in AN patients is not surprising and corresponds to values published by another authors (Lawson *et al.* 2009). On the other hand, increased cortisol above normal physiological range in healthy women can be considered a stress reaction as all subjects had to come for the blood sampling early (at 7AM). From this it can be inferred that women with higher baseline cortisol are more vulnerable to perceive acute strain as more stressful and more negative. At the time of our measurement of nociceptive sensitivity, cortisol as well as DHEA probably decreased according to its circadian variation, but DHEA-S lacks such diurnal variations (Hucklebridge *et al.* 2005) and is relatively stable during prolonged exposure to stress (Ceballos *et al.* 2007).

CONCLUSIONS

Relationship between DHEA(S) and pain perception did not answer the question why do AN patients have increased pain threshold in comparison with healthy women. We observed similar relationship and similar results in both experimental groups. From these observations we can conclude that DHEA(S) can be considered a significant modulator of thermal nociceptive sensitivity, independently on pathology. Although cortisol alone did not correlate with thermal pain, its balance with DHEA(S) brings significant information about the ability to cope with stress, which can be also reflected in sensitivity to pain. From the practical point of view, we suppose that, sensitivity to pain might serve as another objective indicator of a patient's clinical reaction to stress if these findings can be reproduced with a larger group.

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