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CHAPTER 24

The HPA-axis and immune function in burnout

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Abstract: Burnout results from chronic work stress. Its complaints may be related to HPA-axis disturbances or changes in immune function. In our studies the salivary cortisol awakening response, day-curve, and the suppressed level after dexamethasone intake were not different in a burned-out group compared to a control group. Nor was there a change in cortisol after a treatment period. Higher levels of DHEAS and the monocyte released anti-inflammatory cytokine IL-10 were observed, however T-cell stimulated and dexamethasone inhibited cytokine release were not affected. The increased IL-10 level may be related to an increased sensitivity for infections.

Keywords: burnout; chronic stress; cortisol; cytokines; dexamethasone suppression test; DHEAS; follow-up

Introduction

Burnout is the ultimate outcome of a chronic process in which work stress is supposed to play a decisive role. People with burnout feel extremely fatigued, have become alienated from their work, experience reduced professional competence, and report a whole range of complaints such as depressed mood, increased irritability, inability to relax, disrupted sleep, somatic complaints such as aching muscles, headaches, gastro-intestinal problems, and concentration and memory problems (Maslach et al., 2001). When we assume that burnout is a stress-related syndrome, one may expect to find a disturbance in hypothalamus pituitary adrenal (HPA)-axis functioning. Inadequate glucocorticoid signaling has been suggested for other stress-related syndromes like post-traumatic stress disorder (PTSD), chronic fatigue syndrome (CFS), and major depression disorder (MDD). Reviewing the literature on burnout and related stress-syndromes has led to the hypothesis that the fatigue symptoms in burnout are related to a state of hypocortisolism, and increased feedback sensitivity of the HPA-axis (Heim et al., 2000). On the other hand, the depressive symptoms would suggest a hypercortisolemic state, and a relative non-suppression in response to dexamethasone (DEX) (Raison and Miller, 2003). Assuming a disturbance of the HPA-axis in burnout, we expected a reduction in burnout complaints to be related to a recovery of this disturbance. A longitudinal study was set up to correlate changes in complaints with changes in salivary cortisol parameters.
Glucocorticoids play a decisive role in immune functioning. Cortisol inhibits pro-inflammatory cytokine release, e.g., TNF-α, IFN-γ, interleukin (IL)-6 and IL-1, and stimulates anti-inflammatory IL-10 and IL-4 release (Elenkov and Chrousos, 2002). Chronic psychosocial stress has been related to impaired immune functioning leading to physical illness. This process may be mediated by glucocorticoids through affecting the balance between pro- and anti-inflammatory cytokines (Kiecolt-Glaser et al., 2002).

Results

The major finding of our study was the absence of a disturbance in salivary cortisol parameters in burnout. A burnout group (n = 74) was compared to a healthy control group (n = 38). The burnout persons were on sick leave, and had received a clinical diagnosis for work-related neurasthenia according to International Statistical Classification of Diseases and Related Health Problems (ICD-10) criteria. Primary Diagnostic and Statistical Manual of Mental Disorders Edition IV (DSM-IV) disorders such as MDD or anxiety disorder were excluded. The cortisol awakening response (CAR) was measured on 2 days at 0, 15, and 30 min after awakening, and at noon, 18:00 h and 22:30 h to assess the diurnal cortisol course. A low-dose (0.5 mg) DEX was taken to test the feedback sensitivity of the HPA-axis. The suppressed cortisol level after DEX intake was measured at 0, 15, and 30 min after awakening. The cortisol CAR, day-curve and suppressed DEX level were not different between the burnout and control group (Mommersteeg et al., 2006a–c) (Fig. 1). Cortisol was not related to fatigue or depression complaints within the burnout group, thus showing no indication of an opposing hypo- or hyperfunction of the HPA-axis, potentially masking the effect in burnout.

Because there is considerable variation in cortisol levels between and within persons, it is quite well possible that within a group burnout persons the reduction of the burnout complaints will covary with the cortisol parameters after a treatment and a follow-up period. This possibility was studied in the longitudinal part of the previous study (Mommersteeg et al., 2006). Burnout complaints were significantly reduced after a treatment period, without a further reduction at follow-up. Complaints remained substantially higher than norm scores for a healthy population. Cortisol after

![Fig. 1. Cortisol awakening response (CAR, left) and the suppressed CAR after dexamethasone intake (right) in the burnout group before treatment, after treatment and at follow-up, and in the control group. There are no differences between the groups or within the burnout group at consecutive measurements. Means and SEM are shown.](image-url)
awakening and after DEX intake (Fig. 1) showed, however, no parallel changes with complaint reduction. Some isolated associations emerged; the CAR (averaged over the three measurements) was significantly correlated with initial exhaustion level. A decrease in depressive symptoms correlated with an increased CAR, whereas the decrease in fatigue in time correlated with a decrease of the CAR over the three measurements (Mommersteeg et al., 2006). The latter findings are in contradiction to the supposed hyper- and hypoactive state of the HPA-axis in MDD and CFS, respectively, and moreover explained only a minor part of the variance in complaints within (3%) and between (4%) the burnout individuals.

Immune and endocrine variables were studied in another burnout group (n = 56) and compared to 38 controls (Mommersteeg et al., 2006). Again no deviations in the cortisol CAR, or in the DEX suppression test (DST) were observed. The dehydroepiandrosterone-sulphate (DHEAS) level (but not the cortisol/DHEAS-ratio) was significantly elevated in the burnout group. The burnout group had significantly higher levels of the anti-inflammatory cytokine IL-10 produced by LPS stimulated monocytes (Fig. 2). The IL-10 production of stimulated T-cells, however, was not different from the control group, and neither were there differences in the pro-inflammatory cytokine release of monocyte TNF-α (Fig. 2) or T-cell IFN-γ. The capacity of DEX to modulate pro- and anti-inflammatory cytokine release in vitro did not differ between the burnout and the control group, nor was there a change in number of whole blood counts of T-cells, B-cells, and NK-cells.

**Discussion**

The results show that there is no discernable disturbance of salivary cortisol in burnout. There is,
however, an increased production of IL-10 and
salivary DHEAS. These findings in a rather large
sample of clinical burnout persons raise doubts
about the existence of a relevant neuroendocrine
dysregulation in burnout as suggested by some
earlier studies. Still a variety of (neuroendocrine)
factors may show modest disturbances, altogether
leading to a state of ‘allostatic load’ in burnout
patients. Though studies in burnout and CFS that
included allostatic load parameters do not point in
that direction (Cleare, 2003; Grossi et al., 2003;
Schnorpfeil et al., 2003), this type of approach may
be a viable option for further research.

Another option is that central mechanisms are
dysregulated in burnout. To test this possibility the
combined DEX/corticotrophin releasing hormone
(CRH) test, or CRH or adrenocorticotropic hor-
mon (ACTH) infusion are useful techniques. One
may doubt however whether these invasive tech-
niques are acceptable as a research tool for this
(relatively) mild syndrome. Our results point to-
ward an increased stimulated monocyte IL-10 re-
lease and increased DHEAS levels in burnout.
DHEAS has immunostimulatory effects, and at
the same time its non-sulphatized form DHEA has
been found to reduce susceptibility to viral, bact-
erial, and protozoan infections (Chen and Parker,
2004). Thus the relevance of the increased DHEAS
level in burnout for immune function remains to
be determined. Macrophage IL-10 release inhibits
T-cell proliferation and suppresses the release of
pro-inflammatory cytokines like the anti-viral
IFN-γ. People with burnout report more common
cold and flu-like infections (Mohren et al., 2003).
Moreover, vital exhaustion is related to an in-
creased pathogen burden, with higher IL-10 serum
levels (van der Ven et al., 2003). Therefore an in-
creased IL-10 response in burnout may be related
to an increased sensitivity for viral infections. Fu-
ture studies should reveal the relevance of these
findings.

When we started this research project we hy-
pothesized that the HPA-axis should show distur-
bances in burnout. The results showed the absence
of any obvious peripheral deviation in salivary
cortisol, nor feedback by DEX in burnout. The
correlational effects observed in the longitudinal
study are too modest to represent any clinical or
diagnostic value. Overall we conclude that in this
study no obvious disturbance of the HPA-axis in
burnout was demonstrated. The possibility of
some disturbance in immune function and the
hormone DHEAS in burnout deserves further at-
tention, especially in relation to the sensitivity for
infections.

Abbreviations

ACTH adrenocorticotropic hormone
CAR cortisol awakening response
CFS chronic fatigue syndrome
CRH corticotrophin releasing hormone
DEX dexamethasone
DHEAS dehydroepiandrosterone-sul-
phate
DSM-IV Diagnostic and Statistical Man-
ual of Mental Disorders Edition IV
DST dexamethasone suppression test
HPA-axis hypothalamus pituitary adrenal
axis
ICD-10 International Statistical Classifi-
cation of Diseases and Related
Health Problems
IL interleukin
MDD major depression disorder
PTSD post-traumatic stress disorder

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inflammatory and antiinflammatory cytokines, and autoim-


