G Ital Med Lav Erg 2006; 28:1, Suppl Psicologia 1, 34-42
www.gimle.fsm.it

B.M. Kudielka, S. Bellingrath, D.H. Hellhammer

Cortisol in burnout and vital exhaustion: an overview

Department of Theoretical and Clinical Psychobiology, University of Trier, Johanniterufer 15, D-54290 Trier, Germany

ABSTRACT. In this overview, we summarize findings on hypothalamus-pituitary-adrenal (HPA) axis functioning in burned out and (vitally) exhausted though otherwise healthy subjects as well as clinically diagnosed patients. The main focus will be on basal diurnal free cortisol regulation and cortisol responses to acute psychological stress. First, we describe normal HPA axis regulation as well as dysfunction which manifests in hyper- or hypoactivity. We also briefly illustrate three established methods to assess HPA axis activity, reactivity, and feedback functioning, namely the cortisol awakening rise (CAR), Trier Social Stress Test (TSST), and low-dose Dexamethasone Suppression Test (DST). Then, an up-to-date summary of empirical findings on the relationship between burnout, respectively vital exhaustion, and cortisol is provided including field as well as laboratory studies. Finally, we briefly discuss possible methodologically confounders and speculate on underlying mechanisms explaining, at least in part, how burnout and vital exhaustion might relate to disease vulnerability.

Key words: *cortisol, burnout, vital exhaustion, HPA axis, saliva, stress.*

RIASSUNTO. In questo lavoro riassumiamo i risultati sul burnout e sull'esaurimento (vitale) rispetto alla funzione dell'asse ipotalamo-ipofisario (HPA), sia in soggetti sani, sia in pazienti con diagnosi accertata. Il principale obiettivo sarà quello di esaminare la regolazione del cortisolo libero diurno e le sue risposte allo stress psicologico acuto.
All'inizio, descriveremo sia la funzionalità dell'asse normale HPA come pure la disfunzionalità che si può manifestare in situazioni di iper o ipoattività. Illustreremo anche brevemente tre metodi consolidati per valutare l'attività dell'asse HPA, la sua reattività e la sua modalità di risposta, ossia l'innalzamento del cortisolo al risveglio (CAR), il "Trier Social Stress Test" (TSST) e il "Test di soppressione a bassi dosaggi di Dexamethasone" (DST). La trattazione include un aggiornamento dei risultati empirici riguardanti la relazione tra il burnout e il rispettivamente tra esaurimento vitale e cortisolo, riferendo sia a studi sul campo sia di laboratorio. Alla fine del lavoro, verranno brevemente considerate le possibili confusioni metodologiche e le spiegazioni dei meccanismi soggiacenti; mentre, nell'ultima parte, tratteremo come il burnout e l'esaurimento vitale potrebbero essere connessi alla vulnerabilità della malattia.

Parole chiave: cortisolo, burnout, esaurimento vitale, asse ipotalamo-ipofisario, saliva, stress.

1. Normal and dysfunctional hypothalamus-pituitary-adrenal axis regulation

The hypothalamus-pituitary-adrenal (HPA) axis is a central control and regulatory system of the organism connecting the brain with the endocrine system. This stress-responsive neuroendocrine system helps the organism to adapt to increased demands and to maintain homeostasis after challenge but is also vital for supporting normal physiological functioning. The end-product, cortisol, has a wide range of physiological effects since virtually all of the body's single nucleated cells are potential targets for cortisol. Cortisol plays a critical role in metabolism by mobilizing resources to provide energy. This helps to overcome the increased metabolic demand presented by a host of challenges. It also regulates or impacts on other important physiological systems, like the immune system, the sympathetic-adrenal-medullary (SAM) axis, the

Abbreviations:

ACS = Acute Coronary Syndrome
ACTH = adrenocorticotropic hormone
BO = burnout
CAD = Coronary Artery Disease
CAR = Cortisol Awakening Rise
CFS = Chronic Fatigue Syndrome
CRH = corticotropin-releasing hormone
DSM-IV = Diagnostic and Statistical Manual of Mental Disorders
DST = Dexamethasone Suppression Test
HADS = Hospital Anxiety and Depression Scale
HPA axis = hypothalamus-pituitary-adrenal axis
ICD-10 = International Classification of Diseases
IRS = Insulin Resistance Syndrome
MBI = Maslach Burnout Inventory
ns = non-significant
OGTT = Oral Glucose Tolerance Test
SAM = sympathetic-adrenal-medullary
SCN = suprachiasmatic nucleus
sign. = significant
SMBQ = Shirom-Melamed Burnout Questionnaire
TBS = Teacher Burnout Scale
TSST = Trier Social Stress Test
VE = vital exhaustion
vs. = versus

cardiovascular system, as well as affective and cognitive processes.

Under stress, the hypothalamus secretes corticotropin-releasing hormone (CRH). This provokes the release of adrenocorticotropic hormone (ACTH) from the pituitary. Other ACTH secretagogues, like vasopressin, oxytocin, adrenaline and noradrenaline predominantly intensify the effects of CRH. ACTH triggers the secretion of glucocorticoids from the adrenal cortex. In humans the main glucocorticoid is cortisol. Cortisol is predominantly (90-95%) bound to binding proteins in the blood and only 5-10% of the total plasma cortisol circulates as biologically active, unbound, "free" cortisol. Overall functioning is controlled by several negative feedback loops (for an overview see 1, 4).

A dysfunctional HPA axis is associated with manifestations of psychosomatic and psychiatric disorders (for reviews see 1, 4-10). For example, HPA *hyper*activity is often found in major depression (11-14) and also seems to be associated with susceptibility to infectious diseases (15) and cardiovascular problems (16, 17). *Hypo*activity of the HPA axis system is associated with autoimmune processes such as lupus erythematosis (18, 7), multiple sclerosis (19), neurodermatitis (20, 21) or fibromyalgia, chronic fatigue syndrome, and rheumatoid arthritis (see 4, 9, 10). It is generally accepted that exposure to stress can cause and/or intensify numerous diseases. It has been suggested that enhanced HPA axis functioning might serve as one indicator of allostatic load, an index of cumulative toll on the body. A high allostatic load might result from chronic overactivation or inadequate responses of the stress system (17, 22), and result in a number of negative health outcomes in the long run, such as diabetes, hypertension, cancer, and cardiovascular disease (16, 17). Another version of this overview can also be found in (23).

2. Assessment of HPA axis activity, reactivity, and feedback functioning

To characterize different facets of HPA axis functioning, various methods have been applied focusing for example on HPA axis diurnal activity, reactivity to acute stress as well as the system's feedback sensitivity. For instance, it is conceivable that homeostatic control might be maintained under basal conditions while the impact of chronic stress is more prominent or might emerge primarily under stimulated conditions. Therefore, three established and widely-used research tools for the assessment of HPA axis regulation are briefly presented in the following.

2.1 HPA axis activity

The adrenal hormone cortisol shows a pronounced circadian rhythm with typically lowest secretion during the first half of night time sleep (quiescent period), an abrupt elevation during the second half of sleep, peak levels shortly after morning awakening and continuously decreasing levels over the remainder of the day, except for stress-related cortisol surges that superimpose on the normal circadian rhythm (24-26). The two major processes controlling the overall diurnal cortisol variation are the circadian signal generated by the circadian pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus, and the alternation of wakefulness and sleep (24). In particular, the cortisol awakening rise (CAR) is a discrete and distinctive part of the cortisol circadian cycle. In healthy adults, salivary free cortisol concentrations increase by 50 to 160% within the first 30 minutes after awakening (27-29). In several recent studies it could be demonstrated that the CAR reflects subtle changes in HPA axis activity and can serve as a useful index of adrenocortical activity (30-32). Furthermore, the CAR can be easily assessed by four saliva samples gained with strict reference to awakening (e.g., +0, +30, +45, +60 minutes after awakening) under a wide variety of clinical and field settings, since it is non-invasive, inexpensive and easy-to-employ (for a review see 33).

2.2 HPA axis reactivity

More than ten years ago, the Trier Social Stress Test (TSST) was introduced as a standardized protocol for the induction of moderate psychosocial stress in laboratory settings (34). In a recent comprehensive meta-analysis of 208 laboratory stress studies the TSST turned out to be one of the few available stress protocols which satisfies the criteria of a motivated performance task that combines elements of uncontrollability and high levels of social-evaluative threat (35). The TSST protocol mainly consists of a brief preparation period (3 min) and a test period in which the subject has to deliver a free speech (5 min; job interview) and perform mental arithmetic (5 min) in front of a trained audience (for more detailed up-to-date descriptions see 36 and 37). Until today, this stress protocol has been applied in more than 4,000 subjects all over the world including younger and older adults, children as well as clinical populations.

2.3 HPA axis feedback sensitivity

The Dexamethasone Suppression Test (DST) is routinely used for the assessment of HPA axis feedback sensitivity. The synthetic glucocorticoid dexamethasone acts primarily at the level of the pituitary and mimics the negative feedback effects of endogenous cortisol on ACTH and the subsequent cortisol release via binding to the glucocorticoid receptor (38-40). Pre-medication with dexamethasone normally takes place the night before cortisol samples are collected (e.g., 23 PM). Application of a low dose of dexamethasone with concentrations of 0.5 mg or even 0.25 mg in humans (so-called low-dose DSTs) is preferable in order to not completely suppress endogenous cortisol levels measured at the following day, for example allowing for hypersuppression (strong suppression) or indications of "non"-suppression (less suppression) (41, 42). In sum, the DST is a test of HPA axis negative feedback efficiency, indicated by the amount of cortisol suppression after oral dexamethasone intake.

3. Burnout and vital exhaustion: definitions

Burnout (BO) is a non-psychiatric syndrome mostly defined by the three core dimensions 1. emotional

exhaustion, 2. a cynical work attitude, and 3. feelings of work inefficacy and is thought to be a prolonged response to chronic emotional and interpersonal stress probably accompanied by insufficient recovery (43). Others identified burnout as a work-related construct uniquely characterized by the chronic depletion of an individual's intrinsic energetic or coping resources (44). Burned out individuals may experience additional physical symptoms (e.g., nonspecific pain, recurrent headaches, gastro-intestinal problems) and disturbed sleep or suffer from attentional difficulties which manifest subjectively as well as objectively (45). BO has often been described in individuals with a high sense of job ideals and whose jobs require a high degree of social interactions (so-called people-oriented professionals) such as teachers, caregivers, nurses, doctors, social workers, firefighters, policemen, etc. (43, 46, 47).

BO is mostly measured using the Maslach Burnout Inventory (MBI) encompassing the three subscales Emotional Exhaustion, Depersonalization, and Lack of Accomplishment (48). Others applied the Shirom-Melamed Burnout Questionnaire (SMBQ) comprised of up to four subscales (emotional exhaustion and physical fatigue, tension, listlessness, and cognitive weariness; 49, 50) or less frequent the Teacher Burnout Scale (TBS) based on the four scales Career Satisfaction, Perceived Administrative Support, Coping with Job-related Stress, and Attitude towards Students (51). For further more detailed discussion of the conceptual basis of BO and other measures of burnout not included in this review see Shirom and coworkers (46, 52). Although research on the relationship between burnout or vital exhaustion and health is relatively new, accumulated evidence suggests that BO acts as a risk factor for mental and physical ill health via different pathways (for reviews see 47, 53).

A psychological state that is also viewed as a potential consequence of long-term, chronic stress, or a chronic state of burnout is vital exhaustion (VE). VE is characterized by 1. unusual fatigue, 2. loss of mental and physical energy, 3. increased irritability, and 4. a feeling of demoralization and is measured by the Maastricht Vital Exhaustion Questionnaire (MVEQ; 54, 55). Interestingly, in several epidemiological studies, VE has been established as an independent risk factor for coronary artery disease (CAD; 56-58) (for reviews see also 59, 60). A recent outline of the history of the concept of vital exhaustion can be found in Appels (61).

Based on these definitions, it is obvious that burnout and vital exhaustion share conceptual similarities. Consequently, a high correlation was for example reported between burnout and vital exhaustion (r=.68, p=.001, N=56, measurements: SMBQ and MVEQ; 62) and subjects scoring high and low on burnout also differed significantly on VE (63). Appels & Schouten (64) hypothesized that the state of vital exhaustion before a myocardial infarction may be a reactivation of an earlier period of burnout. In addition, symptoms of burnout and vital exhaustion appear to overlap with such conditions as the chronic fatigue syndrome (CFS) or fibromyalgia and correlate moderately with depression and anxiety (47, 53, 61, 65, 66). However, we could recently show in a factor analysis based on a sample of N=822 workers that vital exhaustion (MVEQ) constitutes a distinct psychological concept compared to depressive symptomatology as measured by the depression subscale of the Hospital Anxiety and Depression Scale (HADS) and negative affectivity as measured by the respective subscale of the Type-D Questionnaire (67).

4. HPA axis regulation in burnout and vital exhaustion: empirical findings

To-date, there is still a paucity of data on HPA axis regulation in burnout and even less is known about HPA axis functioning in vital exhaustion. Furthermore, published studies seem to render contradictory results. In the following, we summarize the existing literature on cortisol regulation under (a) basal and (b) acute stress conditions in burned out and (vitally) exhausted subjects. The main focus will be on psychological stress, but studies using pharmacological stimulation procedures are also shortly presented. It has to be considered that different pharmacological stimulation tests act at different levels of the HPA axis involving different feedback loops at different levels in the system which complicates the comparability of different study designs and interpretation of results. In each section, we will first report on data based on burned out or exhausted but otherwise healthy subjects (without any clinical diagnosis) and then summarize evidence including patients with a clinical diagnosis, if available. As recently outlined by Shirom (53) there are still no clinically validated cut-off points available with respect to any of the above-described psychometric instruments used to assess burnout. The presently reviewed studies mostly based their clinical diagnoses of burnout on the DSM-IV *(Diagnostic and Statistical Manual of Mental Disorders)* and ICD-10 *(International Classification of Disease and Related Problems)* and include patients who meet the criteria for adjustment disorder (DSM-IV 309.xx; ICD-10 F43.xx) (see 68), work-related neurasthenia (ICD-10 F48.xx) or undifferentiated somatoform disorder (DSM-IV 300.81) (see 69, 70). Others based their clinical diagnosis on semi-structured diagnostic interviews conducted by a clinical psychologist (see 71 and 72).

4.1 HPA axis activity

4.1.1 Burnout (BO)

As indicated, we first resume studies based on non-clinical subjects. Examining total cortisol levels in a single blood sample, two studies by Grossi and coworkers (63, 73) applying the SMBQ and an unpublished dissertation by Söderfeldt (74) could not reveal associations between cortisol and burnout (measured by the emotional exhaustion subscale of the MBI). These insignificant results can presumably be attributed to the chosen blood sampling designs (single venipunctures). Contrary, the unpublished diploma thesis of J. Hellhammer (75) raised the idea of low 8 AM levels of salivary cortisol in nurses suffering from burnout accompanied by multiple bodily complaints. Based on these preliminary findings, school teachers scoring high

(N=30) and low (N=36) on two burnout questionnaires (MBI and TBS) were requested to collect four cortisol samples in the first hour after awakening on three consecutive days (sampling here: +0, +15, +45, +60 minutes after awakening). The third testing included a low-dose (0.5 mg) DST (76). According to J. Hellhammer's initial finding, subjects high on burnout showed a lower cortisol awakening rise (CAR) at day 1 and 2 as well as a greater suppression of the free cortisol secretion after dexamethasone premedication the night before sampling. Also, in a sample of 41 US soldiers, Morgan et al. (77) observed that higher levels of burnout were related to lower cortisol levels in the morning, but higher cortisol concentrations in the evening, which might be indicative of a reduced diurnal variation of cortisol or a flattened diurnal secretory cycle in burned out military personnel. In contrast, Melamed and coworkers (78) observed higher salivary cortisol levels in the morning and afternoon in industrial workers with non-chronic (N=22) and chronic burnout (N=37) compared to employees without burnout symptomatology (N=52). However, in the two latter studies only two samples per subject were gained at fixed time points. Finally, Ekstedt and coworkers (79) did not observe differences in a single morning plasma cortisol level, a cortisol awakening profile nor the diurnal cortisol cycle (measured by nine saliva samples) in a relatively small sample of 24 employees of a computer company scoring high versus low on the SMBQ (personal communication).

Finally, a few studies can be cited that investigated basal HPA axis functioning in clinically diagnosed burnout patients compared to healthy controls or subjects with low or medium burnout scores. Over a four month period, Moch et al. (72) measured the free cortisol secretion in 24/h urine samples before and after a stress management program in 16 female burnout patients (measurements once a month) and a healthy untreated control group (measurements at first and fourth month). Compared to controls, patients showed a reduced cortisol excretion regardless of clinical and psychological improvement due to the intervention. Also, 8 AM cortisol serum concentrations (but not ACTH levels) were significantly lower in patients than controls at month four. In a pilot study, Mommersteeg et al. (69) found lower salivary cortisol levels after awakening in clinically diagnosed burnout patients (N=22) who were either on partial or full sick-leave compared to a healthy control group (N=21). However, the groups did not differ in cortisol levels during the remainder of the day. Fourteen sessions of psychotherapeutic intervention led to a significant increase of the initially lowered morning cortisol levels, but there were no significant correlations between changes in CAR and improvements of psychological complaints. Contrary, De Vente and colleagues (71) observed higher cortisol levels after awakening in a group of 22 clinically diagnosed burnout patients compared to 23 healthy controls, and no differences at 12 AM. Very recently, Grossi and coworkers (68) recruited 22 subjects scoring low on burnout (LB), 20 subjects scoring moderate on burnout (MB) as well as 22 burnout patients scoring high on burnout (HB). Sex-specific ANOVA analysis of morning cortisol profiles revealed that there was no significant main effect of group in men while female patients (HB: N=13) had a significantly higher CAR than subjects with low burnout (LB: N=13), while cortisol curves of subjects with moderate burnout fall in between (MB: N=9). Finally, in a highly controlled study by Mommersteeg and colleagues (70) comprising 74 clinically diagnosed burnout patients and 35 healthy controls, clinical burnout was not reflected in the CAR, the diurnal cortisol day curve (12 AM, 6 PM, 10:30 PM) nor the low-dose (0.5 mg) DST (each covered by three saliva samples).

4.1.2 Vital exhaustion (VE)

Much less evidence can be found on vital exhaustion. In 34 healthy white collar workers, Dahlgren et al. (80) collected five salivary cortisol samples during one day of each a work week with high as well as low stress. While one group of subjects showed higher morning cortisol levels in the high stress week compared to the low stress week, the other group showed an opposite pattern. The latter group was characterized by higher workload, fatigue, and exhaustion during both weeks. Based on an initial questionnaire screening of 577 male volunteers, 54 potential VE cases and 33 control subjects were selected for the Maastricht Interview for Vital Exhaustion, a structured interview designed to evaluate frequency, severity, and duration of VE symptoms. In a final sample of 29 VE and 30 controls, Nicolson & van Diest (81) observed a pattern of marginally lower basal salivary cortisol levels throughout a day (covered by five saliva samples) with significantly lower cortisol concentrations in the evening (two samples) in exhausted subjects versus healthy controls. In contrast, in a large sample of N=238 female patients with acute coronary syndrome, Koertge et al. (58) found a small but significant positive association between vital exhaustion and total cortisol measured by a single morning blood sample ($r=.13$, $p\leq.05$).

4.2 HPA axis reactivity

4.2.1 Burnout

In addition to the assessment of basal HPA axis activity, De Vente and colleagues (71) also applied a laboratory stress protocol. Although significant differences in cortisol levels over the course of the test session are reported between burnout patients and controls, a closer inspection of stress responses revealed that the chosen task (speech, mental arithmetic) did not elicit a task-related cortisol response and observed group differences were based on higher pre-stress ("baseline") cortisol levels in burnout patients.

4.2.2 Vital exhaustion

Kristenson and coworkers compared Lithuanian versus Swedish men in a cross-cultural comparison and found that low peak cortisol responses to a standardized laboratory stress battery (anger recall, mental arithmetic, cold pressure test) were significantly related to high baseline cortisol levels and vital exhaustion (82-84). Also, the data from Nicolson & van Diest (81) support the idea of a subtle hyporeactivity in participants with high vital exhaustion. Although controls and thoroughly selected vitally

exhausted subjects showed statistically comparable overall cortisol responses to a laboratory speech task, exhausted subjects were less likely to show a significant response (six responders in 30 controls and no responder in 28 VE subjects). However, provoked cortisol increases were extremely small with mean increases of 1.36 nmol/l in controls and 0.79 nmol/l in VE. Recently, we applied the TSST three times in 25 healthy middle-aged male employees with test sessions one week apart (85). Focusing in a first step on the first stress session, the study results show that VE may rather be associated with reduced cortisol responses to acute stress, although the respective analysis was not significant (p=.14). Accounting for the repeated stress procedure, data revealed that mean cortisol responses showed the well-known general habituation effect across test exposures. Interestingly, mean cortisol responses varied across stress sessions depending on the extent of exhaustion. Linear regression revealed a negative dose-response relationship between exhaustion and the degree of habituation. We identified 19 individuals showing a response habituation (negative slope) and six individuals showing a response sensitization over the three sessions (positive slope) with the latter reporting higher exhaustion scores. We assume that situational or psychological factors initially "mask" an existing impact of exhaustion since in this study effects of exhaustion became fully apparent only after repeated stress exposure.

In a research project based on 69 normotensive and 21 borderline hypertensive men, Keltikangas-Järvinen and coworkers investigated the hypothesis that various psychological and behavioral characteristics (including vital exhaustion, depression, type A behavior, hostility, and anger) might be associated with the insulin resistance syndrome (IRS) as indicated by neuroendocrine responses to pharmacological stimulation (86-90). Their results showed that vital exhaustion combined with depression was negatively correlated with mean ACTH levels and positively correlated with the mean cortisol/ACTH ratio during oral glucose tolerance testing. Furthermore, the net increase of cortisol after intravenous ACTH stimulation with DEX-premedication differed significantly between subjects scoring high versus low on exhaustion with higher cortisol increases in the highly exhausted group.

5. Possible confounders and mechanisms

The above cited literature shows that the evidence on possible relationships between burnout and vital exhaustion on the one hand and HPA axis (dys)regulation on the other remain somewhat inconsistent. For example, there are studies showing either lower, higher or unchanged cortisol awakening profiles in groups with higher levels of burnout. It can only be speculated why the picture of results is relatively inconsistent. Inconstancies between studies can probably be, at least in part, ascribed to methodological aspects as well as confounding or intervening factors of HPA axis regulation. First of all, the cited studies used different psychometric scales to measure burnout or used different clinical diagnosis criteria for the inclusion of patient groups. Furthermore, different HPA axis outcome parameters were measured (ACTH, total cortisol in blood, salivary free cortisol) and different sampling procedures have been applied (single venipuncture, CAR, etc.). Only some studies controlled for psychological factors that might have influenced self-report, like negative affectivity, depression, or anxiety. Furthermore, burnout and vital exhaustion may differentially be related to HPA axis regulation in men and women, as indicated by Grossi et al. (68). In most of the past studies, data was only available in men or women, while others collected data in both men and women, but subsequently combined the groups to form one sample. Consequently, there is still a paucity of data on the potential modifying role of gender. Future studies should be aware of such possible gender-specific effects. It is also conceivable that other subgroups exist which remain to be defined in the future (for example, age or years of employment might be further important factors).

Likewise important, other factors are known to impact significantly on basal or stress-related cortisol concentrations, like medication intake, time of awakening (for assessment of CAR), subjects compliance (for ambulant saliva sampling), the female menstrual cycle phase or intake of oral contraceptives (for HPA axis outcomes under stress), smoking habits, kind of applied stress protocol, etc. (28, 30, 91; for reviews see 33, 36, 37). While several examples could be generated, we just want to outline a few: If time of awakening is not standardized or controlled while assessing morning cortisol levels, it is not unlikely that absolute cortisol levels as well as morning increases differ between high versus low burnout subjects or hospitalized patients just because of different awakening times (29, 92, 93). It is also conceivable that subjects' compliance with an ambulant saliva sampling procedure is significantly associated with the level of chronic stress. So, if chronically stressed subjects are systematically less or more adherent than controls, different cortisol profiles will be observed between groups of interest (94-96). In respect to HPA axis stress responses, total and free cortisol responses are significantly dependent on the female menstrual cycle phase and intake of oral contraceptives (97).

Besides these important methodological issues, we would like to speculate on possible underlying mechanisms. Based on their null-findings in a highly controlled and very well-conducted study, Mommersteeg et al. (70) speculated whether HPA axis dysregulation might be apparent during the development of burnout but wane in the period after the diagnosis of burnout. This hypothesis remains to be tested empirically. In respect to possible other mechanisms it might be hypothesized if chronic stress may first lead to hyperactive functioning, while the system turns to hypoactive functioning when a state of exhaustion is reached and the individual is no longer able to cope with environmental stress. This reasoning would be in line with several other empirical reports on increased basal free cortisol levels in the morning in chronically stressed individuals due to work overload, social stress and lack of social recognition, or chronic unemployment (30, 98-100). Additionally, in the above outlined study on burnout by Pruessner and coworkers (76), perceived stress correlated with increased cortisol levels

Table I. ***Summary of empirical studies on HPA axis regulation in (A) burnout and (B) vital exhaustion***

(A) Burnout			
Subjects high versus low on BO (without clinical burnout diagnosis)			
Grossi et al., 1999	• single blood sample between 8-10 AM: total cortisol	• no association BO and cortisol	ns
Grossi et al., 2003	• single blood sample between 8-10 AM: total cortisol	• no group differences high versus low BO	ns
Pruessner et al., 1999	• CAR (4 samples) on 3 consecutive days: salivary cortisol • low-dose DST (0.5 mg DEX) and CAR (4 samples): salivary cortisol	• lower CAR in high BO • after DEX lower CAR in high BO	↓ ↓
Morgan et al., 2002	• morning and evening samples: salivary cortisol (exact time points not given, p/F statistics not given) • [total cortisol]	• lower morning levels in high BO • higher evening levels in high BO • [results not reported]	↓ ↑
Melamed et al., 1999	• 8 AM and 4 PM salivary cortisol	• higher 8 AM levels in BO • higher 4 PM levels in BO	↑ ↑
Ekstedt et al., 2004	• single blood sample between 8-9 AM: total cortisol • CAR (4 samples): salivary cortisol • diurnal cortisol cycle (5 samples): salivary cortisol	• no group differences high versus low BO • no group differences high versus low BO • no group differences high versus low BO	ns ns ns
Clinically diagnosed burnout patients versus controls			
Moch et al., 2003	• 24/h cortisol in urine (before and after intervention) • single blood sample 8 AM: total cortisol • single blood sample 8 AM: ACTH	• lower levels in BO patients • lower 8 AM levels in BO patients at month 4 • no group differences	↓ ↓ ns
Mommersteeg et al., in press	• CAR (3 samples): salivary cortisol • diurnal cortisol cycle (3 samples): salivary cortisol • CAR (3 samples): salivary cortisol after psychotherapy	• lower CAR in BO patients • no group differences (patients vs. controls) • increased CAR in BO patients after psychotherapeutic intervention	↓ ns
De Vente et al., 2003	• CAR (3 samples): salivary cortisol • 12 AM: salivary cortisol • laboratory stress test (speech, mental arithmetic): salivary cortisol	• higher CAR in BO patients • no group differences • no task-related response (sign. group differences attributable to higher pre-stress ("baseline") levels in BO patients	↑ ns
Grossi et al., 2005	• CAR (4 samples): salivary cortisol	• higher CAR in female BO patients • no group differences in men	↑ (females) ns (men)
Mommersteeg et al., 2006	• CAR (3 samples): salivary cortisol • diurnal cortisol cycle (3 samples): salivary cortisol • low-dose DST (0.5 mg DEX) and CAR (3 samples): salivary cortisol	• no group differences (patients vs. controls) • no group differences (patients vs. controls) • no group differences (patients vs. controls)	ns ns ns
(B) Vital Exhaustion			
Dahlgren et al., 2004	• diurnal cortisol cycle (5 samples: +15 min after awakening, 10 AM, 1 PM, 4 PM, bedtime) once during each a week with high and low stress levels: salivary cortisol	• group with low morning cortisol levels in high stress week compared to the low stress week had higher workload, fatigue, and exhaustion	↓
Nicolson & van Diest, 2000	• day 1 - evening samples (9:30 PM, 10:35 PM): salivary cortisol • day 2 - diurnal cortisol cycle (6:55 AM, 11 AM, 4 PM, 5:40 PM, 7 PM): salivary cortisol • laboratory speech task	• lower levels in VE patients • marginally lower levels in VE patients (p=.08) • significant response less likely in VE patients	↓ (↓) ↓
Koertge et al., 2002	• single blood sample between 8-9 AM: total cortisol	• small positive association between VE and cortisol in females with ACS (r=.13, p≤.05)	↑
Kristenson et al., 1998, 2001, 2005	• standardized laboratory stress battery (anger recall, mental arithmetic, cold pressure test): total cortisol and salivary cortisol (cross-cultural comparison of Lithuanian versus Swedish men)	• baseline saliva cortisol marginally positively associated with VE (r=.13, p=.09) • peak saliva (r=-.16, p=.04) and total cortisol (r=-.22, p=.003) negatively associated with VE	(↑) ↓
Kudielka et al., 2006	• 3 TSST exposures one week apart: salivary cortisol	• VE associated with reduced habituation across 3 stress exposures in males • VE marginally associated with lower cortisol responses to first stress exposure (p=.14)	↓ (↓)
Keltikangas-Järvinen et al., 1996a, 1996b, 1997, 1998 Räikkönen et al., 1996	• OGTT: ACTH and total cortisol • DST (1 mg DEX) - ACTH stimulation: total cortisol	• VE + depression negatively correlated with mean ACTH, positively correlated with mean cortisol/ACTH ratio (normotensive and hypertensive men) • higher cortisol net increases in high VE group	↓ ↑ ↑

during the first hour after awakening. As indicated in the Table, studies on vital exhaustion, by the majority, point to a hypoactive HPA axis while studies on burnout are much more controversial. However, for stress reactivity conclusions are more difficult, since some stress protocols applied in chronically stressed individuals did not evoke significant cortisol increases (101, 102) and others did not observe different cortisol responses in groups with and without chronic life stress (103). However, the latter observation fits to our finding, showing that the impact of VE appears not until repeated stress exposures (85). Impaired habituation to repeated stress might be one potential pathway (beside others) how exhaustion relates to increased disease vulnerability over time. While in the allostatic load model (see above) lack of habituation is conceptualized as a high initial stress response and a lack of habituation to subsequent (comparable) stress exposures, our data (85) suggest that a lack of habituation might also be associated with a weakened initial stress response, indicating a reduced capability of the subjects' HPA axis to adapt to repeated stress exposure. This fits also to the findings by Nicolson & van Diest (81) and Kristenson and coworkers (82-84). It might even be speculated that a non-adaptive stress system (here: inability to habituate to stress) might cause the inability to show a normal activation when confronted with a new stressor. Such a pattern could be disadvantageous in two ways: in situations with a high need of energy there is no adequate supply (e.g., in highly demanding, stressful, new situations etc.) while in the long run a lack of adaptation (no response reduction when repeatedly confronted with similar situations) repeatedly leads to system activation. In the long run, both mechanisms could contribute to the wear and tear of the organism. In sum, the now classical statement by Rose (104) that so-called response habituation after repeated stimulation is a key characteristic of HPA axis functioning could be supplemented by the finding that a consequence of chronic stress (exhaustion) might moderate this habituation process. Of course, this observation has first to be confirmed in future studies. Such habituation probably reflects changes over time in multiple situational factors like perceived novelty, uncontrollability, threat, etc. (see 105). Since an insufficient ability to adjust or habituate to repeated exposure to the same stressor is considered as one condition that leads to allostatic load and could reflect a state of increased vulnerability, it may be concluded that absence of normal habituation to repeated stress might be one potential mechanism how exhaustion relates to increased disease vulnerability.

Overall, there seems to be a considerable divergence on data regarding HPA axis functioning in chronically distressed individuals. *Hyperactivity* of the HPA axis (including excess release of cortisol and a consequent suppression of immune-mediated inflammation) has been seen during chronic stress while HPA axis *hypoactivity* with a decrease of cortisol release and an increased susceptibility to immune-mediated inflammation has been reported in the chronic fatigue syndrome and after chronic stress (6, 9, 106-108). As suggested earlier, hypocortisolism may be the consequence of prolonged stress (or trauma) and there may be a time course in the development of this neuroendocrine abnormality (109). Possible mechanisms how initial HPA axis hyperactivity may eventually lead to a hypoactive state include dysregulations on several levels of the HPA axis. As outlined in detail by Heim and coworkers (9), the development and persistence of hypocortisolism may be due to reduced biosynthesis or depletion at several levels of HPA axis (CRH, ACTH, cortisol), CRH hypersecretion and adaptive down-regulation of pituitary CRH receptors or change in receptor sensitivity, increased feedback sensitivity of the HPA axis, and morphological changes (109). For further discussion see also Melamed et al. (47).

To summarize, chronic stress in terms of burnout and vital exhaustion seems to be associated with dysregulations of basal HPA axis functioning as well as HPA axis responses under stress. However, the observed direction remains still inconsistent and even some very well-conducted studies could not find associations between burnout and HPA axis dysregulations. Therefore, future studies should (a) pay attention to already known intervening and moderating factors of HPA axis regulation and (b) carefully differentiate acutely stressed, chronically stressed, and vitally exhausted, respectively burned out, subgroups. Regarding the HPA axis, one may attempt to differentially discriminate activity and reactivity patterns with respect to specific alterations of extrahypothalamic, hypothalamic, pituitary, adrenal, and receptor functions (endophenotyping).

References

1) Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. *JAMA* 267: 1244-52, 1992.
2) Dallman MF, Bhatnagar S, Viau V. Hypothalamo-pituitary-adrenal axis. In Fink G (ed), Encyclopedia of stress, Vol. 3. San Diego: Academic Press, 1st Edition, 2000, 468-477.
3) Watts AG. Hypothalamo-pituitary-adrenal axis, Anatomy of. In Fink G (ed), Encyclopedia of stress, Vol. 3. San Diego: Academic Press, 1st Edition, 2000, 477-483.
4) Tsigos C, Chrousos GP. Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. *J Psychosom Res* 53: 865-71, 2002.
5) Holsboer F. Psychiatric implications of altered limbic-hypothalamic-pituitary-adrenocortical activity. *Eur Arch Psychiatry Neurol Sci* 238: 302-22, 1989.
6) Tsigos C, Chrousos GP.: Physiology of the hypothalamic-pituitary-adrenal axis in health and dysregulation in psychiatric and autoimmune disorders. *Endocrinol Metab Clin North Am* 23: 451-66, 1994.
7) Stratakis CA, Chrousos GP. Neuroendocrinology and pathophysiology of the stress system. Annals of the New York academy of sciences. In Chrousos GP, McCarty R, Pacâk K, Cizza G, Sternberg E, Gold PW, Kvetnanský R (eds), Stress: Basic mechanisms and clinical implications, Vol. 771. New York, The New York Academy of Sciences, 1995, 1-18.
8) Young EA. Sex differences and the HPA axis: implications for psychiatric disease. *J Gend Specif Med* 1: 21-7, 1998.
9) Heim C, Ehlert U, Hellhammer DH. The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. *Psychoneuroendocrinology* 25: 1-35, 2000.
10) Raison CL, Miller AH. When not enough is too much: the role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. *Am J Psychiatry* 160: 1554-65, 2003.
11) Sachar EJ, Hellman L, Fukushima DK, Gallagher TF. Cortisol production in depressive illness. A clinical and biochemical clarification. *Arch Gen Psychiatry* 23: 289-98, 1970.
12) Carroll BJ, Curtis GC, Mendes J. Neuroendocrine regulation in depression. I. Limib system-adrenocortical dysfunction. *Arch Gen Psychiatry* 33: 1039-44, 1976.

13) Gold PW, Chrousos G, Kellner C, Post R, Roy A, Augerinos P, Schulte H, Oldfield E, Loriaux DL. Psychiatric implications of basic and clinical studies with corticotropin-releasing factor. *Am J Psychiatry* 141: 619-27, 1984.
14) Björntorp P. Behavior and metabolic disease. *Int J Behav Med* 3: 285-302, 1996.
15) Mason D. Genetic variation in the stress response: susceptibility to experimental allergic encephalomyelitis and implications for human inflammatory disease. *Immunol Today* 12: 57-60, 1991.
16) McEwen BS. Stress, adaptation, and disease. Allostasis and allostatic load. *Ann N Y Acad Sci* 840: 33-44, 1998.
17) McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med* 338: 171-9, 1998.
18) Weiner H. Social and psychosocial factors in autoimmune disease. In Ader A, Felten DL, Cohen N (eds), Psychoneuroimmunology. San Diego, Academic Press, 1991, 955-1012.
19) Adams RD, Victor M. Multiple sclerosis an allied demyelinative disease. Principles of neurology. New York, McGill-Hill, 1989.
20) Schnyder UW. Neurodermitis, asthma, rhinitis. Basel, Karger, 1960.
21) Buske-Kirschbaum A, Jobst S, Psych D, Wustmans A, Kirschbaum C, Rauh W, Hellhammer D. Attenuated free cortisol response to psychosocial stress in children with atopic dermatitis. *Psychosom Med* 59: 419-26, 1997.
22) McEwen BS, Stellar E: Stress and the individual. Mechanisms leading to disease. *Arch Intern Med* 153: 2093-101, 1993.
23) Kudielka BM, Kirschbaum C. Sex differences in HPA axis responses to stress: a review. *Biol Psychol* 69: 113-32, 2005.
24) van Cauter E. Diurnal and ultradian rhythms in human endocrine function: a minireview. *Horm Res* 34: 45-53, 1990.
25) Born J, Hansen K, Marshall L, Molle M, Fehm HL. Timing the end of nocturnal sleep. *Nature* 397: 29-30, 1999.
26) Kirschbaum C, Hellhammer DH. Salivary cortisol. In Fink G (ed), Encyclopedia of stress, Vol. 3. San Diego: Academic Press, 1st Edition, 2000, 379-383.
27) Pruessner JC, Wolf OT, Hellhammer DH, Buske-Kirschbaum A, von Auer K, Jobst S, Kaspers F, Kirschbaum C. Free cortisol levels after awakening: a reliable biological marker for the assessment of adrenocortical activity. *Life Sci* 61: 2539-49, 1997.
28) Wüst S, Wolf J, Hellhammer DH, Federenko I, Schommer N, Kirschbaum C. The cortisol awakening response - normal values and confounds. *Noise Health* 2: 79-88, 2000.
29) Kudielka BM, Kirschbaum C. Awakening cortisol responses are influenced by health status and awakening time but not by menstrual cycle phase. *Psychoneuroendocrinology* 28: 35-47, 2003.
30) Wüst S, Federenko I, Hellhammer DH, Kirschbaum C. Genetic factors, perceived chronic stress, and the free cortisol response to awakening. *Psychoneuroendocrinology* 25: 707-20, 2000.
31) Schlotz W, Hellhammer J, Schulz P, Stone AA. Perceived work overload and chronic worrying predict weekend-weekday differences in the cortisol awakening response. *Psychosom Med* 66: 207-14, 2004.
32) Kunz-Ebrecht SR, Kirschbaum C, Steptoe A. Work stress, socioeconomic status and neuroendocrine activation over the working day. *Soc Sci Med* 58: 1523-30, 2004.
33) Clow A, Thorn L, Evans P, Hucklebridge F. The awakening cortisol response: methodological issues and significance. *Stress* 7: 29-37, 2004.
34) Kirschbaum C, Pirke KM, Hellhammer DH. The 'Trier Social Stress Test'-a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology* 28: 76-81, 1993.
35) Dickerson SS, Kemeny ME. Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. *Psychol Bull* 130: 355-91, 2004.
36) Kudielka BM, Wüst S, Kirschbaum C, Hellhammer DH. The Trier Social Stress Test (TSST). In Fink G, Chrousos G, Craig I, de Kloet ER, Feuerstein G, McEwen BS, Rose NR, Rubin RT, Steptoe A (eds), Encyclopedia of stress, 2nd Edition. New York and Oxford, Elsevier, 2007/in press.
37) Kudielka BM, Hellhammer DH, Kirschbaum C. Ten years of research with the Trier Social Stress Test (TSST) - revisited. In Harmon-Jones E, Winkielman P (eds), Social Neuroscience. New York, Guilford Press, 2006/in press.
38) de Kloet ER. Why dexamethasone poorly penetrates in brain. *Stress* 2: 13-20, 1997.
39) de Kloet ER, Vreugdenhil E, Oitzl MS, Joels M. Brain corticosteroid receptor balance in health and disease. *Endocr Rev* 19: 269-301, 1998.
40) Cole MA, Kim PJ, Kalman BA, Spencer RL. Dexamethasone suppression of corticosteroid secretion: evaluation of the site of action by receptor measures and functional studies. *Psychoneuroendocrinology* 25: 151-67, 2000.
41) Yehuda R, Southwick SM, Krystal JH, Bremner D, Charney DS, Mason JW. Enhanced suppression of cortisol following dexamethasone administration in posttraumatic stress disorder. *Am J Psychiatry* 150: 83-6, 1993.
42) Huizenga NA, Koper JW, De Lange P, Pols HA, Stolk RP, Burger H, Grobbee DE, Brinkmann AO, De Jong FH, Lamberts SW. A polymorphism in the glucocorticoid receptor gene may be associated with and increased sensitivity to glucocorticoids in vivo. *J Clin Endocrinol Metab* 83: 144-51, 1998.
43) Maslach C, Schaufeli WB, Leiter MP. Job burnout. *Annu Rev Psychol* 52: 397-422, 2001.
44) Shirom A. Burnout in work organizations. In Cooper CL, Robertson I (eds), International review of industrial and organizational psychology. New York, John Wiley & Sons, 1989.
45) van der Linden D, Keijsers GP, Eling P, van Schaijk R. Work stress and attentional difficulties: an initial study on burnout and cognitive failure. *Work & Stress* 19: 23-36, 2005.
46) Shirom A. Job-related burnout. In Quick JC, Tetrick LE (eds), Handbook of occupational health psychology. Washington, DC, American Psychological Association, 2003, 245-265.
47) Melamed S, Shirom A, Toker S, Berliner S, Shapira I. Burnout and risk of cardiovascular disease: Evidence, possible causal paths, and promising research directions. *Psychol Bull*, 2006/in press.
48) Maslach C, Jackson SE. Maslach burnout inventory, manual. Palo Alto, CA, Consulting Psychologists Press, 1986.
49) Kushnir T, Melamed S. The Gulf War and its impact on burnout and well-being of working civilians. *Psychol Med* 22: 987-95, 1992.
50) Melamed S, Kushnir T, Shirom A. Burnout and risk factors for cardiovascular diseases. *Behav Med* 18: 53-60, 1992.
51) Seidman SA, Zager J. The teacher burnout scale. *Educational Research Quaterly* 11: 26-33, 1986/1987.
52) Shirom A, Ezrachi Y. On the discriminant validity of burnout, depression, and anxiety: A re-examination of the burnout measure. *Anxiety, Stress and Coping* 16: 83-99, 2003.
53) Shirom A, Melamed S, Toker S, Berliner S, Shapira I. Burnout, mental and physical health: A review of the evidence and a proposed explanatory model. *International Review of Industrial and Organizational Psychology* 20: 269-309, 2005.
54) Appels A, Mulder P. Excess fatigue as a precursor of myocardial infarction. *Eur Heart* J 9: 758-64, 1988.
55) Appels A, Höppener P, Mulder P. A questionnaire to assess premonitory symptoms of myocardial infarction. *Int J Cardiol* 17: 15-24, 1987.
56) Appels A, Falger PR, Schouten EG. Vital exhaustion as risk indicator for myocardial infarction in women. *J Psychosom Res* 37: 881-90, 1993.
57) Kop WJ, Appels AP, Mendes de Leon CF, de Swart HB, Bar FW: Vital exhaustion predicts new cardiac events after successful coronary angioplasty. *Psychosom Med* 56: 281-7, 1994.
58) Koertge J, Al-Khalili F, Ahnve S, Janszky I, Svane B, Schenck-Gustafsson K. Cortisol and vital exhaustion in relation to significant coronary artery stenosis in middle-aged women with acute coronary syndrome. *Psychoneuroendocrinology* 27: 893-906, 2002.
59) Gidron Y, Gilutz H, Berger R, Huleihel M. Molecular and cellular interface between behavior and acute coronary syndromes. *Cardiovasc Res* 56: 15-21, 2002.
60) Kop WJ. The integration of cardiovascular behavioral medicine and psychoneuroimmunology: new developments based on converging research fields. *Brain Behav Immun* 17: 233-7, 2003.
61) Appels A. Exhaustion and coronary heart disease: the history of a scientific quest. *Patient Educ Couns* 55: 223-9, 2004.
62) Lerman Y, Melamed S, Shragin Y, Kushnir T, Rotgoltz Y, Shirom A, Aronson M. Association between burnout at work and leukocyte adhesiveness/aggregation. *Psychosom Med* 61: 828-33, 1999.
63) Grossi G, Perski A, Evengard B, Blomkvist V, Orth-Gomer K. Physiological correlates of burnout among women. *J Psychosom Res* 55: 309-16, 2003.
64) Appels A, Schouten E. Burnout as a risk factor for coronary heart disease. *Behav Med* 17: 53-9, 1991.
65) Kopp MS, Falger PR, Appels A, Szedmak S. Depressive symptomatology and vital exhaustion are differentially related to behavioral risk factors for coronary artery disease. *Psychosom Med* 60: 752-8, 1998.
66) Toker S, Shirom A, Shapira I, Berliner S, Melamed S. The association between burnout, depression, anxiety, and inflammation bio-

markers: C-reactive protein and fibrinogen in men and women. *J Occup Health Psychol* 10: 344-62, 2005.
67) Kudielka BM, von Känel R, Gander ML, Fischer JE. The interrelationship of psychosocial risk factors for coronary artery disease in a working population: do we measure distinct or overlapping psychological concepts? *Behav Med* 30: 35-43, 2004.
68) Grossi G, Perski A, Ekstedt M, Johansson T, Lindström M, Holm K. The morning salivary cortisol response in burnout. *J Psychosom Res* 59: 103-11, 2005.
69) Mommersteeg PMC, Keijsers GPJ, Heijnen CJ, Verbraak MJPM, van Doornen LJP. Cortisol deviations in people with burnout before and after psychotherapy; a pilot study. *Health Psychol*, in press.
70) Mommersteeg PM, Heijnen CJ, Verbraak MJ, van Doornen LJ. Clinical burnout is not reflected in the cortisol awakening response, the day-curve or the response to a low-dose dexamethasone suppression test. *Psychoneuroendocrinology* 31: 216-25, 2006.
71) De Vente W, Olff M, Van Amsterdam JG, Kamphuis JH, Emmelkamp PM. Physiological differences between burnout patients and healthy controls: blood pressure, heart rate, and cortisol responses. *Occup Environ Med* 60 Suppl 1: i54-61, 2003.
72) Moch SL, Panz VR, Joffe BI, Havlik I, Moch JD. Longitudinal changes in pituitary-adrenal hormones in South African women with burnout. *Endocrine* 21: 267-72, 2003.
73) Grossi G, Theorell T, Jurisoo M, Setterlind S. Psychophysiological correlates of organizational change and threat of unemployment among police inspectors. *Integr Physiol Behav Sci* 34: 30-42, 1999.
74) Söderfeldt M. Burnout? Dissertation. Lund, Sweden, School of Social Work, Lund University, 1997.
75) Hellhammer J. Burnout bei Pflegepersonal - Eine psychoendokrinologische Untersuchung. Diploma thesis, University of Trier, Germany, 1990.
76) Pruessner JC, Hellhammer DH, Kirschbaum C. Burnout, perceived stress, and cortisol responses to awakening. *Psychosom Med* 61: 197-204, 1999.
77) Morgan CA, Cho T, Hazlett G, Coric V, Morgan J. The impact of burnout on human physiology and on operational performance: a prospective study of soldiers enrolled in the combat diver qualification course. *Yale J Biol Med* 75: 199-205, 2002.
78) Melamed S, Ugarten U, Shirom A, Kahana L, Lerman Y, Froom P. Chronic burnout, somatic arousal and elevated salivary cortisol levels. *J Psychosom Res* 46: 591-8, 1999.
79) Ekstedt M, Akerstedt T, Soderstrom M. Microarousals during sleep are associated with increased levels of lipids, cortisol, and blood pressure. *Psychosom Med* 66: 925-31, 2004.
80) Dahlgren A, Akerstedt T, Kecklund G. Individual differences in the diurnal cortisol response to stress. *Chronobiol Int* 21: 913-22, 2004.
81) Nicolson NA, van Diest R: Salivary cortisol patterns in vital exhaustion. *J Psychosom Res* 49: 335-42, 2000.
82) Kristenson M, Orth-Gomer K, Kucinskiene Z, Bergdahl B, Calkauskas H, Balinkyniene I, Olsson AG. Attenuated cortisol response to a standardized stress test in Lithuanian versus Swedish men: the LiVicordia study. *Int J Behav Med* 5: 17-30, 1998.
83) Kristenson M, Kucinskiene Z, Bergdahl B, Ort-Gomer K. Risk factors for coronary heart disease in different socioeconomic groups of Lithuania and Sweden-the LiVicordia Study. *Scand J Public Health* 29: 140-50, 2001.
84) Kristenson M, Olsson AG, Kucinskiene Z. Good self-rated health is related to psychosocial resources and a strong cortisol response to acute stress: the LiVicordia study of middle-aged men. *Int J Behav Med* 12: 153-60, 2005.
85) Kudielka BM, von Känel R, Preckel D, Zgraggen L, Mischler K, Fischer JE. Exhaustion is associated with reduced habituation of free cortisol responses to repeated acute psychosocial stress. *Biol Psychol*, 2006/in press.
86) Keltikangas-Järvinen L, Räikkönen K, Hautanen A. Type A behavior and vital exhaustion as related to the metabolic hormonal variables of the hypothalamic-pituitary-adrenal axis. *Behav Med* 22: 15-22, 1996.
87) Keltikangas-Järvinen L, Räikkönen K, Hautanen A, Adlercreutz H. Vital exhaustion, anger expression, and pituitary and adrenocortical hormones. Implications for the insulin resistance syndrome. *Arterioscler Thromb Vasc Biol* 16: 275-80, 1996.
88) Keltikangas-Järvinen L, Räikkönen K, Adlercreutz H. Response of the pituitary-adrenal axis in terms of type A behaviour, hostility and vital exhaustion in healthy middle-aged men. *Psychology and Health* 12: 533-42, 1997.
89) Keltikangas-Järvinen L, Ravaja N, Räikkönen K, Hautanen A, Adlercreutz H. Relationships between the pituitary-adrenal hormones, insulin, and glucose in middle-aged men: moderating influence of psychosocial stress. *Metabolism* 47: 1440-9, 1998.
90) Räikkönen K, Hautanen A, Keltikangas-Järvinen L. Feelings of exhaustion, emotional distress, and pituitary and adrenocortical hormones in borderline hypertension. *J Hypertens* 14: 713-8, 1996.
91) Kirschbaum C, Wüst S, Strasburger CJ. 'Normal' cigarette smoking increases free cortisol in habitual smokers. *Life Sci* 50: 435-42, 1992.
92) Edwards S, Evans P, Hucklebridge F, Clow A. Association between time of awakening and diurnal cortisol secretory activity. *Psychoneuroendocrinology* 26: 613-22, 2001.
93) Federenko I, Wüst S, Hellhammer DH, Dechoux R, Kumsta R, Kirschbaum C. Free cortisol awakening responses are influenced by awakening time. *Psychoneuroendocrinology* 29: 174-84, 2004.
94) Kudielka BM, Broderick JE, Kirschbaum C. Compliance with saliva sampling protocols: electronic monitoring reveals invalid cortisol daytime profiles in noncompliant subjects. *Psychosom Med* 65: 313-9, 2003.
95) Broderick JE, Arnold D, Kudielka BM, Kirschbaum C. Salivary cortisol sampling compliance: comparison of patients and healthy volunteers. *Psychoneuroendocrinology* 29: 636-50, 2004.
96) Jacobs N, Nicolson NA, Derom C, Delespaul P, van Os J, Myin-Germeys I. Electronic monitoring of salivary cortisol sampling compliance in daily life. *Life Sci* 76: 2431-43, 2005.
97) Kirschbaum C, Kudielka BM, Gaab J, Schommer NC, Hellhammer DH. Impact of gender, menstrual cycle phase, and oral contraceptives on the activity of the hypothalamus-pituitary-adrenal axis. *Psychosom Med* 61: 154-62, 1999.
98) Ockenfels MC, Porter L, Smyth J, Kirschbaum C, Hellhammer DH, Stone AA. Effect of chronic stress associated with unemployment on salivary cortisol: overall cortisol levels, diurnal rhythm, and acute stress reactivity. *Psychosom Med* 57: 460-7, 1995.
99) Schulz P, Kirschbaum C, Pruessner JC, Hellhammer DH. Increased free cortisol secretion after awakening in chronically stressed individuals due to work overload. *Stress Med* 14: 91-97, 1998.
100) Lundberg U, Hellström B. Workload and morning salivary cortisol in women. *Work & Stress* 16: 356-363, 2002.
101) Matthews KA, Gump BB, Owens JF. Chronic stress influences cardiovascular and neuroendocrine responses during acute stress and recovery, especially in men. *Health Psychol* 20: 403-10, 2001.
102) Benschop RJ, Brosschot JF, Godaert GL, De Smet MB, Geenen R, Olff M, Heijnen CJ, Ballieux RE. Chronic stress affects immunologic but not cardiovascular responsiveness to acute psychological stress in humans. *Am J Physiol* 266: R75-80, 1994.
103) Pike JL, Smith TL, Hauger RL, Nicassio PM, Patterson TL, McClintick J, Costlow C, Irwin MR. Chronic life stress alters sympathetic, neuroendocrine, and immune responsivity to an acute psychological stressor in humans. *Psychosom Med* 59: 447-57, 1997.
104) Rose RM. Overview of endocrinology of stress. In Brown GM, Koslow SH, Reichlin S (eds), Neuoendocrinology and psychiatric disorder. New York, Raven Press, 1984, 95-122.
105) Mason JW. A review of psychoendocrine research on the pituitary-adrenal cortical system. *Psychosom Med* 30: Suppl: 576-607, 1968.
106) Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. *N Engl J Med* 332: 1351-62, 1995.
107) Demitrack MA, Crofford LJ. Evidence for and pathophysiologic implications of hypothalamic-pituitary-adrenal axis dysregulation in fibromyalgia and chronic fatigue syndrome. *Ann N Y Acad Sci* 840: 684-97, 1998.
108) Gaab J, Hüster D, Peisen R, Engert V, Heitz V, Schad T, Schürmeyer TH, Ehlert U. Hypothalamic-pituitary-adrenal axis reactivity in chronic fatigue syndrome and health under psychological, physiological, and pharmacological stimulation. *Psychosom Med* 64: 951-62, 2002.
109) Hellhammer DH, Wade S. Endocrine correlates of stress vulnerability. *Psychother Psychosom* 60: 8-17, 1993.

Reprint request: *Brigitte M. Kudielka, PhD - Department of Theoretical and Clinical Psychobiology, University of Trier - Johanniterufer 15 - 54290 Trier, Germany - Phone: +49-651-201-2981, Fax: +49-651-201-3690, E-mail: kudielka@uni-trier.de*