Exhaustion is associated with reduced habituation of free cortisol responses to repeated acute psychosocial stress

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Abstract

We investigated the association between exhaustion and the habituation of free cortisol responses to repeated stress exposure. The study comprised 25 healthy male subjects (38–59 years) who were confronted three times with the Trier Social Stress Test. Mean cortisol responses showed the well-known general habituation effect. A two-way interaction day by exhaustion ($p < 0.05$) indicated that mean cortisol responses vary across stress sessions depending on the extent of exhaustion. Linear regression revealed a negative dose–response relationship between exhaustion and the degree of habituation ($p < 0.02$). We identified 19 individuals showing a response habituation (negative slope) and 6 individuals showing a response sensitization over the three sessions (positive slope) with the latter reporting higher exhaustion scores. It might be hypothesized that impaired habituation to repeated exposure to the same stressor could reflect a state of increased vulnerability for allostatic load. Absence of normal habituation might be one potential mechanism how exhaustion relates to increased disease vulnerability.
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Keywords: Exhaustion; Salivary free cortisol; Acute psychosocial stress; Habituation; Slope; Trier Social Stress Test (TSST)

1. Introduction

Accumulating evidence from animal (Brodish and Odio, 1989; Akana et al., 1992; Pecoraro et al., 2004) and human data (McEwen and Stellar, 1993; Chrousos, 1995) show that chronic stress can modulate the functioning of the hypothalamus–pituitary–adrenal (HPA) axis. Furthermore, dysregulation of the HPA axis have been associated with onset and course of several psychosomatic and psychiatric disorders (Holsboer, 1989; Chrousos and Gold, 1992; Tsigos and Chrousos, 1994; Björntorp and Rosmond, 1999; Heim et al., 2000; Raison and Miller, 2003). A psychological state that is viewed as a potential consequence of long-term, chronic stress is vital exhaustion (VE). VE is characterized by unusual fatigue, loss of mental and physical energy, increased irritability, and a feeling of demoralization (Appels et al., 1987; Appels and Mulder, 1988). In epidemiological studies, VE has been established as an independent risk factor for coronary artery disease (CAD; Appels et al., 1993; Kop et al., 1994; Koertge et al., 2002). To date, only few studies investigated whether exhaustion affects the responsiveness of the HPA axis to stressful situations. Previous research points to altered HPA axis functioning in exhaustion. Nicolson and van Diest (2000) observed a pattern of lower basal salivary cortisol levels throughout the day, with significant differences in the evening in vitally exhausted subjects versus healthy controls. However, a single exposure to a laboratory speech task did not reveal any differences in cortisol stress responses between groups (Nicolson and van Diest, 2000). Kristenson et al. (1998, 2001) compared Lithuanian versus Swedish men in a cross-cultural comparison and found that low peak cortisol responses to a standardized laboratory stress battery were significantly related to vital exhaustion and high baseline cortisol levels. Recently, Dahlgren et al. (2004) reported on higher workload, fatigue, and exhaustion levels in a group of white-collar workers with lowered cortisol levels in a high stress condition.

A hallmark of the adaptive propensity of the human HPA axis stress response is the rapid habituation to repeated exposure to the same stimulus (Levine, 1978; Gunnar et al., 1989; Deinzer et al., 1997; Pruessner et al., 1999; Gerra et al., 2001). An insufficient ability to adjust or habituate to repeated exposure to the same stressor is considered as one of four different scenarios that leads to allostatic load (namely repeated "hits", lack of adaptation, prolonged response, or inadequate response; McEwen, 1998; McEwen and Seeman, 1999). Allostasis means 'maintaining stability through change' (Sterling and Eyer, 1988) and allostatic load is the cumulative long-term effect of the physiological systems' attempts to adapt to life's demands (McEwen and Stellar, 1993; McEwen, 1998). The proposed allostatic load index consists of at least 10 biological parameters including cortisol (Seeman et al., 1997, 2001; Schnorpfeil et al., 2003). Failing to habituate – or the loss of allostasis, might lead to a higher susceptibility to disease or declines in physical and cognitive functioning (Seeman et al., 2001; Karlamangla et al., 2002). We hypothesized that exhaustion might impair an individuals' ability to show habituation. In this analysis, we, therefore, investigated the association between exhaustion as measured by the Maastricht-Vital-Exhaustion-Questionnaire and repeated exposure to acute psychosocial stress using the Trier Social Stress Test (TSST). The TSST is a standardized and validated stress protocol for laboratory settings, which reliably elicits endocrine stress responses in the majority of individuals (Kirschbaum et al., 1993; Dickerson and Kemeny, 2004; Kudielka et al., 2004a). A general habituation effect has been consistently reported for a variety of stress paradigms including the Trier Social Stress Test (Pruessner et al., 1999; Schommer et al., 2003; Federenko et al., 2004; Wüst et al., 2005). In sum, the aim of the present study was to elucidate whether exhaustion attenuates the endocrine stress response habituation to psychosocial stress in healthy adults.

2. Methods and materials

2.1. Study design and recruitment of participants

The study protocol was formally approved by the ethics committee of the Federal Institute of Technology (ETH), Zurich, Switzerland. All participants gave written consent.

As part of a large survey on "Work and Health", the permanent non-faculty employees of the Federal Institute of Technology, older than 35 years were invited to participate in a written health assessment. The questionnaire inquired about the personal and family medical history. It assessed a range of data including demographic and job-related variables as well as behavioral, somatic, and psychosocial risk factors for cardiovascular diseases (Schnorpfeil et al., 2002). The employees were then approached to participate in a separate study on the effects of acute stress on blood coagulation. The health questionnaires of volunteers were closely reviewed by a board certified specialist in internal medicine, while a brief physical exam and an in-depth personal history were obtained by two trained medical students. All subjects in this study were free of any regular medication throughout the protocol. Females were not eligible in the present analysis because the female cycle may influence salivary free cortisol responses to acute stress (Kirschbaum et al., 1999).

2.2. Stress protocol

In total, 27 participants were scheduled and subjected three times to the stress protocol in weekly intervals. The final study population comprised 25 male subjects who provided saliva samples for each of the three testing sessions. Two subjects dropped from the present analysis after the first or second test session due to time restrictions.

We used the Trier Social Stress Test (Kirschbaum et al., 1993), which consists of a 3 min preparation phase followed by a 5 min free speech phase (job interview) and a 5 min mental arithmetic task before an audience. A recent meta-analysis concluded that the components of social evaluative threat and uncontrollability of the TSST render it a reliable tool to elicit robust physiological stress responses (Dickerson and Kemeny, 2004). Furthermore, it has been shown that the TSST can be used with equal reliability in the morning and afternoon hours (Kudielka et al., 2004b).

Either two or three subjects were tested on each morning with an interval of 30–45 min between subjects and with the first subject arriving at the laboratory at 07:30 a.m. Participants were instructed to refrain from physical exercise and eating on test days. After a resting period of 10 min, an indwelling venous catheter was inserted into the cubital vein of the right arm to obtain blood samples for later assessment of coagulation responses (reported elsewhere). After catheter placement, subjects received a light standardized breakfast without caffeine and remained seated until further instruction. One hour after arrival at the laboratory, the subject was informed on the nature of the stress protocol. After completion of the task, subjects remained seated for another 105 min. To prevent any emotional arousal during recovery, participants were offered a volume of landscape photography and travel magazines in a quiet room. Subjects underwent the stress protocol three times with an interval of approximately 1 week. After the first test session (week 1), subjects were informed that the two subsequent testing sessions (weeks 2 and 3) would be identical. To avoid effects of learning and repetition, the theme for the free speeches and the initial number for the serial subtraction tasks across the stress sessions were minimally modified following the recently applied TSST protocol for repeated stress exposure (Schommer et al., 2003).

2.3. Sample collection and biochemical analysis

Sampling for saliva collection followed earlier protocols investigating cortisol responses to acute stress (Kudielka et al., 2004a). Saliva samples were obtained into purpose designed tubes for saliva collection (IBL, Hamburg, Germany) immediately before the preparation phase ("baseline"), immediately after stress, as well as 15, 30, 45, and 105 min after stress. Saliva samples were kept at room temperature throughout one test session and then stored at $-20\,^{\circ}C$. All samples were centrifuged at 3000 rpm for 5 min to provide clear supernatant fractions. Free cortisol was assayed by luminescence immuno assay (IBL, Hamburg, Germany; Westermann et al., 2004). Values are expressed as nmol/l.

2.4. Psychological assessment

2.4.1. Maastricht-Vital-Exhaustion-Questionnaire

Vital exhaustion is a mental or psychological (not a physical) state, which is defined as mental fatigue, increased irritability, and demoralization. VE was measured as a part of the above mentioned health assessment offered to the ETH staff members. We applied the nine-item short form (Kopp et al., 1998) derived from the original Maastricht-Questionnaire by Appels et al. (1987, 1989). In detail, the nine items asked about undue tiredness, troubles falling asleep, repeated waking up at night, general malaise, listlessness, irritability, loss of energy, demoralization, and waking up exhausted. Scores obtained from the short version correlate well with those from the original 21-item questionnaire ($r = 0.94$, $p < 0.001$, $n = 452$; Kopp et al., 1998). For the purpose of an earlier study (Schnorpfeil et al., 2002), the nine items were translated into German in close cooperation with the authors of the instrument (translation was double checked by original authors). Possible answers are "*no*", scored as 0; indeterminate, which is marked as "?" and scored as 1; and "*yes*", scored as 2. We used the same presentation of the answering format and the same scoring system, giving rise to a range of scores from 0 to 18, where scores from 0 to 3 indicate no exhaustion, from 4 to 10 mild to moderate exhaustion, from 11 to 14 substantial exhaustion, and scores > 14 are consistent with severe exhaustion. Cronbach's alpha was 0.78, reflecting good reliability.