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Dexamethasone stimulated gene expression in peripheral blood indicates glucocorticoid-receptor hypersensitivity in job-related exhaustion

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Summary Work-related stress can lead to various health problems ranging from job-related exhaustion to psychiatric and somatic diseases. Biomarkers of job-related exhaustion could help to improve our understanding of the biological mechanisms and might be useful to guide prevention and treatment strategies.

The present study included 12 male cases suffering from job-related exhaustion and 12 matched healthy controls. Severity of exhaustion was assessed with the Maslach Burnout Inventory (MBI) and the Shirom-Melamed Burnout Measure (SMBM). Whole genome expression profiles derived from whole blood cells (baseline and following glucocorticoid-receptor (GR) stimulation with 1.5 mg dexamethasone p.o.) and corresponding plasma cortisol levels were analyzed. All cases participated in regular aerobic exercise for 12 consecutive weeks and were then re-assessed at follow-up for exhaustion symptoms as well as for cortisol levels and gene expression profiles.

At baseline, we found increased basal cortisol levels and an enhanced suppression of plasma cortisol concentrations following dexamethasone in cases suffering from job-related exhaustion. Gene expression analysis revealed that 1.6-fold more transcripts were significantly regulated by

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dexamethasone in cases as compared to controls. At follow-up after 12 weeks of regular exercise training which was accompanied by significantly improved exhaustion severity scores, cortisol levels and gene expression profiles of cases normalized to the levels observed in controls.

In conclusion, we detected GR-induced neuroendocrine and gene expression changes in cases suffering from job-related exhaustion which are in line with an increased sensitivity of GR function. This GR dysregulation normalized with symptom recovery.

1. Introduction

Job-related exhaustion may occur when individuals are exposed to chronic work-related stress that exceeds their ability to cope with or control the demands of their work environment (European Social Dialogue, 2004). According to the Fourth European Working Conditions Survey in 2005, stress was experienced on average by 22% of workers from 25 member states and 2 acceding countries of the European Union (European Foundation for the Improvement of Living and Working Conditions, 2006). Studies suggest that between 50% and 60% of all missed working days have some link with work-related stress (Cox et al., 2000). These numbers reflect huge costs in terms of both human distress and impaired economic performance. In 2002, the European Commission reported that the yearly cost of work-related stress in the 15 original European Union Member States was 20 billion euro each year (Levi and Levi, 2000). Beyond financial concerns, stress and job-related exhaustion represent risk factors for the development of stress-related psychiatric disorders such as major depression (Ahola et al., 2005) and other diseases (Melamed et al., 1992). Taken together, job-related exhaustion is of major concern for employees, companies and for public health authorities and burden the society with enormous costs due to absenteeism and also unproductive presenteeism at work as well as high healthcare costs.

A number of studies have tried to identify biological markers that are associated with job-related exhaustion, e.g. dysregulation of the hypothalamus-pituitary adrenocortical (HPA) axis. These studies investigated the cortisol awakening response in the morning (Pruessner et al., 1999) and the cortisol response after suppression with dexamethasone (Bellingrath et al., 2008). Meta-analyses of these studies showed mixed results with no differences for basal cortisol blood levels and for the saliva cortisol awakening response between patients suffering from job-related exhaustion and healthy controls (Danhof-Pont et al., 2011).

The present study submits the hypothesis that a previously described GR supersensitivity in job-related exhaustion is accompanied by differences in GR-induced gene expression changes. We also tested whether altered GR functioning during job-related exhaustion would normalize after improvement of exhaustion symptoms. To this aim we used a GR stimulation with an oral administration of a low dose of dexamethasone to reveal GR mediated changes in cortisol levels and gene expression as previously described (Menke et al., 2012). To avoid any confounding effects of psychopharmacologic interventions, cases with job-related exhaustion performed a standardized aerobic exercise training as the only stress coping procedure allowed during study participation.

2. Methods

2.1. Recruitment of cases and procedures

For recruitment, advertisements were published in local newspapers and posted electronically on homepages of larger local companies, and public institutions such as universities, hospitals, and public authorities. In order to avoid confounding effects of gender (Young and Korszun, 2010) on GR activation we investigated a sample of only male participants. All participants gave written informed consent after they have received a complete description of the study. The study protocol was approved by the local ethics committee. Prior to study enrollment, all candidates were assessed by an experienced rater for the presence of job-related exhaustion after prolonged exposure to work-related stress. Inclusion criteria comprised a high score on the Maslach Burnout Inventory subscales "Emotional Exhaustion" ($\geq$27) or "Depersonalization" ($\geq$10), male gender, age between 35 and 55 years, non-smoking, good physical health who did not perform regular aerobic exercise in the last two years. Subjects who met one of the following exclusion criteria were excluded from the study: neurological illness; endocrinological and metabolic illness; liver or renal dysfunction; acute or chronic infectious diseases; neoplasias. Psychiatric disorders were ruled out by a short structured diagnostic interview based on the DSM-IV, Axis I diagnostic criteria and ICD-10 (M.I.N.I.; Sheehan et al., 1998). Subjects with pharmacologic or psychotherapeutic treatment were also excluded from the study. After thorough examination a total of 12 Caucasian male cases (mean age 45.8 $\pm$ 6.8 SD) suffering from job-related exhaustion according to Maslach's concept of occupational burnout (Maslach et al., 2001) were enrolled in the study. All 12 cases concluded the entire study. Three participants (25%) worked in engineering, three participants worked in personal care and service (25%) and six participants worked in the business or financial sector (50%). None of the cases suffering from job-related exhaustion received pharmacotherapy or psychotherapy during the study and all of them continued working during study participation.

2.2. Recruitment of controls

Twelve healthy controls matched for age (mean age 45.4 $\pm$ 6.2 SD), education level and working hours/week were enrolled in the study (see Table 1). At the time of data collection, all participants were working and none received pharmacotherapy or psychotherapy, also none performed regular aerobic exercise in the last two years. All subjects