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Healthy working school teachers with high effort–reward-imbalance and overcommitment show increased pro-inflammatory immune activity and a dampened innate immune defence

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ABSTRACT

To test whether chronic work stress is accompanied by altered immune functioning, changes in lymphocyte subsets and in lymphocyte production of cytokines were examined in reaction to acute psychosocial stress. Work stress was measured according to Siegrist's effort–reward-imbalance (ERI) model. ERI reflects stress due to a lack of reciprocity between costs and gains at work. Overcommitment (OC) is conceptualized as a dysfunctional coping pattern mainly characterized by the inability to withdraw from work obligations. Fifty-five healthy teachers (34 women, 21 men, mean age 50.0 ± 8.47 years) were exposed to a standardized laboratory stressor (Trier Social Stress Test). Lymphocyte subset counts and lymphocyte production of tumor-necrosis-factor (TNF)-α, interferon (IFN)-γ, interleukin (IL)-2, -4, -6 and -10 were measured before and after challenge. High levels of ERI and OC were associated with lower natural killer (NK) cell (CD16+/56+) numbers whereas high levels of OC were related to a lower increase in T-helper cells (CD4+) after stress. Furthermore, subjects with higher ERI showed an overall increased pro-inflammatory activity, with higher TNF-α production at both time points and elevated pre-stress IL-6 production. IL-10 production decreased with higher ERI after stress. The ratios of TNF-α/IL-10 and IL-6/IL-10 were significantly increased in subjects high on ERI. Finally, OC was associated with higher IL-2 production post-stress. The present findings suggest a dampened innate immune defence, reflected in lower NK cell numbers together with an increased pro-inflammatory activity in teachers high on ERI and OC. Such pathways could partly be responsible for the increased vulnerability for stress-related diseases in individuals suffering from chronic work stress.

1. Introduction

Long-term exposure to harmful job conditions can be a major determinant of disability and increased susceptibility for stress-related diseases. A work stress model which provides a conceptual framework for possible associations between adverse psychosocial workplace characteristics and long-term negative health outcomes is the effort–reward-imbalance (ERI) model as suggested by Siegrist and co-workers. A lack of reciprocity between personal costs (effort) and personal gains (reward) at the workplace is assumed to elicit stress, which in the long run may results in the development of stress-related disorders (Siegrist, 2002). Overcommitment, the intrinsic component of the ERI model, reflects a cognitive-motivational pattern of coping with demands that is characterised by an extreme ambition in combination with a special need for control and approval (van Vegchel et al., 2005). There is a growing body of both prospective as well as cross-sectional studies underscoring the predictive power of the ERI model in respect to a variety of health outcomes, such as cardiovascular disease (CVD), type 2 diabetes, depression, alcohol dependence, sleep disturbances and chronic fatigue syndrome (CFS) (Dragano et al., 2008; Head et al., 2004; Kivimäki et al., 2002; Kudielka et al., 2004; Kumari et al., 2004; Tsutsumi et al., 2001; Wada et al., 2008). Overcommitment has similarly been associated with musculoskeletal pain (Joksimovic et al., 2002), CVD incidence (Bosma et al., 1998; Kivimäki et al., 2002), cardiovascular risk factors (Vrijkotte et al., 1999), depression (Dragano et al., 2008), CFS (Wada et al., 2008) as well as neuroendocrine stress reactivity (Wirtz et al., 2008). To date, however, the physiological mechanisms potentially involved in these associations are still underexplored. Thus, the aim of the present study was to investigate the immune response to acute stress in healthy subjects with potentially high levels of chronic work stress in order to explore whether alterations in immune regulation after an acute stressor could

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provide explanations for the observed links between ill-health and the ERI/OC model before actual disease manifestation.

It is well established that the acute stress response prepares the organism for 'fight or flight' and one can speculate that this preparation also entails the activation of the immune system to respond to challenges such as wounding and infection that (in evolutionary terms) are likely outcomes of the stressor. Thus, the rapid recruitment of leukocytes into sites of surgery, wounding, infection, or vaccination is essential for an effective immune defence network and numbers and proportions of leukocytes in the blood can be interpreted as a proxy measure of the state of activation of the immune system. As numerous studies have shown significant changes in absolute numbers and relative proportions of leukocytes in the blood in reaction to acute stress (for a review see Dhabhar, 2009), in a first step we were interested whether a state of chronic work stress potentially modulates acute stress-induced alterations in lymphocyte subset counts. Secondly, we investigated lymphocyte production of cytokines before and after stress with respect to effort–reward-imbalance and overcommitment. Chronic stress has been reported to alter the pattern of cytokines that are secreted in response to an antigen. A shift from T-helper 1 (Th1) cytokines to T-helper 2 (Th2) was observed under conditions of chronic stress (Elenkov, 2004; Glaser and Kiecolt-Glaser, 2005). In contrast, patients with acute coronary syndromes and stable coronary artery disease show a shift towards Th1 dominance (Szodoray et al., 2006). Thus, as ERI as well as OC aim to capture a state of chronic stress, high levels could be associated with a shift towards humoral immunity. One the other hand as ERI/OC have been shown to predict cardiovascular disease, one could also hypothesize that high levels are related a shift towards cellular immunity.

Generally, one can assume that especially an increase in inflammatory markers contributes to the increased risk for CVD and depressive symptomatology in individuals with high levels of chronic work stress. A state of chronic low-grade systemic inflammation, characterized by an increase in circulating levels of pro-inflammatory cytokines and acute phase reactants, such as tumor-necrosis-factor (TNF)-α, interleukin (IL)-6 and C-reactive protein (CRP), on the one hand and by a decrease in levels of anti-inflammatory cytokines (such as IL-4 or IL-10) on the other, crucially contributes to the development of atherosclerosis (Kilic et al., 2006). Elevated plasma levels of TNF-α and IL-6, as well as decreased circulating IL-10 levels have been associated with an increased risk of future myocardial infarction independent of other risk factors (Ridker et al., 2000a,b; Seljeflot et al., 2004). Systemic inflammation is furthermore significantly increased in clinical depression (Miller et al., 2002) and elevated levels of the pro-inflammatory cytokine TNF-α have been shown to be higher in healthy female employees with high levels of burnout (Grossi et al., 2003). In the first part of the Trier Teacher Stress Study, we reported that high levels of ERI were related to higher Allostatic Load (AL) in a sample of healthy female teachers (Bellingrath et al., 2009). This relationship between high ERI and increased AL might be a first hint towards an association between increased inflammatory activity and chronic work stress, as circulating levels of TNF-α and CRP were part of our extended AL sum score. In the present study, we aimed to further explore this association. Thus, we were not only interested in immune measures at one given (basal) time point. Instead, here we assessed immune regulation before and after confrontation with an acute psychosocial laboratory stressor, the Trier Social Stress Test (TSST), based on the assumption that differences in stress vulnerability might be more pronounced under acute challenge conditions.

Furthermore, to model the dynamics of inflammatory signalling pathways also under conditions of immune challenge, we here quantified the expression of pro- as well as anti-inflammatory cytokines after stimulation with the mitogen phytohemagglutinin (PHA). To the best of our knowledge, there is yet no study available that analyzed whether the ERI/OC model is associated with changes in lymphocyte subsets and lymphocyte production of pro- and anti-inflammatory cytokines in response to acute standardized psychosocial stress. Teachers have been chosen since the teaching profession has been repeatedly described as a potentially stressful occupation (Guglielmi and Tatrow, 1998), as reflected in alarmingly high rates of early retirement among German school teachers, mainly due to psychosomatic complaints, muscle and skeletal problems and cardiovascular disease (Weber et al., 2001).

2. Methods

2.1. Participants and general experimental outline

Sixty-two currently employed school teachers from the region of Trier (Germany) and Luxembourg (Luxembourg) consented to participate in this laboratory stress study. Eligibility, demographics, the current health status and health behaviour (e.g., smoking status, medication intake) were assessed in a telephone interview. Exclusion criteria were psychiatric disorders, diabetes, pregnancy, and corticosteroid or psychotropic medication. The study protocol was approved by the ethics committee of the University of Trier as well as the Rheinland–Pfalz State Medical Association. Written informed consent was provided by all participants. Participants received €70 after completion of the study protocol.

2.2. Experimental protocol

Participants reported to the laboratory in the afternoon between 15:00 and 16:00 h, where an intravenous catheter was inserted in the antecubital vein of the dominant arm and the pre-stress blood sample was obtained. After a rest period of 50 min following catheter insertion, the subject was informed about the nature of the stress protocol and immediately exposed to the Trier Social Stress Test (TSST) (Kirschbaum et al., 1993), which consists of a free speech and a mental arithmetic task performed in front of a panel and a camera (for recent reviews and a detailed description see Kudielka et al., 2007a,b). The panel members were graduate students well trained for this task and the panel always comprised one female and one male member. Blood samples for the assessment of ACTH and plasma cortisol were collected in EDTA containing monovettes (Sarstedt, Nümbrecht, Germany) 1 min before as well as 1, 10, 20, 30, and 90 min after cessation of the TSST. In parallel, subjects obtained native saliva in 2 ml reaction tubes (Sarstedt, Nümbrecht, Germany) for later assessment of salivary free cortisol. Additional saliva samples were obtained at 45 and 60 min after cessation of the TSST. Premenopausal women not taking oral contraceptives were invited during the luteal phase of the menstrual cycle. The menstrual phase was estimated on the basis of the first day of the last menses and the subject's usual cycle length. Only women with a regular cycle between 28 and 35 days were included and the luteal phase was defined as the last 14 days of the cycle. Participants were instructed to refrain from physical exercise, a heavy lunch, and alcoholic beverages on test days.

2.3. Immune assays

Peripheral blood was collected into EDTA tubes (Sarstedt, Nümbrecht, Germany) 45 min before as well as 1 min after cessation of the TSST. Total numbers of leukocytes were determined by a cell counter in each sample (Coulter AcT diff™, Krefeld, Germany). To determine lymphocyte surface antigens, 5×10^6 leukocytes (approximately 100 μl whole blood) were incubated with monoclonal murine antibodies and isotype control antibodies that had been