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Stressful life events predict one-year change of leukocyte composition in peripheral blood

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ABSTRACT

A plethora of cross-sectional studies suggest that psychological stress resulting from experiencing stressful life events (SLE) can result in an altered immune response. Potential maladaptive immune changes may outlast the event and affect the organism long after stress cessation. As a consequence, an increased vulnerability for immune-mediated pathologies (e.g. arthritis, diabetes) may develop over the life span. The objective of the present study was to monitor the longitudinal kinetics of peripheral white blood cells (WBCs; neutrophils, lymphocytes, and monocytes) in response to SLE. Here we present blood, hair, and behavioural measures obtained in the Dresden Burnout Study, at first visit (T1; N = 446) and one year later (T2; N = 173). Cumulative impact of SLE was assessed at T1 with the Life Stressor Checklist (LSC-R). Results indicate a significant increase in neutrophils (+2.8% per each 10 LSC-R points) between T1 and T2 in association with reported SLE. The change in neutrophils tended to correlate with the change in hair cortisol (Coheńs f = 0.6).

We propose that SLE trigger immunological alterations that persist across time and thereby promote a continuous effect on WBC distribution. Such an effect might advance subclinical inflammatory processes, reduce an individualś immune defence, and promote a link between psychological stress and physical disease.

1. Introduction

More than 65% of all individuals worldwide experience at least one traumatic event during their life-time (Benjet et al., 2016). Trauma experience can be based on stressful life events (SLE) like an unexpected death of a loved one, criminal offenses including robbery and rape, experience of life-threatening illnesses, or traffic accidents (Benjet et al., 2016). SLE can happen to everybody at any time and it seems plausible that these experiences may affect an individual long after stress cessation. Exposure to a SLE furthermore increases the risk for subsequent adverse life experiences (Benjet et al., 2016), for example by the cause of secondary stressors (e.g. poverty as a consequence of property loss caused by a natural disaster; Lock et al., 2012). It has been shown that experiencing a stressful life event augments the risk for adverse mental health consequences (Beards et al., 2013; Cattaneo et al., 2015; Danese et al., 2008; Kendler et al., 1999; Kraan et al., 2015; Tennant, 2002). Besides the challenge of an individual's mental health, exposure to SLE might also contribute to the variation in physical health (Glaser and Kiecolt-Glaser, 2005). Even if the underlying pathways of a link between SLE and health/disease are not fully understood, epidemiological research consistently suggests associations between SLE and negative health outcomes, e.g. arthritis (Keyes et al., 2013), heart disease, diabetes (Scott et al., 2013) and inflammatory disorders like asthma and atopic dermatitis (Kilpeläinen et al., 2002). Oilman and Siegel (1996) demonstrated in a sample of 3132 adults that the risk for chronic physical malfunctioning increased 3-fold, if the person reported at least one life-time stressful event. Likewise, SLE have been discussed as one major factor that accounts for inequalities in the human population according to disease, illness, and mortality, comparable with socioeconomic status (Pearlin et al., 2005). The relevance of SLE for adverse mental and physical health outcomes is further underlined by the observation of an cumulative increase of disease with the number of SLE a person experienced (Scott et al., 2013; Turner and Lloyd, 1995). Thus, there is suggestive evidence that (cumulative) life stress can leave physical 'scars' that render an individual more vulnerable to a variety of adverse health conditions over the life span.

2. Psychophysiological background

The immunosuppression theory represents one theoretical framework to explain the above outlined associations between SLE and adverse health outcomes. The underlying assumption is that sustained

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stress heightens the risk for adverse health outcomes by suppressing the immune response, leaving the host vulnerable for disease pathogenesis (Miller et al., 2002). A potential pathway for immunosuppression as a consequence of SLE can be explained by the glucocorticoid-resistance (GCR) model (Cohen et al., 2012; Cole, 2008; Miller et al., 2002; Miller et al., 2005; Pariante, 2017). The GCR model is based on the premise that chronic stress diminishes the immune systems sensitivity to glucocorticoid (GC) hormones that normally terminate the inflammatory cascade. An initial exposure to high GC levels leads to a counter-regulatory mechanism at level of white blood cells (WBCs), that down-regulate expression and/or function of GC-binding receptors. As a consequence, GCs lose their place of activity and CG-regulated dampening of inflammation might be impaired (Miller et al., 2002).

Evidence for the GCR model is provided by many animal and human studies, underpinning that the hypothalamic pituitary adrenal (HPA) axis and thus the availability of the GC cortisol can be influenced by negative events and emotions (review: Miller et al., 2007). Likewise, life stress probably contributes to the peripheral distribution of WBCs, resulting for instance in a decline in lymphocyte proliferation (review: Segerstrom and Miller, 2004). Several authors have speculated that GC and immune alterations due to stress exposure outlast the event and become irreversible at a certain level of stress severity and duration, for example by linking adverse childhood experience to health consequences in later life (reviews: Baumeister et al., 2015; Coelho et al., 2014). SLE are indicative of psychological distress that is generally neither transient nor persistent in a classic sense. Exposure to SLE can affect a personś life in a way that goes far beyond the event, e.g. by rumination about the negative event (Garnefski et al., 2001) or grief and reorganization of live and self (Gillies and Neimeyer, 2006). Therefore, individuals who experienced a SLE might suffer from a steady, chronic stress load following the event even after stress cessation.

2.1. HPA axis alterations and immune defence

HPA axis and immune system are bidirectionally interwoven, representing two constantly interacting systems. GC receptors are expressed on most immune cells (Cain and Cidlowski, 2017) and GCs have the potential to suppress inflammation by switching off multiple inflammatory genes that code for cytokines, chemokines, adhesion molecules, inflammatory enzymes, or receptors (Barnes and Adcock, 2009). They modulate immune-enhancing as well as immune-suppressive effects (Cain and Cidlowski, 2017; Franchimont et al., 2002; Sapolsky et al., 2000) at the level of the innate/adaptive immune response (Franchimont et al., 2002). Furthermore, monokines and cytokines including IL-1, IL-6, or TNF stimulate the hypothalamus leading to HPA axis activation and an increased availability of cortisol (Cain and Cidlowski, 2017).

GCs can curb leukocyte migration by the production of several chemokines and chemoattractants and by direct GC receptor binding to chemokine-encoding mRNA transcripts. They can further influence peripheral blood flow and leukocyte cell death (Cain and Cidlowski, 2017), which might affect the total number of circulating WBCs. The susceptibility of WBCs to GCs was shown by Dhabhar et al. (2012), by exposing rodents to a 120 min restraint stressor. Neutrophils for example showed a 45% increase during the first 6 min of stress exposure and a 75% increase after 120 min stress exposure. Contrarily, lymphocytes reached a peak of 26% increase after 6 min stress, following by a subsequent decline. After 120 min of restrained stress, lymphocytes showed a 45% decrease. Monocytes did not alter significantly during stress exposure. Hormone injection with GCs resulted in a significant decrease of monocyte and lymphocyte numbers that was not observed in neutrophils. Further rodent data on cumulative stress were reported by Engler et al. (2004). They showed that repeated social defeat (using the social disruption (SDR) paradigm; Avitsur et al. (2001) altered neutrophil and monocyte distribution in bone marrow, peripheral blood, and spleen in male mice. The increase in total number of circulating neutrophils and monocytes in peripheral blood became more pronounced the more SDR cycles a mouse was exposed to. After six cycles over 6 consecutive days, circulating neutrophil numbers increased 5-fold compared with controls, monocytes by a factor of two, suggesting that cumulative stress exposure enlarges the stress-regulated immune adaption.

The total number of WBCs and their subsets (neutrophils, lymphocytes, monocytes) from peripheral blood, represent a basic parameter to detect activation of the immune system and inflammation (Vozarova et al., 2002). Even if normal ranges are quite large, a correct proportion of immune cell types can indicate a proper immune defence (Segerstrom and Miller, 2004). Maladaptive WBC alterations are associated with several adverse health conditions, like diabetes (Vozarova et al., 2002), stroke (Christensen and Boysen, 2004), or death after a myocardial infarction (Horne et al., 2005). It may be speculated that GC-driven alterations in the peripheral distribution of WBCs are at the basis of an increased vulnerability to disease.

2.2. Research agenda

In line with the above explained GCR model we hypothesize, that the cumulative SLE a person faces during his or her life promotes maladaptive immune defence that could further lead to a higher vulnerability for several adverse inflammatory and health conditions. We expect GC-mediated alterations in WBCs to be one major source for higher disease vulnerability in individuals that are affected by SLE.

Based on a large cohort study of stressed individuals, we examined WBCs (neutrophils, lymphocytes, and monocytes) at first visit (T1) and 1-year follow-up (T2) in association with cumulative SLE experience. GCs were measured as hair cortisol concentrations (HCC) at both time points, which serve as a marker for cumulative 3-month cortisol secretion. Considering that inflammation has reciprocal effects on lymphopoiesis and granulopoiesis in the bone morrow (Ueda et al., 2005; Ueda et al., 2004), we additionally considered the neutrophil/lymphocyte ratio in our analyses. Our theoretical research model is summarized in Fig. 1.

3. Material and methods

3.1. Study population

The current study included participants from the ongoing prospective Dresden Burnout Study (DBS; Penz et al., in press) that was conducted in accordance with the Declaration of Helsinki and therefore approved by the local ethics committee. DBS participants had been recruited Germany-wide through public media platforms and the civil register of the city Dresden. Inclusion criterion was restricted to working age (between 18 and 68 years) and language (sufficient language skills to fill out German questionnaires). All DBS participants with residence Dresden and within a 60 km radius around the city were invited for the assessment of biological markers. The DBS was conducted with emphasis on the city and region Dresden, which contributed approx. one third of the whole sample. 1864 participants were invited for the first visit of biomarker sampling that was conducted from September to October 2015, out of that 446 accepted our invitation. 2795 participants were invited for the second visit (857 recruited by the Dresden civil register) resulting in data from 507 participants at visit two. The second study wave was conducted from October to November 2016 and from January to February 2017. Altogether 173 participants attended both, study visit one (T1) and study visit two (T2; first follow up), which represents the current longitudinal study sample. Due to unsuccessful blood sampling at T1 and/or T2, longitudinal WBC data were available from 154 participants (mean ± SD age at T1: 42.16 ± 11.74; 67.5% female). Detailed sample characteristics for T1 and T2 are summarized in Table 1. All participants received a monetary