Brain, Behavior, and Immunity xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Acute psychosocial stress induces differential short-term changes in catecholamine sensitivity of stimulated inflammatory cytokine production

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ARTICLE INFO

Article history:
Received 10 January 2014
Received in revised form 24 July 2014
Accepted 25 July 2014
Available online xxxx

Keywords:
Acute psychosocial stress
Inflammation
Cytokines
Cortisol
Catecholamines
Sympathetic nervous system
Catecholamine sensitivity

ABSTRACT

Background: We have previously shown that psychosocial stress induces acute changes in glucocorticoid (GC) sensitivity of pro-inflammatory cytokine production. However, hormones of the sympathetic adrenal medullary system complement endocrine regulation of inflammatory responses. The current study therefore aimed at investigating the effects of repeated acute stress exposure on catecholamine sensitivity of inflammatory cytokine production.

Methods: Twenty healthy male participants were subjected to the Trier Social Stress Test on two consecutive days. Blood samples were taken before and repeatedly after stress. Whole blood was stimulated with lipopolysaccharide and incubated with increasing concentrations of epinephrine (E) and norepinephrine (NE) for 18 h. Tumor-necrosis-factor (TNF) alpha and interleukin (IL)-6 were measured in culture supernatants.

Results: Overall, incubation with E and NE induced dose-dependent suppression of TNF-alpha (NE: $F = 77.66$, $p < .001$; E: $F = 63.38$, $p < .001$), and IL-6 production (NE: $F = 28.79$, $p < .001$; E: $F = 24.66$, $p < .001$). Acute stress exposure resulted in reduced sensitivity of TNF-alpha (NE: $F = 6.36$, $p < .001$; E: $F = 4.86$, $p = .005$), but not IL-6 (NE: $F = 1.07$, $p = .38$; E: $F = 0.88$, $p = .50$) to the inhibitory signals of E and NE. No evidence of habituation of these effects was found (all $p \geqslant .22$).

Conclusions: The present findings extend our knowledge on changes in inflammatory target tissue sensitivity in response to acute psychosocial stress from glucocorticoid-dependent effects to catecholamine-dependent effects. Stress-induced decreases in catecholamine sensitivity thereby suggest intracellular processes aiding in maintaining a healthy endocrine–immune interplay. Longitudinal studies will have to investigate the processes leading from a supposedly beneficial short-term catecholamine resistance in response to acute stress to basal catecholamine resistance observed in relation to negative health outcomes.

1. Introduction

Systemic inflammation has been identified as one of the major pathophysiological mechanisms underlying life-threatening human diseases such as coronary heart disease and stroke (e.g., Danesh et al., 2000; Hansson, 2005; Pradhan et al., 2001; Ridker et al., 1998). Importantly, inflammation can be activated not only by infectious but also by non-immunological environmental, behavioral, and psychological stimuli. In this context, inflammation is emerging as an important pathway linking stress experience with human health (e.g., Miller and Blackwell, 2006). More specifically, it has been shown that chronic psychosocial stress is prospectively associated with increased concentrations of inflammatory biomarkers in human blood, such as interleukin-6 (IL-6; Kiecolt-Glaser et al., 2003), C-reactive protein (CRP; Rohleder et al., 2009), and expression of pro-inflammatory genes (Cole et al., 2007; Miller et al., 2008).

Biological candidates for mediating these increases are the two major stress axes and their respective end products: the hypothalamus–pituitary–adrenal (Besharat et al., 2011) axis with its glucocorticoid (GC) hormone cortisol, and the sympathetic nervous system (SNS) with its end hormones epinephrine and norepinephrine (Elenkov et al., 2000; Sapolsky et al., 2000).

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http://dx.doi.org/10.1016/j.bbi.2014.07.014
0889-1591/

The effects of the HPA axis hormone cortisol have been characterized as mainly anti-inflammatory, and down-regulation of inflammatory mechanisms by GCs have been well-described (McKay and Cidlowski, 1999). However, although mainly anti-inflammatory, GCs' effects on the immune system are known to vary depending on the specific immune process as well as by timing and dose of GC exposure (e.g. short-term vs. long-term effects on cell trafficking, Dhabhar et al., 2012). Contrary, effects of the SNS on inflammation have been described as being both pro- and anti-inflammatory, with several factors determining the directionality of the effect. For instance, catecholamine signaling has been found to up-regulate DNA-binding activity of the main inflammatory transcription factor NF-kappaB (NF-kB; Bierhaus et al., 2003; Wolf et al., 2009). In accordance with this mechanism, infusion of isoproterenol, a beta-adrenergic agonist, as well as exposure to acute psychosocial stress induces short-term increases in IL-6 (Mohamed-Ali et al., 2001; Steptoe et al., 2007). On the other hand, catecholamines have also been found to act as anti-inflammatory agents, by suppressing, for example, mitogen-stimulated production of inflammatory cytokines in cell culture (see Elenkov et al., 2000 for a review). These divergent effects can partly be explained by taking into account catecholamine concentration and time of incubation, as well as by considering the state of the respective cell or tissue: an already activated inflammatory cascade appears to be suppressed by adrenergic signaling, while in non-activated immune cells, adrenergic signals appear to be able to activate the inflammatory cascade (Elenkov et al., 2000; Sapolsky et al., 2000). Taken together, these findings suggest well-orchestrated stress hormone effects on the immune system. More specifically, while the SNS can activate inflammatory responses in cells not exposed to infectious antigens, the HPA axis as well as SNS signaling occurring during ongoing inflammatory processes can act to suppress these inflammatory responses originally initiated by the SNS.

In light of these mechanisms, it could be hypothesized that chronic stress-induced increases in circulating inflammatory mediators (Kiecolt-Glaser et al., 2003; Rohleder et al., 2009) are the result of changes in stress system activity, particularly a lack of proper stress hormone responses, permitting disinhibition of inflammatory signaling pathways. However, dysregulated stress systems alone do not sufficiently explain disease susceptibility. For example, in a longitudinal study on cancer caregivers, we found increases in CRP over time in caregivers, but no changes in basal HPA axis activity. We did, however, observe a gradual decrease in GC sensitivity of stimulated inflammatory cytokine production (Rohleder et al., 2009). Thus it appears that chronic stress induced increases in inflammation cannot be completely understood without taking into account the ability of the target tissue to react to a given stress hormone signal. Indeed, diminished GC sensitivity has been found in response to acute psychosocial stress (Miller et al., 2005; Rohleder et al., 2003a), and in response to exercise (DeRijk et al., 1996). Furthermore, altered GC sensitivity has been found in chronic stress (Jeckel et al., 2010; Miller et al., 2002; Murphy et al., 2013; Wirtz et al., 2003; but see also Bellingrath et al., 2013) and in posttraumatic stress disorder (PTSD; Rohleder et al., 2004). As such, assessment of GC sensitivity in these conditions has contributed to a better understanding of the relationships between psychosocial stress, stress system changes, and potential health outcomes (Raison and Miller, 2003; Rohleder et al., 2009).

However, measuring GC sensitivity addresses only one of the major stress systems presumably involved in regulating inflammation, and can thus only provide a partial understanding of target tissue responses to stress hormones. Few studies have assessed the ability of inflammatory cells to respond to catecholamine signals in healthy subjects. This limited evidence suggests a dose-dependent suppression of cytokines in LPS-stimulated cell cultures (Mohamed-Ali et al., 2001; van der Poll et al., 1994). In human chronic stress studies, patients with autoimmune or inflammatory diseases were found to show a relative catecholamine resistance under basal conditions (Kavelaars et al., 2000; Langhorst et al., 2007; Lopes et al., 2012; Lucas et al., 2007; Pawlak et al., 1999) and in chronically stressed caregivers, a relative beta2-adrenoceptor resistance was observed (Mausbach et al., 2008). Little is known, however, about acute responses of catecholamine sensitivity to psychosocial stress. Indirect evidence stems from a study showing increased beta2-adrenoceptor expression in response to psychosocial stress in healthy individuals (Pawlak et al., 1999). Thus, the main goal of the current study was to assess whether acute stress induces alterations of *in vitro* sensitivity of inflammatory cytokine production to the effects of catecholamines epinephrine and norepinephrine. Since habituation to repeated stress has been suggested to be an adaptive mechanism (McEwen, 1998) and has been shown for glucocorticoid stress responses but not for catecholamine stress responses (Kirschbaum et al., 1995; Schommer et al., 2003), we further set out to examine the stability of catecholamine sensitivity responses to repeated psychosocial stress.

2. Methods

2.1. Participants

Twenty healthy male participants were recruited through advertisements in local newspapers. Eligibility, demographics, current health status and health behaviors (e.g. smoking status, medication) were assessed in a telephone screening. Exclusion criteria were acute or chronic medical or psychiatric diseases, body mass index (BMI) below 20 and above 25 kg/m^2, as well as corticosteroid, adrenergic, or psychotropic medication, and chronic tobacco or alcohol consumption. The study protocol was approved by the local institutional review board, and written informed consent was provided by all participants.

2.2. Experimental procedure

Eligible participants were scheduled for two laboratory visits in the afternoons of two consecutive weekdays. Experimental procedures where similar on both study days: After arrival in the laboratory, an intravenous catheter was inserted into an antecubital vein of the non-dominant arm, followed by a resting period of 45 min. After the resting period, a baseline blood and saliva sample was taken. Immediately afterwards, participants were 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 an evaluative two-person panel and a video camera. Further blood samples were taken 10 min and 45 min after cessation of the TSST, resulting in a total of three blood sample collection time-points. To track neuroendocrine response trajectories, additional saliva samples were obtained immediately after, as well as 10, 20, and 45 min after the TSST (total of five saliva samples). Participants were instructed to refrain from physical exercise, heavy lunch, and alcoholic beverages on both test days.

2.3. Psychometric assessment

2.3.1. Perceived chronic stress

Participants completed the 10-item Perceived Stress Scale (PSS) to assess self-reported perceived chronic stress (Cohen et al., 1983). Responses were given on a Likert rating scale ranging from 'never' to 'very often' (0–4). An example item is: "In the last month,

Please cite this article in press as: Strahler, J., et al. Acute psychosocial stress induces differential short-term changes in catecholamine sensitivity of stimulated inflammatory cytokine production. Brain Behav. Immun. (2014), http://dx.doi.org/10.1016/j.bbi.2014.07.014