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Glucocorticoid mediated regulation of inflammation in human monocytes is associated with depressive mood and obesity

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ABSTRACT

Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis is observed in various conditions, including depression and obesity, which are also often related. Glucocorticoid (GC) resistance and desensitization of peripheral GC receptors (GRs) are often the case in HPA dysregulation seen in depression, and GC plays a critical role in regulation of inflammation. Given the growing evidence that inflammation is a central feature of some depression cases and obesity, we aimed to investigate the immune-regulatory role of GC–GR in relation to depressive mood and obesity in 35 healthy men and women. Depressive mood and level of obesity were assessed, using Beck Depression Inventory (BDI-Ia) and body mass index (BMI), respectively. We measured plasma cortisol levels via enzyme-linked immunosorbent assay and lipopolysaccharide-stimulated intracellular tumor necrosis factor (TNF) production by monocytes, using flow cytometry. Cortisol sensitivity was determined by the difference in monocytic TNF production between the conditions of 1 and 0 μM cortisol incubation ("cortisol-mediated inflammation regulation, CoMIR"). GR vs. mineralocorticoid receptor (MR) antagonism for CoMIR was examined by using mifepristone and spironolactone. A series of multiple regression analyses were performed to investigate independent contribution of depressive mood vs. obesity after controlling for age, gender, systolic blood pressure (SBP), and plasma cortisol in predicting CoMIR. CoMIR was explained by somatic subcomponents of depressive mood (BDI-S: $\beta = -0.499$, $p = 0.001$), or BMI ($\beta = -0.466$, $p < 0.01$) in separate models. The effects of BMI disappeared when BDI-S was controlled for in the model, while BDI-S remained a significant independent predictor for CoMIR ($\beta = -0.369$, $p < 0.05$). However, BMI remained the only independent predictor when BDI-T or BDI-C were controlled for in the model. Mediation analyses also revealed that the relationship between BMI and CoMIR was mediated by BDI-S. The exploratory findings of the relative GR vs. MR roles in CoMIR, using GR and MR blockers, indicated that CoMIR in our cellular model was predominantly mediated by GRs at the higher cortisol dose (1 μM). There was initial indication that greater obesity and somatic depressive symptoms were associated with smaller efficacy of the blockers, which warrants further investigation. Our findings, although in a preclinical sample, signify the shared pathophysiology of immune dysregulation in depression and obesity and warrant further mechanistic investigation.

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1. Introduction

The link between depression and inflammation has been shown via numerous reports of increased levels of various inflammatory markers among depressed patients (Dowlati et al., 2010), including elevated circulating cytokines interleukin (IL)-6 (Alesci et al., 2005), C-reactive protein (Ford and Erlinger, 2004), and tumor necrosis factor (TNF). Increased inflammatory cytokines appear to induce clinically significant depressive symptoms, as seen in longitudinal studies that report elevated CRP and IL-6 levels with future depressive symptom development (Valkanova et al., 2013) and in interferon treatment studies among hepatitis (Udina et al., 2012) and melanoma patients (Musselman et al., 2001). The depression-inflammation association appears to be bi-directional, as studies also report a temporal relationship of depression to future inflammatory cytokine levels (Copeland et al., 2012). Notably, the inflammation-related depression is evident only in a subset of depressed patients (Glassman and Miller, 2007; Kiecolt-Glaser et al., 2015; Raison and Miller, 2011).

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Although pathogenesis of the depression-inflammation link remains to be further elucidated, a likely primary pathway is the hypothalamic–pituitary–adrenal (HPA) axis through immunomodulatory actions of glucocorticoids (GCs) (Popova et al., 2011; Varga et al., 2014). Increased levels of cortisol, corticotropin releasing hormone, and the size and activity of pituitary and adrenal glands are often, although not always, found in major depression (Pace and Miller, 2009; Stetler and Miller, 2011; Zunszain et al., 2011). Elevation of cortisol levels in depression is indicative of HPA dysregulation, as many patients with depression exhibit impaired negative feedback of cortisol production by dexamethasone administration (Zunszain et al., 2011), likely attributed to down-regulation or desensitization of glucocorticoid receptors (GRs) (Carvalho and Pariante, 2008; Mokhtari et al., 2013). Phosphorylation of GRs in peripheral blood mononuclear cells (PBMCs) differs between depressed patients and healthy individuals such that GRs of depressed individuals exhibit decreased transcriptional activity and nuclear translocation (Simic et al., 2013). In addition, impaired or reduced GR function co-exists with increased circulating and upregulation of inflammatory markers in patients with depression (Carvalho et al., 2014; Nikkheslat et al., 2015). In examining development of depression, a large longitudinal study also found that decreased GC response by monocytes and T-cells of soldiers before deployment predicted development of greater depressive symptoms after returning (van Zuiden et al., 2015). Given the well-documented immunomodulatory role of GCs, GR functions in inflammatory cytokine regulation may be of clinical significance in mood disorders and other conditions that present with HPA dysregulation and hypercortisolism such as chronic stress (Rohleder et al., 2010).

GC sensitivity is also impaired in obesity, supported by similar data to depression such as blunted dexamethasone suppression in obese children (Longui et al., 2003) or decreased GC feedback sensitivity in obese men (Mattsson et al., 2009). Glucocorticoid elevation is associated with higher abdominal obesity, impaired glucose tolerance, and blood lipid levels (Bose et al., 2009; Schäfer et al., 2013; Wallerius et al., 2003). Chronic exposure to cortisol is associated with accumulation of visceral fat, though systemic cortisol elevation is not required for obesity to occur (Chapman et al., 2013b). Furthermore, increased expression of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD-1), which converts inert cortisone to active cortisol, facilitates weight gain in mice models of diet-induced obesity (Kershaw et al., 2005; Lee et al., 2014; Liu et al., 2008). Thus, impaired GR function is likely a shared mechanism for elevated inflammation in depression and obesity. Elevated11β-HSD-1 activity is hypothesized to influence inflammation in obesity (Chapman et al., 2013a), potentially through decreased feedback inhibition that would normally suppress inflammatory processes. BMI was associated with lower GC sensitivity assessed by lipopolysaccharide (LPS)-stimulated TNF release with dexamethasone treatment in response to a laboratory psychological stressor (Wirtz et al., 2008). Therefore, impaired responsivity of GRs to GC may be the critical factor that drives chronic low-grade inflammation in obesity (McInnis et al., 2014).

Co-morbidity of depression and obesity is found in a high percent of affected individuals, and bi-directional temporal predictability between depression and obesity is evident (Carey et al., 2014; Luppino et al., 2010; Onyike et al., 2003). Furthermore, obesity is related to sustained depressive symptoms even among the individuals without clinical depression (Heo et al., 2006; van der Merwe, 2007). In spite of the accumulating evidence for the association between GC/GR-mediated inflammation regulation and depression or obesity separately, there are limited existing data to clarify cellular mechanisms that underlie the co-condition of obesity and subclinical depressive mood. Thus, we hypothesized that regulation of inflammation mediated by GC/GR is a pathophysiology that underlies the link between depressive symptoms and obesity even among individuals without clinical depression. We investigated the level of cortisol-mediated suppression of TNF production among healthy individuals with a wide range of depressive mood and obesity states. A previously established ex vivo model of LPS-stimulated intracellular expression of TNF by peripheral blood monocytes (Dimitrov et al., 2013; Hong et al., 2014) was adapted to examine responsivity of monocytes to cortisol in inhibition of TNF production. By using a whole blood set-up and cortisol doses representing physiological levels, we aimed to create an ex vivo cellular system that closely resembled an in vivo environment. In addition, given the cortisol action on both GRs and mineralocorticoid receptors (MRs), pharmacological antagonists were used to differentiate cortisol effects on each receptor type in the context of TNF production, which has not been examined in previous studies.

2. Materials and methods

2.1. Participants

35 otherwise healthy participants with normal to mildly elevated blood pressure (BP) from an ongoing parent prehypertension study at University of California San Diego (UCSD) participated in this investigation. All participants gave written informed consent and were compensated for time and travel. The protocol for recruitment and human subject treatment was approved by the UCSD Institutional Review Board.

Initial screening of participants via telephone interviews followed by face-to-face confirmation determined the absence of several exclusion criteria: diabetes, current or recent history (past 6 months) of smoking or substance abuse, history of cardiovascular disease (e.g., symptomatic coronary or cerebral vascular disease, arrhythmia, myocardial infarction, cardiomyopathy, heart failure), history of bronchospastic pulmonary disease, inflammatory disorder or health conditions affecting immune function (e.g., recent vaccinations within 10 days of the study visit, active and current infections/illness, use of immunomodulatory medication, uncontrolled thyroid disease), psychosis, clinical depression, and clinical hypertension indicated by current intake of antihypertensive medication or laboratory-assessed BP >145/90 mmHg, with an exception of one participant (152/76 mmHg) whose BP values fluctuated greatly.

2.2. Procedures

Average basal BPs and heart rates (HR) were calculated from two sets of three consecutive measurements at 5-min intervals, using a Dinamap Compact BP® monitor (Critikon, Tempa, FL). Each BP and HR measurement took less than a minute on average, and the two sets were separated by 40 to 60 min. To assess levels of obesity, standard anthropometrics (i.e., height, weight, waist and hip circumference) were collected via conventional tape ruler and scale. Subsequently, Body Mass Index (BMI) was calculated by the formula: BMI = weight in kg/(height in m)^2. Depressive mood was measured via the Beck Depression Inventory (BDI-Ia), a comprehensive and clinically robust self-report 21-item questionnaire (Beck et al., 1996). Each question was scored from 0–3, summed to a BDI total score (BDI-T) that was also subcategorized into cognitive (BDI-C) and somatic (BDI-S) depressive mood scores.

Blood samples were obtained between 8am and 10am for all participants after 12 h of fasting via an antecubital vein and collected in vacutainers (BD, Franklin Lakes, NJ), containing either heparin or ethylenediaminetetraacetic acid (EDTA) as an anticoagulant. Cellular assay was performed on whole blood aliquots from heparin vacutainer within one hour of collection, and EDTA-treated