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Measures of adiposity predict interleukin-6 responses to repeated psychosocial stress

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ABSTRACT

Objective: Overweight and obese individuals, who comprise approximately two-thirds of the U.S. population, are at increased risk for developing a range of diseases. This increased risk may be due in part to maladaptive stress responses within this group, including heightened low-grade inflammation and HPA axis non-habituation. In this study we tested the relationship between adiposity, plasma interleukin-6 (IL-6) and HPA axis responses to repeated stress.

Methods: Sixty-seven healthy participants were exposed to the Trier Social Stress Test (TSST) on two consecutive days. We collected saliva for cortisol measurements at baseline and at 1, 10, 30, 60 and 120 min post-TSST, and blood for plasma IL-6 measurements at baseline and 30 and 120 min post-TSST.

Results: Stress exposure induced significant increases of cortisol and IL-6 on both days (cortisol: $F = 38$, $p < 0.001$; IL-6: $F = 90.8$; $p < 0.001$), and repeated exposure was related with cortisol habituation ($F = 8.2$; $p < 0.001$) and IL-6 sensitization ($F = 5.2$; $p = 0.022$). BMI and body fat were related with higher cortisol responses to repeated stress (BMI: beta = 0.34; $p = 0.014$; body fat: beta = 0.29; $p = 0.045$), and with higher IL-6 responses to repeated stress (BMI: beta = 0.27, $p = 0.044$; body fat: beta = 0.37; $p = 0.006$).

Conclusions: Taken together, individuals with higher measures of adiposity showed less efficient HPA axis habituation as well as sensitization of IL-6 responses to repeated acute stress. These findings point to maladaptive stress response patterns in overweight humans, which, through exposure to higher levels of inflammatory mediators, might partially explain diseases related with overweight and/or obesity.

1. Introduction

Approximately two thirds of Americans are overweight or obese, and worldwide obesity has almost doubled since 1980 (WHO, 2013). Obesity is a major risk factor for many conditions including hyperlipidemia, hypertension, heart disease, stroke and Type II Diabetes (Lapidus et al., 1984; Kissebah and Krakower, 1994; Grundy, 2002; Lavie et al., 2009). Adipose tissue is recognized as an endocrine organ capable of regulating metabolic function as well as secreting signaling molecules and cytokines (Trayhurn, 2005). Chronic low-grade inflammation is a hallmark of obesity, and the dysregulated inflammation seen in obesity contributes to the pathology of a number of co-morbid conditions, including atherosclerosis, type 2 diabetes and fatty liver disease (Danesh et al., 1998; Danesh, 1999; Black and Garbutt, 2002). In addition, obesity-related inflammation is emerging as a mechanism for increased cancer risk (Roberts et al., 2010).

While there is strong evidence supporting the association of obesity with basal levels of inflammation (Rexrode et al., 2003; Panagiotakos et al., 2005; Himmerich et al., 2006; Thorand et al., 2006; Brydon, 2011), very little is known about how obesity affects psychosocial stress-induced increases of IL-6 concentrations. Among normal weight individuals, acute psychosocial stress induces an increase in plasma inflammatory molecules such as IL-6 (Steptoe et al., 2007), which does not typically habituate to repeated stress. Therefore, recurrent psychosocial stressors result in repeated exposure to increased IL-6 (von Kanel et al., 2006; Rohleder, 2014). Due to its relatively slow response and recovery, and its failure to habituate to repeated stressors, it has been suggested that low-grade peripheral inflammation up-regulated by psychosocial stress exposes individuals to sustained higher

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concentrations of inflammatory mediators over time, which in turn may increase disease risk (Rohleder, 2014). This risk might be even more exaggerated in overweight and obese individuals because of the relationship between adipose tissue and inflammation, as well as increased basal IL-6 levels seen in overweight and obese individuals (Rexrode et al., 2003; Panagiotakos et al., 2005; Himmerich et al., 2006; Thorand et al., 2006; Brydon, 2011). One study examined the effect of central adiposity on response to a single mild psychological stressor in young women and found that while waist circumference was related to baseline IL-6, there was no relationship between adiposity and IL-6 response to stressor (Brydon, 2011). However, this study was done in a sample limited to young women, with a mild psychological stressor administered only once. It is possible that differences in stress responses due to adiposity emerge with a more robust stressor administered repeatedly.

In addition to its relationship with chronic inflammation, there is evidence that obesity modulates the glucocorticoid response to stress, although the literature is inconsistent with regard to the directionality of associations. Obesity has been found to be associated with elevated baseline cortisol secretion and higher HPA-axis reactivity to psychological stress as well as physiological and pharmacological stimulation (Bjorntorp, 1993). In line with these earlier findings, greater cortisol responses to stress have recently been noted in overweight women compared to leaner women (Benson et al., 2009). However, Jones et al. (2012) using a novel, magnetic resonance (MR) imaging-based method of body fat quantification found lower cortisol stress responses in individuals with adiposity (Jones et al., 2012). Only one study has addressed HPA axis habituation to repeated stress. Individuals with a high Waist-to-Hip Ratio (WHR), indicative of increased central adiposity, showed less efficient cortisol habituation in response to repeated stress compared to lean individuals with a low WHR (Epel et al., 2000). Taken together, the relationships of measures of adiposity with cortisol responses to psychosocial stressors are documented in a limited number of studies and findings are inconsistent.

To our knowledge, there have been no studies reporting the effect of repeated psychosocial stress on low-grade inflammation in overweight individuals. In the present study we therefore aimed to examine whether measures of adiposity, including Body Mass Index (BMI), body fat percentage, waist circumference and waist to hip ratio, were associated with altered IL-6 and cortisol responses to repeated stress. We hypothesized that greater adiposity will be associated with increased IL-6 responses as well as altered cortisol responses, including less habituation to repeated stress. We also expected to replicate previous findings of higher baseline IL-6 and cortisol in overweight individuals.

2. Methods

2.1. Participants

Data were collected as part of a larger research project conducted over 2 years to investigate the effects of stress on endocrine and inflammatory parameters. Young adults (age 18–35 years) and older adults (age 50–65 years) were recruited from the Greater Boston area and the Brandeis University campus via newspaper, magazine, and Facebook advertisements. All participants underwent a brief medical and psychological screening by telephone before testing and were invited to participate only if they met the following selection criteria: (a) body mass index (BMI) within the reference range between 18 and 35 kg/m^2; (b) luteal phase of menstrual cycle at time of participation, for females; (c) absence of psychiatric, endocrine, or cardiovascular diseases, or other specific chronic diseases; (d) no intake of psychoactive drugs, beta-blockers, gonadal steroids (hormonal contraceptives), GCs; (e) non-smoker, and (f) no previous experience with the stress protocol. Individuals were paid for their participation.

We recruited $n = 72$ individuals for participation in this study. Five participants were excluded from IL-6 analyses because their IL-6 baseline or responses were greater than 2.5 standard deviations above the mean. In addition, one participant discontinued after the first session, and two participants displayed signs of infection during session two, and therefore only their biological data from session one was used. This left a final sample of $n = 67$ for day 1 IL-6 and $n = 64$ for day 2 IL-6 analyses. $N = 6$ participants included in the IL-6 analysis were excluded from cortisol analyses because they did not have cortisol data. $N = 9$ participants were excluded because their baseline cortisol was over 15 nmol/l. This left a final sample of $n = 56$ participants for day 1 and 2 cortisol analyses. Two participants were missing body fat percentage data.

2.2. Procedure

Eligible participants were scheduled for laboratory sessions on two consecutive days. All laboratory sessions were scheduled in the afternoon (13:30–18:30 h) to control for circadian variation of cortisol, and participants came in at the same time for both sessions. Participants were instructed to refrain from eating or drinking anything but water for 1 h before the laboratory sessions. Written informed consent was obtained prior to participation. The Brandeis University Institutional Review Board approved all procedures.

Each laboratory session lasted approximately 3 h and included a 30-min resting period followed by exposure to the Trier Social Stress Test (TSST; Kirschbaum et al., 1993) Saliva samples for measurement of free cortisol were collected using Salivette collection devices (Sarstedt, Newton, NC) at baseline, as well as 1, 10, 30, 60 and 120 min post TSST on both study days. Details on the saliva collection procedure are included below.

For assessment of IL-6 concentrations, blood was drawn via the antecubital vein using a peripheral venous catheter (BD Nexiva IV catheter, Becton–Dickinson, Franklin Lakes, NJ) and collected in Vacutainers (Becton–Dickinson, Franklin Lakes, NJ), containing EDTA. Initial placement of the catheter was followed by a resting period of 30 min to ensure recovery from potential stress response to catheter placement or traveling to the laboratory. Because previous research has found that IL-6 peaks 120 min post-stressor (von Kanel et al., 2006; Breines et al., 2014; Rohleder, 2014), blood was drawn at baseline, 30, and 120 min following the TSST on both study days.

2.2.1. Stress induction paradigm

Acute psychosocial stress was induced using the Trier Social Stress Test (TSST, (Kirschbaum et al., 1993)), a widely used standardized laboratory stress paradigm. The TSST used in the present study consisted of a three-minute preparation period, a five-minute public speech, and a five-minute mental arithmetic task in front of an audience of two judges wearing lab coats and maintaining a neutral evaluative facial expression. The public speech involved describing how one's personality makes one qualified for a dream job and the mental arithmetic ask involved counting backwards from 2043 by deduction of 17 on the first study day and from 2011 by 13 on the second study day. Participants were informed that the judges were trained in analyzing verbal and non-verbal behavior and that their performance would be videotaped. The TSST has demonstrated reliability and validity and has been shown to produce strong biological responses to stress (Dickerson and Kemeny, 2004).