Psychoneuroendocrinology (2008) 33, 1102—1110

available at www.sciencedirect.com

ScienceDirect

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

Higher body mass index (BMI) is associated with reduced glucocorticoid inhibition of inflammatory cytokine production following acute psychosocial stress in men

Petra H. Wirtz [a,*], Ulrike Ehlert [a], Luljeta Emini [a], Tobias Suter [b]

[a] *Department of Clinical Psychology and Psychotherapy, University of Zurich, Switzerland*
[b] *Clinical Immunology, Department of Internal Medicine, University Hospital, Zurich, Switzerland*

Received 11 January 2008; received in revised form 21 April 2008; accepted 23 May 2008

KEYWORDS
BMI;
Atherosclerosis;
Stress;
Glucocorticoid sensitivity;
TNF-α

Summary
Background: Body mass index (BMI) and mental stress seem to exert part of their cardiovascular risk by eliciting inflammation. However, the adverse effects of stress on inflammatory activity with BMI are not fully understood. We investigated whether higher BMI is associated with reduced glucocorticoid inhibition of inflammatory cytokine production following stress in men while controlling for age and blood pressure. We measured glucorticoid inhibition of lipopolysaccharide (LPS)-stimulated release of the proinflammatory cytokine tumor necrosis factor (TNF)-α.
Methods: Forty-two men (age range 21—65 years; BMI range 21—34 kg/m^2) underwent the Trier Social Stress Test (combination of mock job interview and mental arithmetic task). Whole blood samples were taken immediately before and after stress, and during recovery up to 60 min post-stress. Glucocorticoid sensitivity of LPS-stimulated TNF-α expression was assessed in vitro with and without coincubating increasing doses of dexamethasone. Moreover, salivary cortisol was measured during the experiment and on a normal day for assessment of baseline circadian cortisol.
Results: Higher BMI was associated with lower glucocorticoid sensitivity of monocyte TNF-α production after stress (main effect of BMI: $p < 0.001$) and with more pronounced decreases of glucocorticoid sensitivity following stress (interaction of stress-by-BMI: $p = 0.002$). Neither LPS-stimulated TNF-α release nor baseline glucocorticoid sensitivity were associated with BMI. Similarly, BMI was not associated with salivary cortisol, either in reaction to stress or in circadian cortisol secretion.
Conclusions: Our data suggest that with increasing BMI, glucocorticoids are less able to inhibit TNF-α production following stress. This might suggest a new mechanism linking BMI with elevated risk for adverse cardiovascular outcomes following stress.

* Corresponding author. Department of Clinical Psychology and Psychotherapy, University of Zurich, Binzmühlestrasse 14/Box 26, CH-8050 Zurich, Switzerland. Tel.: +41 44 635 7367; fax: +41 44 635 7359.
E-mail address: p.wirtz@psychologie.uzh.ch (P.H. Wirtz).

0306-4530/$ — see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.psyneuen.2008.05.002

1. Introduction

The risk of cardiovascular disease and the underlying process of atherosclerosis increases with increasing body mass index (BMI) (Jee et al., 2006). Particularly obesity, the severe form of overweight, is a main independent risk factor for atherosclerosis and heart failure (Kenchaiah et al., 2002).

Atherogenesis is an inflammatory process occurring in the vessel wall (Ross, 1999). Monocytes infiltrate the vessel, produce cytokines and chemokines and thereby attract more leukocytes and propagate the inflammation (Ross, 1999). There is evidence that elevated inflammatory activity with increasing BMI plays an important role in linking higher BMI with increased incidence of atherosclerosis: animal and human studies suggest that obesity and obesity-related parameters like BMI are associated with elevated levels of inflammatory cardiovascular risk markers including monocyte-derived inflammatory cytokines like tumor necrosis factor (TNF)-α (Yamakawa et al., 1995; Visser et al., 1999; Ridker et al., 2000; Elkind et al., 2002; Laimer et al., 2002; Bray, 2004; Pai et al., 2004; Pickup, 2004; Vendrell et al., 2004; Gonzalez et al., 2006). Indeed, a very recent study found elevated inflammatory activity in obese men with acute myocardial infarction (Piestrzeniewicz et al., 2007). The mechanisms that link higher BMI with the presence of a low-grade systemic inflammation and thereby with atherosclerotic risk are beginning to be understood. In addition to genetic predispositions (Esteve et al., 2006), human adipose tissue seems to be involved in up-regulation of inflammation as it expresses and releases proinflammatory cytokines (Hotamisligil et al., 1995; Creely et al., 2007).

An additional mechanism involved in the association between BMI and inflammation might be related to mental stress, a further risk factor for cardiovascular disease and particularly for acute coronary syndromes (ACS) (Hemingway and Marmot, 1999; Strike and Steptoe, 2004; Strike and Steptoe, 2005; Bhattacharyya and Steptoe, 2007). A recent review by Steptoe and co-workers suggests that acute mental stress induces increases in circulating inflammatory factors within less than 2 h (Steptoe et al., 2007). Such increased inflammatory activity might in turn be involved in mediation of ACS risk following acute stress especially in at-risk persons (Gidron et al., 2002; Steptoe et al., 2006; Bhattacharyya and Steptoe, 2007; Steptoe et al., 2007). Indeed, elevated cytokine and CRP levels were found in patients with preinfarction unstable angina within 3 h of symptom onset (Liuzzo et al., 1999).

However, mental stress also induces activation of the hypothalamus-pituitary-adrenal (HPA) axis, leading to glucocorticoid (GC) secretion which, especially in high doses, effectively down-regulates inflammatory activity (Sapolsky et al., 2000). The effects of endogenously released GCs on target tissues strongly depend on the sensitivity of these tissues to GCs (Rohleder et al., 2003). Several studies demonstrated that the GC sensitivity of pro-inflammatory cytokine production is dynamically regulated by psychosocial stress (Rohleder, 2003; Rohleder et al., 2003). Therefore, a potential GC down-regulation of an elevated inflammatory status following psychosocial stress (e.g. following an acute emotional ACS trigger) depends not only on the endogenous GC level but also on stress-induced changes in the sensitivity of inflammatory target tissues to GCs.

Whereas most studies found basal cortisol secretion and cortisol circadian rhythm to be usually normal even in obese persons, some studies report higher cortisol excretion in abdominally obese individuals (Pasquali et al., 2006). Thus, basal HPA activity and cortisol release are not strongly positively related to BMI, if at all. However, the secretion of cortisol after experimental stress induction is elevated with increasing obesity (Epel et al., 1999; Pasquali et al., 2006). Therefore, one would rather expect similar or even lower inflammatory activity with increasing BMI. However, to the best of our knowledge, associations between BMI and stress-induced changes in the ability of GCs to down-regulate inflammatory activity have not yet been studied.

We therefore wondered whether, with increasing BMI within the normal to mildly overweight range, the inflammatory status would be altered following acute stress through modulation of the GC-induced suppression of the monocyte proinflammatory response (i.e. monocyte GC sensitivity). Such an alteration might provide a new biological mechanism linking BMI with elevated levels of inflammatory markers and thereby with elevated risk of ACS following stress. We assessed the GC sensitivity of lipopolysaccharide (LPS)-induced TNF-α production in whole blood samples of men with a BMI ranging broadly from 21 to 34 kg/m^2. Study participants underwent a standardized psychosocial stress test (Trier Social Stress Test, TSST) (Kirschbaum et al., 1993) and we measured GC sensitivity of monocyte TNF-α production at different time points before and after the stressor. We decided to measure TNF-α because it plays a crucial role in the initial activation of inflammatory changes such as stimulation of C-reactive protein production by the liver thought to sustain atherosclerosis development (Plutzky, 2001). Moreover, it contributes to the entry of inflammatory cells into the arterial wall by induction of adhesion molecule expression (Pober and Cotran, 1991; Plutzky, 2001) and it mediates T-cell activation as well as foam cell formation (Ross, 1993; Ross, 1999). To obtain a single measure to assess GC sensitivity, we determined the amount of dexamethasone required to suppress the LPS-stimulated release of TNF-α by 50%. We additionally measured salivary cortisol before and several times after stress to assess the amount of stress-induced GC secretion, as well as a circadian cortisol profile.

2. Materials and methods

2.1. Study participants

The study was part of a larger project (Wirtz et al., 2006; Wirtz et al., 2007a; Wirtz et al., 2007b). We obtained complete GC sensitivity data from 42 men who provided written informed consent and fulfilled the inclusion criteria outlined below. Study participants varied in age (range 21–65 years), screening systolic (range 108–167 mmHg) and diastolic (range 66–114 mmHg) blood pressure (BP), and BMI (range 21–34 kg/m^2). Recruitment was carried out through advertisement at the University of Zurich, and with the help of the Swiss Red Cross of the State of Zurich. The Ethics Committee of the State of Zurich, Switzerland formally approved the study protocol.

All participants were required not to take any regular or occasional medication, to be non-smokers, and to be in excellent physical and mental health as confirmed by an