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Effects of obesity on neuroendocrine, cardiovascular, and immune cell responses to acute psychosocial stress in premenopausal women

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Summary
Objective: To analyze the neuroendocrine and immune cell responses to acute psychosocial stress in obese compared to non-obese premenopausal women.
Methods: $N = 15$ obese (BMI ≥ 30) and $N = 24$ (BMI < 30) non-obese premenopausal women underwent public speaking stress. State anxiety, ACTH, cortisol, and the redistribution of immune cells were measured before, during, and 10 and 45 min after public speaking. Serum hsCRP and serum IL-6 levels were analyzed before, and IL-6 additionally 45 min after stress.
Results: In response to public speaking stress, both groups showed significant but comparable increases in state anxiety, plasma ACTH, and blood pressure (all $p < 0.01$; time effects). The cortisol stress response was significantly enhanced in obese women ($p < 0.05$; interaction effect). In addition, heart rate and diastolic blood pressure were significantly higher in obese women 10 min following stress ($p < 0.05$, *t*-tests). Public speaking stress led to a significant increase in IL-6 concentrations ($p < 0.001$; time effect), and obese women displayed higher IL-6 levels both pre- and post-stress ($p < 0.05$; group effect; between-group *t*-tests: pre-stress $p < 0.05$; post-stress $p < 0.01$). Baseline numbers of circulating leukocytes, granulocytes, $CD3^+$ cells and hsCRP concentration were significantly higher in obese women (between-group *t*-tests: all $p < 0.05$, but the groups did not differ in the stress-induced redistribution of circulating leukocyte subpopulations.

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Conclusions: Our data reveal a strong association of obesity with chronic low-grade inflammation in premenopausal women. This pro-inflammatory state, together with altered neuroendocrine and cardiovascular stress responsiveness, may conceivably constitute one of the mechanisms linking psychological stress and the long-term health risks associated with obesity.

1. Introduction

The incidence of obesity is rapidly increasing in industrialized nations, including the United States (Ogden et al., 2006) and Western Europe (Fry and Finley, 2005). In Germany, approximately 70% of adult males and 50% of females are overweight or obese (Mensink et al., 2005). As in other countries (Ogden et al., 2006), the prevalence of obesity in children and adolescents is dramatically increasing (Zellner et al., 2007), by inference, the health risks associated with obesity will be increasingly relevant for a growing number of relatively young individuals, including premenopausal women. The health implications of obesity are both numerous and serious, and include medical as well as psychosocial problems. Amongst the most significant medical consequences are cardiovascular diseases (CAD) and type 2 diabetes (T2DM), with markedly increased morbidity and mortality (Manson et al., 1995; Tilg and Moschen, 2006; Flegal et al., 2007). The mediators include endocrine and metabolic alterations (e.g., insulin resistance, dyslipidemia, hypertension), as well as immune system changes. It is increasingly recognized that obesity-related alterations in cytokine profiles and activation of the innate immune system contribute to a pro-inflammatory state, i.e., chronic low-grade inflammation (Tilg and Moschen, 2006). Indeed, prospective studies revealed an association between inflammatory mediators, including C-reactive protein (CRP), interleukin-6 (IL-6) or leukocytes, and the risk for cardiovascular diseases and T2DM (Pradhan et al., 2001; Fernandez-Real and Ricart, 2003).

Obesity is also associated with psychosocial problems, including reduced health-related quality-of-life, depression, and chronic stress (Stunkard et al., 2003; Bray, 2004; Petry et al., 2008;), which are relevant for several reasons. First, psychological factors likely contribute to the development, progression, and maintenance of fat accumulation (Rosmond, 2005; Pasquali et al., 2006a,b). Second, psychological factors including depression and stress appear to constitute risk factors for cardiovascular morbidity and mortality as well as for T2DM, particularly in the presence of other risk factors and/or pre-existing morbidity (Rozanski et al., 1999; Black, 2006). Long-term stress was also found to be associated with increased risk for incident coronary heart disease (Player et al., 2007), although controversial results have also been reported (Lahiri et al., 2007). Finally, increased levels of the stress hormone cortisol markedly increased the probability of coronary stenosis, particularly in combination with high levels of vital exhaustion (Koertge et al., 2002).

The mechanisms by which psychological stress contributes to obesity and obesity-related pathophysiology remain incompletely understood, but likely involve several pathways, including stress effects on mediators of the hypothalamic–pituitary–adrenal (HPA)-axis, such as cortisol (Bjoerntorp, 2001), and of the immune system, such as cytokines (Black, 2003; Von Känel et al., 2005). With the exception of two studies (Epel et al., 2000; Brydon et al., 2008), little data exists thus far addressing possible effects of obesity on neuroendocrine and immune cell responses to acute psychological stress in premenopausal women. Therefore, we recruited obese premenopausal women and analyzed the neuroendocrine and immune cell responses to acute psychosocial stress compared to non-obese controls. We specifically aimed to address the hypotheses that obese women would show (1) greater HPA-axis activation in response to stress and (2) evidence of basal immune alterations and an enhanced pro-inflammatory stress response.

2. Methods

2.1. Recruitment, screening and characterization of study participants

Healthy, premenopausal women between 18 and 40 years of age and either a BMI $\geq 30\,kg/m^2$ (obese group) or a BMI $< 30\,kg/m^2$ (non-obese control group) were recruited through public advertisement in a local newspaper and the surrounding community. We chose to stratify based on BMI given the BMI-based definition of obesity (Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, 1998). Exclusion criteria for all subjects included any medical condition, including endocrine, cardiovascular, neurological, and immunological conditions. Previous psychiatric or psychological diagnoses, use of psychiatric medications including antidepressants, or a Beck Depression Inventory (BDI) score ≥ 18 (Hautzinger et al., 1995) were exclusionary to avoid confounding of the results since psychiatric conditions, including depression, are known to affect basal endocrine and immune functions (Miller et al., 2002; Tichomirowa et al., 2005), as well as the stress response (Pace et al., 2006). To exclude endocrine conditions, including thyroid disorders and conditions involving androgen disturbances such as the polycystic ovary syndrome, testosterone, SHBG, LH, FSH, estradiol, and prolactin were analyzed and women were assessed for signs of hyperandrogenism such as hirsutism. Only subjects who were not using hormonal contraceptives and reported normal menstrual cycles were included. Hysterectomy or other known conditions which would affect reproductive hormones and/or the menstrual cycle were also exclusionary. Participants were scheduled on days 1–10 of their menstrual cycle. The study protocol was approved by the Ethics Committee of the University of Duisburg-Essen. All subjects gave written informed consent before entering the study and were paid for their participation. Notably, the study public speaking stress protocol (see below) was not fully disclosed. Participants were only told they would be asked to complete a cognitive task requiring focused attention, speed, and concentration.