



## Adiposity, leptin and stress reactivity in humans

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### ABSTRACT

Evidence suggests that individuals who are more obese may be more responsive to stress. Stress activates the sympathetic nervous system (SNS) and the adipose-tissue cytokine leptin stimulates SNS activity in animals. We examined the relationship between adiposity, leptin and physiological responses to acute laboratory stress in 67 women. We predicted that individuals with greater adiposity and/or higher plasma leptin would be more stress-responsive. Adiposity was unrelated to cardiovascular or neuroendocrine stress reactivity. However, women with larger waists had greater stress-induced increases in plasma leptin and interleukin-1 receptor antagonist (IL-1Ra). Similarly, women with higher basal leptin displayed greater stress-induced increases in heart rate and plasma interleukin-6, and larger decreases in heart rate variability and cardiac pre-ejection period. Heightened cardiovascular and inflammatory stress responses are predictive of future cardiovascular risk. Our findings suggest that the cytokines leptin and IL-1Ra may play a role in the association between obesity, stress and cardiovascular health.

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### 1. Introduction

The prevalence of obesity has risen sharply in recent years, reaching epidemic proportions world-wide. According to latest figures from the World Health Organisation approximately 1.6 billion adults are currently overweight (body mass index, BMI  $\geq 25 \text{ kg m}^{-2}$ ), and at least 400 million are clinically obese (BMI  $\geq 30 \text{ kg m}^{-2}$ ). These figures are estimated to reach an alarming 2.3 billion and >700 million by 2015 (WHO Global InfoBase, 2006). Obesity is a major risk factor for several chronic conditions including hypertension, cardiovascular disease (CVD), type 2 diabetes, and certain types of cancer and as such poses a major challenge to public health care (Lavie et al., 2009). Understanding the biological mechanisms linking obesity and health is therefore of fundamental importance.

Psychological stress is associated with an increased risk of hypertension and CVD and evidence emerging in the past decade suggests that individuals who are more obese may be more responsive to stress. Two of the principle pathways activated by stress are the hypothalamic–pituitary–adrenal axis, leading to elevations in circulating glucocorticoids and the sympathetic nervous system (SNS), resulting in increases in blood pressure, heart rate and circulating catecholamines (Black, 2006). Studies have shown that women with a larger waist circumference or waist–hip ratio have heightened cortisol responses to acute laboratory stress, as well as impaired dexamethasone suppression of cortisol (Epel et al., 2000;

Pasquali et al., 2002). Similarly, central obesity has been associated with elevated or prolonged cardiovascular responses to acute stress in some but not all studies (Steptoe and Wardle, 2005; Goldbacher et al., 2005; Carroll et al., 2008; Davis et al., 1999; Waldstein et al., 1999; Barnes et al., 1998), and a recent report found larger cortisol and cardiovascular responses to public speaking stress in obese versus non-obese women (Benson et al., 2009).

The biological mechanisms linking obesity and stress reactivity are poorly understood. Adipose tissue is now recognised as a major endocrine organ that secretes signalling molecules playing a central role in inflammation, weight regulation and metabolic function including cytokines (Trayhurn, 2005). Circulating levels of the hormone-like cytokine leptin are markedly elevated in obese humans and animals and correlate with adiposity measures in non-obese healthy individuals (Considine et al., 1996; Trayhurn and Bing, 2006). Leptin is secreted into the blood stream in proportion to adipose tissue mass, and binds to receptors on specific hypothalamic nuclei to regulate energy balance by reducing appetite and stimulating SNS activity (Trayhurn and Bing, 2006). In rodents, acute systemic or central leptin infusion increases sympathetic nerve activity (SNA) to thermogenic tissues such as brown adipose tissue (BAT) as well as non-thermogenic organs including kidneys and adrenal glands (Ren, 2004). Similarly, chronic leptin infusion increases heart rate, arterial blood pressure and circulating catecholamines, and these effects are inhibited by  $\alpha_1$  and  $\beta_1/\beta_2$  adrenergic antagonists (Ren, 2004; da Silva et al., 2006). The relationship between leptin and SNS activity in humans is less clear. Elevated plasma leptin levels have been reported in patients with hypertension, compared to normotensive individuals (Thomopoulos et al., 2009). Similarly, cross-sectional studies have

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found positive associations between circulating leptin and sympathetic activity indexed by blood pressure, heart rate and heart rate variability in obese and lean normotensive humans (Bravo et al., 2006; Flanagan et al., 2007; Ma et al., 2009), and a recent prospective analyses of 489 normotensive men showed that individuals with high serum leptin levels had a 33% increased risk of developing hypertension over 8 years, independent of BMI (Galletti et al., 2008). Nevertheless, most intervention studies have found no effect of either acute or chronic leptin infusion on SNS activity in humans (Hukshorn et al., 2003; Brook et al., 2007; Mackintosh and Hirsch, 2001; Chan et al., 2007). It is conceivable that the sympatho-activating effects of leptin in humans may be more apparent under conditions of heightened SNS activation induced by factors such as psychological stress.

We set out to investigate the relationship between adiposity, leptin and physiological responses to acute psychological stress in a sample of healthy young women. We predicted that women with greater adiposity would have heightened or prolonged cardiovascular, neuroendocrine and inflammatory responses to stress. We also predicted that leptin would potentiate sympathetic cardiovascular reactivity to stress, so that women with higher basal plasma leptin levels would have larger cardiovascular stress responses.

## 2. Methods

### 2.1. Sample

Sixty-nine female student volunteers were recruited from University College London. Participants were aged between 18 and 25 years, and were screened by structured interview to ensure that they were healthy, not taking any medication and had no previous history of any relevant physical or mental illness. They were instructed not to take antibiotics, ibuprofen or aspirin for 10 days prior to the study and to avoid caffeine, alcohol and excessive exercise during the 12 h prior to testing. On the day of the study, participants were advised to eat a low fat breakfast and were provided with a standardised low fat lunch consisting of vegetable couscous, fruit salad and fresh orange juice. Two participants were excluded from the final analyses since one was extremely obese (BMI 43.3) and another was greatly underweight (BMI 15.6). The study was approved by the joint University College London/University College London Hospital Committee on the Ethics of Human Research and all participants gave their informed consent. We chose to study a healthy population with a wide range of adiposity levels rather than specifically comparing obese versus non-obese individuals, since obese individuals are more likely to have co-morbid conditions such as diabetes or hypertension that may have influenced our measures.

### 2.2. Anthropometric measures

Anthropometric measures were taken by a research nurse at the beginning of the session. Height was measured to the nearest 0.1 cm using the Frankfort plane to standardise the measurement. Body weight was measured to the nearest 0.1 kg. Body mass index (BMI) was calculated as body weight in kilograms divided by height in metres squared. Waist circumference was measured midway between the lowest rib and ileac crest. Body fat mass was estimated using a Bodystat 1500 bioelectrical impedance body composition analyses device (Bodystat, Douglas, Isle of Man). Fat percentage was calculated as fat weight divided by total (fat + lean) body weight.

### 2.3. Autonomic and neuroendocrine measures

Cardiovascular data for the study were collected continuously and then averaged over specified 5 min trials. Blood pressure was monitored from the finger using a Portapres 2, a portable version of the Finapres device (TNO-TPD Biomedical Instrumentation, Amsterdam, The Netherlands). Heart rate and heart rate variability (HRV) were assessed by impedance cardiography (ICG; VU-AMS, Amsterdam, The Netherlands) as described previously (Willemsen et al., 1996). HRV was calculated as the root mean square of successive R-R interval differences (RMSSD). A reduction in RMSSD indicates a shift in cardiac sympathovagal balance towards sympathetic control over the rhythm of the heart (Malik, 1996). Cardiac pre-ejection period (PEP) was measured as an index of cardiac sympathetic drive (Sherwood et al., 1990). One minute ensemble averages were derived for the ICG for each minute of tasks and averaged. PEP was defined as the interval between R-wave and B-point plus a fixed Q-R interval of 48 ms. Cortisol was measured in saliva samples obtained throughout the session. Saliva was collected using Salivettes (Sarstedt, Inc. Leicester, UK) and stored at  $-80^{\circ}\text{C}$  prior to analyses. Salivary cortisol was analyzed using a commercially available time-resolved immunoassay with chemiluminescence detection (CLIA; IBL-Hamburg, Hamburg, Germany), at the Technical University of Dresden,

Germany. This assay had a detection limit of 0.16 ng/ml and intra- and inter-assay coefficients of variation of <10 and <12% respectively.

### 2.4. Immune measures

For assessment of circulating cytokines, blood samples (10 ml) were drawn using a 21-gauge butterfly needle into Vacutainer tubes containing EDTA as an anti-coagulant, then centrifuged immediately at  $1250 \times g$  for 10 min at room temperature. The plasma layer was removed, aliquoted and stored at  $-80^{\circ}\text{C}$  until analyses. Plasma IL-6 levels were measured using a high-sensitivity two-site enzyme-linked immunosorbent assay (ELISA) from R & D Systems (Oxford, UK). This assay had a detection limit of 0.09 pg/ml with intra- and inter-assay coefficients of variation (CVs) of 5.3 and 9.2% respectively. Plasma IL-1Ra concentrations were measured using a commercial ELISA from R & D Systems, with a detection limit of 15 pg/ml and intra- and inter-assay CVs of <10%. Plasma leptin levels were assessed using a commercial ELISA from Ray Biotech at Insight Biotechnology Ltd. (Middlesex, UK). This assay had a detection limit of 6 pg/ml and intra- and inter-assay CVs of <10% and <12% respectively. Plasma samples were diluted 1:200 prior to leptin analyses.

### 2.5. Behavioural tasks

Mental stress was induced by two 5-min behavioural tasks, administered under time pressure. The first was a computerized Stroop task, involving the successive presentation of target color words (e.g. red) printed in a different color (e.g. green). The task was to press a computer key that corresponded to the position at the bottom of the screen of the name of the color in which the target word was printed. The second task was presented after an interval of 5 min and involved simulated public speaking. Participants were presented with a hypothetical scenario in which they had been wrongly accused of shoplifting, and were instructed to give a speech in their defense by addressing the camera directly in front of them. They were told that their speech would be video recorded and later judged for efficacy and fluency. The experimenter remained in the room with the participant during each of the tasks, and instructed them when to start and stop.

### 2.6. Laboratory procedure

All sessions were run in the afternoon in a light and temperature-controlled laboratory, and participants were tested individually. They were provided with water but were not allowed to eat during testing. Anthropometric measures were obtained and the impedance cardiogram was fitted for continuous assessment of heart rate, HRV and cardiac PEP. Participants were then seated comfortably and fitted with finger cuffs so that blood pressure (BP) could be monitored using the Portapres-2. A venous cannula was inserted into the lower arm for blood sampling, and they were left to rest for 30 min. Cardiovascular measures (BP, heart rate, HRV and cardiac PEP) were recorded for the last 5 min of the baseline rest period, then a saliva sample was obtained and a baseline blood sample was drawn. At this time, participants were asked to rate their subjective feelings of stress on a 7-point Likert scale ranging from 1 = low to 7 = high. Next, the two tasks were administered in a fixed order. Five-minute recordings of cardiovascular activity were made during each of the tasks and cortisol samples and subjective stress ratings were obtained after each task. Following the tasks, a second blood sample was taken and participants rested for a further 45 min. Additional recordings of cardiovascular activity were obtained at 10–15, 25–30 and 40–45 min post-tasks, and a third blood sample was drawn at 45 min. Further measures of subjective stress and cortisol were obtained at 15, 30 and 45 min post-task.

### 2.7. Statistical analyses

First, we tested whether the tasks used in our study were indeed stressful, by assessing participants' subjective and physiological responses to these tasks using repeated measures analyses of variance (ANOVA). The repeated measures analyses of subjective stress and salivary cortisol involved six trials (baseline, post-Stroop, post-speech, 15, 30 and 45 min post-tasks). Similarly, analyses of heart rate, HRV, cardiac PEP and blood pressure involved six trials (baseline, Stroop, speech, 10–15, 25–30 and 40–45 min post-tasks), while the analyses of plasma cytokines involved three trials (baseline, immediately post-tasks and 45 min post-task). The Greenhouse-Geisser correction of degrees of freedom was applied when sphericity assumptions were violated. The distribution of plasma leptin was skewed so data were square root transformed before analyses. Heart rate variability (RMSSD) data were also skewed and were log transformed, however raw values are presented for comparability with other studies. Post hoc tests were conducted using Tukey's least significant difference (LSD) test.

We then investigated the association between adiposity measures and physiological stress responses using a multiple linear regression approach. Three aspects of physiological response were analyzed: baseline levels, stress reactivity (computed as the change in levels between baseline and stress) and stress recovery (computed as the change between baseline and 45 min post-task). Age, smoking status and ethnicity were included in all models as covariates. In regressions involving reactivity and recovery measures, baseline levels of the relevant dependent measure (HR,

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