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Research report

Associations of ghrelin with eating behaviors, stress, metabolic factors, and telomere length among overweight and obese women: Preliminary evidence of attenuated ghrelin effects in obesity?

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ABSTRACT

Ghrelin regulates homeostatic food intake, hedonic eating, and is a mediator in the stress response. In addition, ghrelin has metabolic, cardiovascular, and anti-aging effects. This cross-sectional study examined associations between total plasma ghrelin, caloric intake based on 3 day diet diaries, hedonic eating attitudes, stress-related and metabolic factors, and leukocyte telomere length in overweight (n = 25) and obese women (n = 22). We hypothesized associations between total plasma ghrelin and eating behaviors, stress, metabolic, cardiovascular, and cell aging factors among overweight women, but not among obese women due to lower circulating ghrelin levels and/or central resistance to ghrelin. Confirming previous studies demonstrating lowered plasma ghrelin in obesity, ghrelin levels were lower in the obese compared with overweight women. Among the overweight, ghrelin was positively correlated with caloric intake, giving in to cravings for highly palatable foods, and a flatter diurnal cortisol slope across 3 days. These relationships were non-significant among the obese group. Among overweight women, ghrelin was negatively correlated with insulin resistance, systolic blood pressure, and heart rate, and positively correlated with telomere length. Among the obese subjects, plasma ghrelin concentrations were negatively correlated with insulin resistance, but were not significantly correlated with blood pressure, heart rate or telomere length. Total plasma ghrelin and its associations with food intake, hedonic eating, and stress are decreased in obesity, providing evidence consistent with the theory that central resistance to ghrelin develops in obesity and ghrelin's function in appetite regulation may have evolved to prevent starvation in food scarcity rather than cope with modern food excess. Furthermore, ghrelin is associated with metabolic and cardiovascular health, and may have anti-aging effects, but these effects may be attenuated in obesity.

Introduction

Ghrelin, the only known appetite-stimulating hormone in humans, is a 28 amino acid protein produced principally in the stomach. Ghrelin and its receptor, growth hormone secretagogue receptor (GHS-R), are found extensively throughout the body, indicating widespread central and peripheral functions (Gnanapavan et al., 2002; Korbonits, Goldstone, Gueorguiev, & Grossman, 2004; Muccioli, Baragli, Granata, Papotti, & Ghigo, 2007). When energy supply is low, ghrelin is secreted from gut mucosa and acts centrally by signaling to the hypothalamic arcuate nucleus and also stimulates the vagal afferent nerves (Date & Kangawa, 2012) to increase appetite and food intake. After food ingestion, plasma levels decrease (Couce et al., 2006).

In addition to the regulation of homeostatic food intake ghrelin appears to be involved in hedonic eating, and may be necessary for the experience of food-induced reward (Diz-Chaves, 2011; King, Isaacs, O'Farrell, & Abizaid, 2011; Kirsz & Zieba, 2011; Skibicka, Hansson, Alvarez-Crespo, Friberg, & Dickson, 2011). There is evidence that ghrelin increases preference for sweet taste (Disse et al., 2010; Malik, McGlone, Bedrossian, & Dagher, 2008). Moreover, ghrelin was found to *increase*, rather than decrease, in response to palatable food intake under conditions of satiety, suggesting that ghrelin's central signaling may drive hedonic food

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consumption in the absence of caloric need (Monteleone et al., 2013).

Furthermore, accumulating evidence suggests that ghrelin signaling is important in the neurological response to stressors (Asakawa et al., 2001; Chuang et al., 2011; Raspopow, Abizaid, Matheson, & Anisman, 2010; Rouach et al., 2007) and stress increases ghrelin in humans (Harrold, Dovey, Blundell, & Halford, 2012; Lowe & Butryn, 2007). As stress induces eating and the motivation to eat comfort foods (Adam & Epel, 2007; Dallman, 2010), increased ghrelin may mediate the motivation to eat under stress.

Studies of diet-induced obese mice have demonstrated hypothalamic resistance to ghrelin, in which ghrelin no longer stimulates activation of neuropeptide Y (NPY) and agouti-related peptide (AgRP) neurons, which trigger hunger (Briggs, Enriori, Lemus, Cowley, & Andrews, 2010; Briggs et al., 2013; Finger, Dinan, & Cryan, 2012). Diet-induced obesity in mice suppresses the neuroendocrine ghrelin system by decreasing mRNA of ghrelin and the enzyme which converts ghrelin to its active acylated form (ghrelin o-acyltransferase) in the stomach, expression of GHS-R in the hypothalamus, and acylated and total plasma ghrelin (Briggs et al., 2010). In humans, plasma ghrelin levels have been found to be substantially lower among obese compared to lean adults (Druce et al., 2005; McLaughlin, Abbasi, Lamendola, Frayo, & Cummings, 2004; Ozkan et al., 2009; Tschop et al., 2001). These findings have led to the speculation that obesity may induce central ghrelin resistance in humans, and relationships between ghrelin and eating behavior observed in lean adults may not apply to obese populations (Andrews, 2011). However, little research has examined the central resistance theory in obese humans. Furthermore, it is unclear whether evidence of central ghrelin resistance would be observed in an overweight population, presumably where there is also decreased plasma ghrelin, but perhaps not as low as levels found in obese populations (Cummings, 2006; Sumithran et al., 2011; Tschop et al., 2001).

In terms of other actions of ghrelin, ghrelin has been associated with increased plasma glucose levels, decreased insulin and insulin resistance, and with lower blood pressure and heart rate (Broglio et al., 2001; Eizadi, Afsharmand, Behbudi, & Sohaily, 2011; Freeman, Carmo, Adi, & da Silva, 2013; Garcia & Korbonits, 2006; Okumura et al., 2002; Tong et al., 2010; Verhulst & Depoortere, 2012). Ghrelin may also have anti-aging effects as it reduces inflammation (Dixit et al., 2004) and regulates growth hormone secretion (Veldhuis & Keenan, 2012), which controls secretion of insulin-like growth factor-1 (IGF-1). Lower levels of IGF-1 are related to shorter telomere length, which is a marker of cell aging (Barbieri et al., 2009; Kaplan et al., 2009; Moverare-Skrtic et al., 2009), and which has been linked to diabetes risk factors (Demissie et al., 2006; Gardner et al., 2005) and earlier mortality (Blackburn, Greider, & Szostak, 2006; Cawthon, Smith, O'Brien, Sivatchenko, & Kerber, 2003; Epel et al., 2009; Fitzpatrick et al., 2011). Epidemiological studies have shown that telomere length is moderately correlated with chronological age (for a review, see Sanders & Newman, 2013). Telomere length is thought to represent biological aging of the cell in that the longer the telomere length, the greater the cell's ability to keep dividing, conversely, the shorter the telomere length, the greater the cell's replicative senescence (Blackburn, 2000). As peripherally circulating ghrelin appears to exert some beneficial metabolic, cardiovascular and anti-aging effects (Aoki et al., 2013; Garcia & Korbonits, 2006; Granado, Priego, Martin, Villanua, & Lopez-Calderon, 2005), it is possible that the lowered circulating levels found in obesity may negatively impact ghrelin's favorable physiological effects.

Indeed, there are many putative roles for ghrelin beyond homeostatic appetite control, and research is needed to describe and understand the multiplicity of ghrelin's functions and any differential functions of ghrelin among overweight and obese adults. In this preliminary cross-sectional analysis, we examined associations of ghrelin with caloric intake, hedonic eating, psychological and physiological indicators of stress, metabolic and aging-related factors among overweight and obese women. First, we hypothesized that circulating plasma ghrelin levels would be lower among obese compared to overweight women. Second, we hypothesized that ghrelin may be positively related to food intake, hedonic eating, and stress among overweight women, but that such correlations would be attenuated among obese women. We also aimed to determine whether ghrelin's previously established associations with glucose and insulin levels, blood pressure, and heart rate would be observed among the overweight and obese samples. Finally, we explored the relationship in both groups between ghrelin and leukocyte telomere length, an association that has not yet been examined in humans or animals to our knowledge.

Methods

This study is a cross-sectional, secondary analysis of baseline data collected from a randomized controlled pilot study of a mindfulness intervention to reduce stress eating (Daubenmier et al., 2011). As previously reported in the parent study, overweight and obese women were recruited from the San Francisco Bay Area community using flyers and local media. Exclusion criteria included: weight over 300 lbs, diabetes, taking medication that could affect weight loss, taking pain steroids or antipsychotic medication, post-menopausal, history of bilateral oophorectomy, total hysterectomy, polycystic ovary syndrome, active endocrine disorder, pregnancy, less than 1 year postpartum or breastfeeding, current eating disorder, alcohol addiction, drug addiction, positive urine test for diabetes and opiate use, and English illiteracy. A total of 322 women were screened, and 47 women with Body Mass Index (BMI) of 25–40 were enrolled into the study and completed 2 baseline assessments by staff at the UCSF General Clinical Research Center (GCRC) (Daubenmier et al., 2011). This study was performed at the University of California, San Francisco (UCSF) with approval from the institutional review board.

Biological measures

At the first baseline visit, a digital scale (Wheelchair Scale 6002, Scale-Tronix, Carol Stream, IL) was used to measure weight in kg to the nearest 0.10 kg and a standard stadiometer (Perspective Enterprises, Portage, Mich, USA) was used to measure height to the nearest 1/8 in. to calculate BMI. Blood pressure and heart rate were also measured (CritikonDinamap 1846SX Non Invasive Vital Signs Monitor, GE Healthcare, Milwaukee, WI). To assess blood pressure, participants rested for 5 min and three measurements were taken, each 1 min apart. The three measurements were averaged to determine systolic and diastolic blood pressure values.

At the second baseline visit, nurses confirmed with participants that they completed a 12 h fast the night before. Morning blood plasma samples were taken from an indwelling forearm catheter for total plasma ghrelin levels, insulin, glucose, and telomere length. Blood samples were drawn into tubes on ice containing ethylenediaminetetraacetic acid (EDTA), an anticoagulant, and kept on ice at all times. The tubes were centrifuged for 10 min at 3000 g at 4 °C, transferred to aliquot vials, and frozen at −70 °C until assaying.

Total plasma ghrelin was measured without an extraction step using a commercial RIA (Phoenix Peptide, Phoenix, AZ), as described previously (Cummings, Clement, et al., 2002; Cummings et al., 2001). Insulin was assayed with a radioimmunoassay kit using an I125-Iodinated insulin tracer, anti-Human Insulin Specific antibody, and human insulin standards from Linco Research, Inc.