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The association between leptin and depressive symptoms is modulated by abdominal adiposity

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Summary
Background: Evidence for a role of leptin in depression is limited and conflicting. Inconclusive findings may be explained by the complex effect of obesity on leptin signaling. In particular, both hyperleptinemia due to leptin resistance in obese persons as well as low leptin in lean persons can imply that low leptin biological signaling is associated with an increased risk of significant depressive symptoms. We tested whether the relationship between leptin and depressive symptoms is modulated by abdominal adiposity in two population-based studies.

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Methods: Data were from 851 participants (65—94 years) of the InCHIANTI Study and 1064 (26—93 years) of the Baltimore Longitudinal Study of Aging (BLSA). Plasma concentrations of leptin, waist circumference and depressive symptoms via the Center for Epidemiological Studies-Depression scale (CES-D) were assessed. In longitudinal InCHIANTI analyses onset of depressed mood (CES-D≥20) was evaluated over a 9-year follow-up.
Results: In pooled cross-sectional analyses the interaction between leptin and waist circumference was significantly associated with CES-D scores ((log)leptin-by-waist interaction $p = 0.01$). Also in longitudinal analyses, the (log)leptin-by-waist interaction term significantly ($p = 0.04$) predicted depressed mood onset over time; depressed mood risk was especially increased for high levels of both leptin and waist circumference.
Conclusions: The present findings suggest that low leptin signaling rather than low leptin concentration is a risk factor for depression. Future studies should develop proxy measures of leptin signaling by combining information on abdominal adiposity and leptin level to be used for clinical and research applications.

1. Introduction

Increasing evidence indicates that depression is associated with obesity-related (especially abdominal adiposity) metabolic alterations (Penninx et al., 2013; Xu et al., 2011). In this context a role in depression has been proposed for leptin (Lu, 2007; Zupancic and Mahajan, 2011), the peptide hormone secreted by white adipose tissue that exerts a primary homeostatic function by suppressing nutritional intake and allowing energy expenditure. Leptin receptors are expressed in limbic substrates related to mood regulation (e.g. hippocampus and amygdala), and in animal models leptin has shown to improve learning and memory and to exert antidepressant behavioral effects (Krishnan and Nestler, 2010; Paz-Filho et al., 2010).

However, preliminary small clinical studies in humans have had conflicting results, showing both increased (Antonijevic et al., 1998; Zeman et al., 2009; Rubin et al., 2002) and decreased (Jow et al., 2006; Kraus et al., 2001; Atmaca et al., 2008; Lawson et al., 2012) leptin levels in depressed patients, whereas another study showed no association (Deuschle et al., 1996). These conflicting findings may be explained by the complexity of leptin response as a function of obesity, which is often associated with high levels of leptin. The failure of high levels of leptin to suppress food intake and decrease body weight/adiposity in obese persons is thought to be caused by a mechanism of leptin resistance (similar to the one that links type 2 diabetes and insulin resistance) that blunts leptin central action despite increasing concentrations (Munzberg and Myers, 2005). Based on these observations, it has been hypothesized that is not the absolute leptin concentration but rather reduced leptin signaling to the central nervous system that affects mood (Zupancic and Mahajan, 2011; Lu, 2007). Therefore, hyperleptinemia due to functional resistance in obese persons may represent a phenotype risk for depression similar to leptin insufficiency in lean patients.

In a recent study (Milaneschi et al., 2012) conducted in 2502 community-dwelling older persons, we showed that leptin and visceral fat had an interactive effect in predicting the onset of depressive symptoms over a 5-year follow-up in men, with risk especially high for persons with high levels of both leptin and visceral fat. Another recent cross-sectional study (Morris et al., 2012) in 537 adults reported a borderline significant association between leptin and the interaction of depressive symptoms with body mass index. However, when testing interactive effects the sample size may represent a critical issue.

In the present study we used data from two well-characterized population-based studies, the InCHIANTI Study and the Baltimore Longitudinal Study of Aging. We tested whether the relationship between leptin and depressive symptoms is modulated by abdominal adiposity. We hypothesized that the interaction between leptin and waist circumference would be significantly associated with depressive symptoms cross-sectionally (pooling together data from both studies) and would predict the development of clinically relevant depressive symptoms over a 9-year follow-up (InCHIANTI).

2. Methods and materials

2.1. Study population — InCHIANTI

The InCHIANTI Study is a prospective population-based study of older persons (65 years and older) in Tuscany (Italy) designed to investigate factors contributing to decline in mobility in later life (Ferrucci et al., 2000). Briefly, in 1998—2000 the sample was randomly selected from two sites using a multistage stratified sampling method. Data collection included a home interview, a medical examination and blood drawing. Participants were evaluated again at three-year (2001—2003), six-year (2004—2006) and nine-year (2007—2009) follow-up visits. All respondents signed an informed consent and the Italian National Institute of Research and Care on Aging Ethical Committee approved the study protocol. We selected 876 participants with available data on leptin, waist circumference and depressive symptoms at baseline. We then excluded 15 participants with dementia and another 10 with values above 3 standard deviations for leptin (≥71.1 ng/mL). This left 851 participants (65—94 years of age) as the primary sample. The majority of the sample (51.1%) had depressive symptoms measured at all three follow-ups and 69.7% of participants