ann. behav. med. (2013) 46:5–6
DOI 10.1007/s12160-013-9493-7

INVITED COMMENTARY

Leptin, Somatic Depressive Symptoms and the Metabolic Syndrome: a Comment on Chirinos et al.

Javier Labad, M.D., Ph.D. · Rebecca M. Reynolds, Ph.D.

Published online: 20 March 2013

People with depression are at increased risk of metabolic syndrome and vice versa [1]. Leptin, a hormone secreted by adipose tissue is a plausible link as levels are increased in people with obesity and depression [2, 3]. The article by Chirinos et al. [4] replicates previous findings and adds new evidence to the field: the association of circulating leptin levels with somatic depressive symptoms.

In the study by Chirinos et al. [4], somatic but not cognitive depressive symptoms were associated with increased plasma leptin levels in 135 subjects with metabolic syndrome. These results, together with another recent study linking somatic depressive symptoms with C-reactive protein, interleukin-6 and tumour necrosis factor-α levels [5] suggest that adipokines and inflammatory markers may have a pathogenic role in the expression of somatic depressive symptoms. Interestingly, the association between leptin and somatic depressive symptoms was only found in men [4], which is in accordance with other studies reporting sex differences in the relationship between leptin and depressive symptoms [3], especially in socially isolated men [6]. We have also found a positive association between leptin and poorer neuropsychological performance in men with type 2 diabetes [7]. As animal models suggest that brains of male and female rats are differentially sensitive to the effects of leptin, with reduced effects in male rats [8], it is plausible that the association between leptin and neuropsychiatric symptoms in men may be explained by sex differences in leptin sensitivity at key brain areas (e.g., hypothalamus, hippocampus).

Of all different somatic symptoms, Chirinos et al. found appetite disturbances, fatigue and sleep difficulties were associated with higher leptin levels [4]. Insomnia is a prevalent symptom in major depression and lack of sleep is also thought to be a risk factor for obesity and metabolic syndrome [9]. Anatomical factors related to obesity (reduced pharyngeal lumen size, decreased upper airway muscle force, reduced upper airway size) may cause obstructive sleep apnoea, which contributes to sleep difficulties. However, other patients with obstructive sleep apnoea show instability in ventilatory control that exacerbates otherwise minor anatomical deficits [10]. Hormonal factors secondary to obesity may also contribute to sleep disturbances. Increased serum leptin levels are associated with reduced respiratory drive and a reduced hypercapnic response in obese subjects [11]. As it is difficult to know which is cause, and which effect in the association between metabolic syndrome and obstructive sleep apnea [10], further prospective studies are needed to explore whether the development of leptin resistance may mediate this relationship.

What other factors may be important in the relationship between leptin and sleep changes or appetite disturbances? Circadian alignment, quality sleep and sleep architecture are key elements of the energy- and food-reward homeostasis [12]. Such chronobiological factors are also relevant in major depression (diurnal variance of mood, insomnia, seasonal pattern in recurrences) [13] and obesity (increased risk in shift workers, sleep deprivation, and exposure to bright light at night) [14]. Moreover, genes related to the circadian molecular machinery have been associated with major depression [15] and the metabolic syndrome [16]. As circadian misalignment affects sleep architecture, glucose insulin metabolism and leptin concentrations [12], further studies are needed to address whether the relationship between leptin and sleep problems in depression is influenced by chronobiological factors.

J. Labad (✉)
Hospital Universitari Institut Pere Mata, IISPV, Universitat Rovira i Virgili. CIBERSAM, Ctra. de l'Institut Pere Mata, s/n, 43206 Reus, Spain
e-mail: labadj@peremata.com

R. M. Reynolds (✉)
Endocrinology Unit, University/BHF Centre for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, Edinburgh EH16 4TJ, UK
e-mail: R.Reynolds@ed.ac.uk

Acknowledgments Javier Labad has received an Intensification of Research Activity grant (Programme I3SNS-INT11/323) from the Instituto de Salud Carlos III (Spain) during 2012 and 2013.

Conflict of Interest The authors have no conflict of interest to disclose.

References

1. Katon WJ. Epidemiology and treatment of depression in patients with chronic medical illness. *Dialogues Clin Neurosci*. 2011; 13: 7-23.
2. Pasco JA, Jacka FN, Williams LJ, et al. Leptin in depressed women: Cross-sectional and longitudinal data from an epidemiologic study. *J Affect Disord*. 2008; 107: 221-225.
3. Labad J, Price JF, Strachan MW, et al. Leptin levels and depressive symptoms in people with type 2 diabetes: The edinburgh type 2 diabetes study. *Psychosom Med*. 2012; 74: 39-45.
4. Chirinos DA, Goldberg R, Gellman M, et al. Leptin and its association with somatic depressive symptoms in patients with the metabolic syndrome. *Ann Behav Med*. 2013. doi:10.1007/s12160-013-9479-5.
5. Duivis HE, Vogelzangs N, Kupper N, de Jonge P, Penninx BW. Differential association of somatic and cognitive symptoms of depression and anxiety with inflammation: Findings from the Netherlands Study of Depression and Anxiety (NESDA). *Psychoneuroendocrinology*. 2013. doi:10.1016/j.psyneuen.2013.01.002.
6. Hafner S, Zierer A, Emeny RT, et al. Social isolation and depressed mood are associated with elevated serum leptin levels in men but not in women. *Psychoneuroendocrinology*. 2011; 36: 200-209.
7. Labad J, Price JF, Strachan MW, et al. Serum leptin and cognitive function in people with type 2 diabetes. *Neurobiol Aging*. 2012; 33: 2938-2941. e2932.
8. Clegg DJ, Riedy CA, Smith KA, Benoit SC, Woods SC. Differential sensitivity to central leptin and insulin in male and female rats. *Diabetes*. 2003; 52: 682-687.
9. Van Cauter E, Spiegel K, Tasali E, Leproult R. Metabolic consequences of sleep and sleep loss. *Sleep Med*. 2008; 9(Suppl 1): S23-S28.
10. Pillar G, Shehadeh N. Abdominal fat and sleep apnea: The chicken or the egg? *Diabetes Care*. 2008; 31(Suppl 2): S303-S309.
11. Campo A, Fruhbeck G, Zulueta JJ, et al. Hyperleptinaemia, respiratory drive and hypercapnic response in obese patients. *Eur Respir J*. 2007; 30: 223-231.
12. Gonnissen HK, Hulshof T, Westerterp-Plantenga MS. Chronobiology, endocrinology, and energy- and food-reward homeostasis. *Obes Rev*. 2013. doi:10.1111/obr.12019.
13. McClung CA. Circadian genes, rhythms and the biology of mood disorders. *Pharmacol Ther*. 2007; 114: 222-232.
14. Garaulet M, Ordovas JM, Madrid JA. The chronobiology, etiology and pathophysiology of obesity. *Int J Obes (Lond)*. 2010; 34: 1667-1683.
15. Soria V, Martinez-Amoros E, Escaramis G, et al. Differential association of circadian genes with mood disorders: CRY1 and NPAS2 are associated with unipolar major depression and CLOCK and VIP with bipolar disorder. *Neuropsychopharmacology*. 2010; 35: 1279-1289.
16. Milagro FI, Gomez-Abellan P, Campion J, et al. CLOCK, PER2 and BMAL1 DNA methylation: Association with obesity and metabolic syndrome characteristics and monounsaturated fat intake. *Chronobiol Int*. 2012; 29: 1180-1194.