Plasma leptin concentrations are highly correlated to emotional states throughout the day

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Previous work has shown that leptin appears to regulate the plasma levels of hormones such as adrenocorticotropic hormone (ACTH) and cortisol in humans and that it has antidepressant effects in animals. It is unknown whether fluctuations in circulating leptin levels are correlated to changes in human emotions. This study was conducted to determine whether minute-to-minute fluctuations in the plasma concentrations of human leptin were associated with psychological variables. Leptin was sampled every 7 min throughout the day in 10 healthy subjects (five men and five women) studied in a clinical research center, and visual analog scales were applied every hour. We found highly significant correlations between fluctuations in plasma leptin concentrations and three psychological variables: sadness, carbohydrate craving and social withdrawal. We showed that during the course of the day increases in leptin levels are associated with decreased search for starchy foods, decreased feelings of sadness and increased social withdrawal. Our findings support the hypothesis that during the course of the day as leptin levels increase individuals subjectively feel happier (less sad) and have less inclination to interact socially. Conversely, when leptin levels decrease, we show increases in sadness and social cooperation, which might facilitate the search for food. We suggest that increased human leptin levels may promote positive feelings and that decreased leptin levels might modulate inner states that motivate and facilitate the search for nutrients.

INTRODUCTION

It has been widely observed that food intake, body weight and mood are associated in humans. Alterations in food intake and body weight are cardinal diagnostic features of mood disorders such as major depression.1 The mechanisms underlying the interactions between body weight, food intake and mood have not been elucidated. Leptin, an adipose tissue hormone, acts on hypothalamic receptors to inhibit food intake and stimulate thermogenesis, thereby regulating energy balance and body weight.2–4 Plasma leptin concentrations reflect fat mass; however, within individuals leptin levels fluctuate throughout the day in a pulsatile and circadian manner.5–8 We hypothesized that leptin might affect mood acting as a link between the body’s adipose mass and the brain. Here we show that during the course of the day fluctuations in the plasma leptin level are highly correlated with psychological measures of mood, social stress and food (carbohydrate) craving.

Despite the well-established effects of leptin administration in animals to reduce food consumption and decrease body weight, meals do not immediately influence leptin levels in humans. In a study investigating the circadian patterns of secretion of leptin, meal ingestion and meal-induced increases in plasma insulin and glucose did not influence changes in leptin concentrations during the 24-h period.7 Furthermore, when appetite ratings and leptin levels were compared, subjective feelings of hunger were not affected by postprandial plasma leptin concentrations in healthy volunteers.10 Those data indicate that leptin influences energy metabolism but that it does not act as an immediate satiety factor. In addition to its effect on eating behavior, leptin may have a role in the body’s hormonal response to stress. We have shown that human leptin levels are highly and inversely correlated to the stress hormones cortisol and adrenocorticotropic hormone (ACTH).5 Our group and others have conducted studies supporting the concept that leptin might modulate the bioactivity of neuropeptides, such as corticotropin-releasing hormone (CRH), a neurohormone that regulates the biological and behavioral responses to stress.11–16 Whereas several studies have included single hormone or cytokine measures as they relate to symptoms, including leptin17,18 and interleukin-6 (IL-6),19 we have previously shown that both leptin and IL-6 fluctuate substantially throughout the day.6–8,20,21 Clinical symptoms likewise fluctuate from hour to hour. Single time point measurements are therefore very limited, as they cannot be temporally related to diurnal fluctuations in psychometric variables.

The experiment described here tests the hypothesis that fluctuations in plasma leptin concentrations throughout the day are highly associated with simultaneous fluctuations in psychometric variables such as mood, stress-related behaviors and appetite.

MATERIALS AND METHODS

Ten healthy normal-weight subjects (five male and five female subjects; body mass index = 22.4 ± 0.9 kg/m², age = 29.5 ± 2.2 years) were admitted to a clinical research unit at the Clinical Center at the National Institutes of Health. The research was approved by the Institutional Review Board of the National Institutes of Health Clinical Center (Bethesda, MD, USA). Informed consent was obtained before all procedures in writing. We started the
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RESULTS

We collected a total of 2070 blood samples and 1200 psychometric variable data points. To assess fluctuation in the plasma leptin concentration, we calculated leptin variability, which has been previously defined as a percentage of individual 24-h average, using the formula: variability at time t = (hormone level at time t/24-h individual average level)x100. A higher score in the visual analog scale measurement indicates more pronounced symptoms. Social withdrawal, concentration, self-esteem and physical discomfort were considered as measures analogous to behaviors observed in animal models of stress. Using linear regression (Pearson’s correlation) we found that craving for sugar, social withdrawal and sadness were highly and significantly correlated with leptin variability. The other subjective psychological states did not show significant correlation with leptin levels. Significance was calculated taking into consideration multiple comparisons (Bonferroni’s correction). We found a highly significant negative correlation between leptin variability and craving, indicating that an increase in leptin levels was accompanied by similar decrease in the subjective feelings of carbohydrate craving (Figure 1a). A highly negative correlation was also found when sadness and leptin variability were compared (Figure 1b). On the other hand, social withdrawal had a highly positive correlation with plasma leptin concentrations (Figure 1c). There is a clear increase in leptin values throughout the day, which is followed by a similar pattern in social withdrawal scores. Craving for carbohydrates and sadness have a tendency to diminish towards the end of the day, indicating an hourly negative correlation between leptin and both scores.

DISCUSSION

To our knowledge, this is the first report that fluctuations in longitudinally sampled human leptin concentrations are temporally correlated with psychometric variables.

A study by Larsson et al. examined 64 healthy postmenopausal women and showed a correlation between plasma leptin concentrations and total carbohydrate intake. That study examined the correlation between leptin and carbohydrate intake in a group of subjects whose leptin levels were assessed once and related to actual food intake. In our study we standardized food intake and examined how fluctuations in rapidly sampled plasma leptin concentrations correlated to psychometric variables within subjects. In spite of these very distinct study designs, using group comparisons (Larsson et al.) and within subject variations (this study), it is noteworthy that the results of both studies are consistent with each other, indicating that the psychometric variables we studied may be relevant to actual patterns of ad libitum food intake, as documented by Larsson et al.

Tsouloiu et al. used brisk walking and a chocolate-based snack, in an attempt to replicate typical physical activity and eating behaviors, to investigate the effects on appetite and on associations between serum leptin and appetite. Associations between circulating leptin and suppressed appetite or elevated satiety were found following a bout of moderate physical activity, but not at any time point during the snack or the control
conditions. The authors concluded that moderate physical activity and snack intake suppress the appetite of obese women acutely. They suggested that associations between circulating leptin and appetite satiety ratings might indicate the involvement of leptin in short-term appetite regulation in response to physical activity-induced factors. Moreover, two other studies looked at the correlation between leptin and subjective variables; however, those were based on single point measurements of leptin17,18 and cannot establish a temporal correlation between variability in diurnal leptin levels and fluctuations in psychometric variables throughout the course of the day.

Despite our previous work showing that leptin replacement specifically affects macro- and micronutrient intake in leptin-deficient patients,25,26 in this study we could not detect any correlation between appetite and leptin, which further supports the concept that leptin might not be a short-term satiety factor, at least in baseline levels of energy expenditure. However, the effects of leptin on food intake might explain the negative correlation we found with craving. Other hormones may have a more pronounced role in short-term satiety. This includes gastrointestinal peptides, such as glucagon-like peptide-1,27

Previous work from our group and others have shown that leptin affects brain function in food-related cognitive tasks.28,29 Leptin also increases gray matter in the cerebellum, anterior cingulate gyrus and inferior parietal lobe.30–33 In addition to these effects, leptin has potent pro-cognitive effects.34,35 Leptin levels are inversely correlated to rates of dementia and Alzheimer's disease,56,37 and it acts on dopaminergic midbrain neurons to promote survival and to protect against apoptosis via activation of mitogen-activated protein kinase and phosphoinositide 3-kinase/Akt/nuclear factor kappa B-dependent signaling cascades. Given the functional and structural effects of leptin on the human brain, it is noteworthy, but not unexpected, that leptin might be closely correlated with the diurnal regulation of emotional states, in a manner suggestive of a possible regulatory role by this signal of nutritional status on specific emotions, such as sadness and emotional withdrawal. The possible effects of leptin on human emotions might be understood in terms of evolution. We show that during the course of the day, increases in leptin concentrations are associated with decreased motivation to search for starchy foods, decreased feelings of sadness and increased social withdrawal. This is consistent with the hypothesis that as leptin levels increase individuals subjectively feel happier (less sad) and have less inclination to interact socially in a manner that might facilitate the search for food. Conversely, when leptin levels decrease there are increases in sadness and social cooperation (necessary to obtain food).

CONCLUSIONS

We showed that during the course of the day increases in leptin levels are associated with decreased search for starchy foods, decreased feelings of sadness and increased social withdrawal. Our results support the hypothesis that decreased circulating leptin levels might modulate inner states that facilitate the search for food. Sadness and social withdrawal are the key symptoms of major depression, a disorder that has been postulated to involve abnormal CRH activity.1 The effects of leptin in the brain have been well studied in animals, including its potential role as an antidepressant that can increase neurogenesis.40,41 Moreover, deletion of leptin receptors in the adult hippocampus induces depression-related behaviors in mice.42 However, the specific central mechanisms by which leptin, a peripherally secreted hormone, might regulate human emotional states throughout the course of the day have not yet been identified. Future studies should determine whether the effects of leptin on the regulation of higher brain functions in humans are directly regulated by leptin receptors or whether such effects are mediated by neuropeptides, such as CRH.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

This study was supported by grants from the National Institutes of Health: K30HL045256, RR16969, HG002500, RR017611, DK063240, DK58851 (JL), RR017365, MH062777 and RR000865 (M-LW).

DISCLAIMER

The funders had no role in study design, data collection, analysis, and decision to publish or preparation of the manuscript.

REFERENCES

1. Wong ML, Licinio J. Research and treatment approaches to depression. Nat Rev Neurosci 2001; 2: 343–351.
2. Friedman JM. Obesity in the new millennium. Nature 2000; 404: 632–634.
3. Friedman JM. Leptin, leptin receptors, and the control of body weight. Nutr Rev 1998; 56: 138–146.
4. Blundell JE, Goodson S, Halford JC. Regulation of appetite: role of leptin in signalling systems for drive and satiety. Int J Obes Relat Metab Disord 2001; 25: 529–534.
5. Licinio J, Mantzoros C, Negaro AB, Cizza G, Wong ML, Bongiorno PB et al. Human leptin levels are pulsatile and inversely related to pituitary-adrenal function. Int J Med 1997; 3: 575–579.
6. Licinio J, Negaro AB, Mantzoros C, Kaklamani V, Wong ML, Bongiorno PB et al. Sex differences in circulating human leptin pulse amplitude: clinical implications. J Clin Endocrinol Metab 1998; 83: 4140–4147.
7. Licinio J, Negrao AB, Mantzoros C, Kaklamani V, Wong ML, Bongiorno PB et al. Synchrony of frequently sampled, 24-h concentrations of circulating leptin, luteinizing hormone, and estradiol in healthy women. Proc Natl Acad Sci USA 1998; 95: 2541–2546.
8. Mantzoros CS, Ozata M, Negaro AB, Ziotopoulou M, Caglayan S, Suchard M et al. Nocturnal rise of leptin in lean, obese, and non-insulin-dependent diabetes mellitus subjects. J Clin Invest. 1996; 97: 1344–1347.
9. Joannici JL, Oppert JM, Lahouli N, Basdevant A, Auboiron S, Raison J et al. Plasma leptin and hunger ratings in healthy humans. Appetite 1998; 30: 129–138.
10. Sutton RE, Koob GF, Rios JJ, Vale W. Corticotropic releasing factor mediates neuronal and endocrine activation in rats. Nature 1982; 297: 331–333.
11. Ahima RS, Prabakaran D, Mantzoros C, Qu D, Lowell B, Maratos-Flier E et al. Role of leptin in the neuroendocrine response to fasting. Nature 1996; 382: 250–252.
12. Schwartz MW, Seeley RJ, Campfield LA, Burn P, Baskin DG. Identification of targets of leptin action in rat hypothalamus. J Clin Invest. 1996; 98: 1101–1106.
13. Schwartz MW, Seeley RJ, Campfield LA, Burn P, Baskin DG. Identification of targets of leptin action in rat hypothalamus. J Clin Invest. 1996; 98: 1101–1106.
14. Schwartz MW, Seeley RJ, Campfield LA, Burn P, Baskin DG. Identification of targets of leptin action in rat hypothalamus. J Clin Invest. 1996; 98: 1101–1106.
15. Gardner JD, Rothwell NJ, Luhschi GN. Leptin affects food intake via CRF-receptor-mediated pathways. Nat Neurosci 1998; 1: 103.
16. Chrousos GP. Stress and disorders of the stress system. Nat Rev Endocrinol 2009; 5: 374–381.
17. Olama SM, Elsaid TO, El-Arman M. Serum Leptin in Egyptian patients with fibromyalgia syndrome: relation to disease severity. Int J Rheum Dis 2013; 16: 583–589.
18. Tsoulou F, Pitsilasidis YP, Malkova D, Wallace AM, Lean ME. Moderate physical activity permits acute coupling between serum leptin and appetite-satiety measures in obese women. Int J Obes Relat Metab Disord 2003; 27: 1332–1339.
19. Rohleder N, Aringer M, Boentert M. Role of interleukin-6 in stress, sleep, and fatigue. Ann N Y Acad Sci 2012; 1261: 88–96.
20. Vgontzas AN, Papanicolaou DA, Bixler EO, Lotuikas A, Zachann K, Kales A et al. Circadian interleukin-6 secretion and quantity and depth of sleep. J Clin Endocrinol Metab 1999; 84: 2603–2607.
21. Alesci S, Martinez PE, Kelkar S, Illas I, Ronsovski DS, Listwak SJ et al. Major depression is associated with significant diurnal elevations in plasma interleukin-6.
levels, a shift of its circadian rhythm, and loss of physiological complexity in its secretion: clinical implications. J Clin Endocrinol Metab 2005; 90: 2522–2530.

22 Folstein MF, Luria R. Reliability, validity, and clinical application of the Visual Analogue Mood Scale. Psychol Med 1973; 3: 479–486.

23 Chrousos GP, Gold PW. The concepts of stress and stress system disorders. JAMA 1992; 267: 1244–1252.

24 Larsson H, Elmstahl S, Berglund G, Ahren B. Evidence for leptin regulation of food intake in humans. J Clin Endocrinol Metab 1998; 83: 4382–4385.

25 Licinio J, Milane M, Thakur S, Whelan F, Yildiz BO, Delibasi T et al. Effects of leptin on intake of specific micro- and macronutrients in a woman with leptin gene deficiency studied off and on leptin at stable body weight. Appetite 2007; 49: 594–599.

26 Williamson DA, Ravussin E, Wong ML, Wagner A, Dipaoli A, Caglayan S et al. Microanalysis of eating behavior of three leptin deficient adults treated with leptin therapy. Appetite 2005; 45: 75–80.

27 Boguszewski CL, Paz-Filho G, Velloso LA. Neuroendocrine body weight regulation: integration between fat tissue, gastrointestinal tract, and the brain. Endokrynologia Polska 2010; 61: 194–206.

28 Baicy K, London ED, Monterosso J, Wong ML, Delibasi T, Sharma A et al. Leptin replacement alters brain response to food cues in genetically leptin-deficient adults. Proc Natl Acad Sci USA 2007; 104: 18276–18279.

29 Paz-Filho G, Wong ML, Licinio J. Ten years of leptin replacement therapy. Obes Rev 2011; 12: e315–e323.

30 Berman SM, Paz-Filho G, Wong ML, Kohno M, Licinio J, London ED. Effects of leptin deficiency and replacement on cerebellar response to food-related cues. Cerebellum 2013; 12: 59–67.

31 London ED, Berman SM, Chakrapani S, Delibasi T, Monterosso J, Erol HK et al. Short-term plasticity of gray matter associated with leptin deficiency and replacement. J Clin Endocrinol Metab 2011; 96: E1212–E1220.

32 Matochik JA, London ED, Yildiz BO, Ozata M, Caglayan S, DePaoli AM et al. Effect of leptin replacement on brain structure in genetically leptin-deficient adults. J Clin Endocrinol Metab 2005; 90: 2851–2854.

33 Paz-Filho G, Mastronardi CA, Licinio J. Leptin treatment: facts and expectations. Metabolism advance online publication, 3 August 2014; doi:10.1016/j.metabol.2014.07.014 (e-pub ahead of print). pii: S0026-0495(14)00234-0.

34 Paz-Filho GJ, Babikian T, Asarnow R, Delibasi T, Esposito K, Erol HK et al. Leptin replacement improves cognitive development. PLoS ONE 2008; 3: e3098.

35 Paz-Filho G, Wong ML, Licinio J. The procoagulative effects of leptin in the brain and their clinical implications. Int J Clin Pract 2010; 64: 1808–1812.

36 Lieb W, Beiser AS, Vasan RS, Tan ZS, Au R, Harris TB et al. Association of plasma leptin levels with incident Alzheimer disease and MRI measures of brain aging. JAMA 2009; 302: 2565–2572.

37 Paz-Filho G, Wong ML, Licinio J. Leptin levels and Alzheimer disease. JAMA 2010; 303: 1478, author reply 9.

38 Doherty GH, Oldreive C, Harvey J. Neuroprotective actions of leptin on central and peripheral neurons in vitro. Neuroscience 2008; 154: 1297–1307.

39 Lu XY, Kim CS, Frazer A, Zhang W. Leptin: a potential novel antidepressant. Proc Natl Acad Sci USA 2006; 103: 1593–1598.

40 Garza JC, Guo M, Zhang W, Lu XY. Leptin increases adult hippocampal neurogenesis in vivo and in vitro. J Biol Chem 2008; 283: 18238–18247.

41 Garza JC, Guo M, Zhang W, Lu XY. Leptin restores adult hippocampal neurogenesis in a chronic unpredictable stress model of depression and reverses glucocorticoid-induced inhibition of GSK-3beta/beta-catenin signaling. Mol Psychiatry 2012; 17: 790–808.

42 Guo M, Huang TY, Garza JC, Chua SC, Lu XY. Selective deletion of leptin receptors in adult hippocampus induces depression-related behaviours. Int J Neuropsychopharmacol 2013; 16: 857–867.