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EDITORIAL

Leptin in anorexia nervosa and amenorrhea

In this issue of *Molecular Psychiatry* we publish two articles by Hebebrand *et al*[1] and Köpp *et al*[2] on leptin, the product of the *OB* gene, which is synthesized by white fat cells, and acts in various organs, including the brain. Low leptin levels cause increases in food intake and weight gain, and high leptin levels cause a decrease in food intake, and increases in motor activity, energy metabolism, and body temperature, resulting in weight loss. The leptin receptor gene that has been cloned encodes five or more leptin receptor isoforms, including a form predicted to be soluble, several short forms with small intracellular domains, and one long form with substantial homology to the signaling domain of the type I cytokine receptor family that utilizes the JAK/STAT pathway for signal transduction.[3–5] The discoveries of leptin and leptin receptors have created a new area of investigation in endocrinology and metabolism.

Eating disorders, particularly anorexia nervosa, are psychiatric disorders of high morbidity and mortality that are characterized by alterations in food intake and neuroendocrine function: anorexia nervosa is the only psychiatric disorder that requires a specific endocrine defect, amenorrhea, for diagnosis. Hebebrand's group has shown that as one would expect, leptin levels are low in patients with anorexia nervosa.[1] However, as those individuals gain weight, leptin levels peak at values well in excess of those observed in controls matched for body mass index (BMI). This might help explain why it is so difficult for patients with anorexia nervosa to consistently gain and keep weight. The good news is that after long-term weight restoration, leptin levels return to normal. The findings of a research study are best validated by independent replication, which has been achieved in this case. Mantzoros *et al*[6] have studied leptin levels longitudinally in plasma and cerebrospinal fluid (CSF) in a separate group of patients with anorexia nervosa. They found an increased CSF to plasma ratio for the patients compared with controls, and also found that CSF and plasma leptin levels normalized when patients started to gain weight, but before they reached normal body weight. The conclusion from these studies is that inappropriately high leptin levels before full weight restoration contribute to the resistance to weight gain and/or incomplete weight recovery in anorexia nervosa.

In a separate study,[2] Köpp and colleagues show that low leptin levels are a predictor of amenorrhea in low-weight women. The authors show that in their population menstruation ceased to occur when leptin levels were under the range of 1.85 $\mu g\,L^{-1}$. In those subjects, leptin levels were a better predictor of amenorrhea than BMI, fat mass, and percent body fat. The conclusion from the study is that a critical level of leptin is needed to maintain menstrual function.

Interestingly, studies conducted in the laboratory of Jeffrey Flier have shown that the endocrine alterations that occur during starvation, such as increased adrenocorticotropic hormone (ACTH) and cortisol levels, which are among the biological hallmarks of anorexia nervosa, can be reversed in food-deprived animals by the administration of exogenous leptin.[7] Based on those data, we have tested the hypothesis that in humans endogenous leptin levels are inversely related to pituitary-adrenal function, measuring leptin, ACTH, and cortisol levels every 7 min for 24 h, in healthy individuals (Figure 1).[8] Total circulating leptin levels have a pattern indicative of highly pulsatile release, with 32.0 ± 1.5 pulses per 24 h, and pulse duration of 32.8 ± 1.6 min. Because leptin pulses are of short duration, pulsatility of human leptin levels can only be

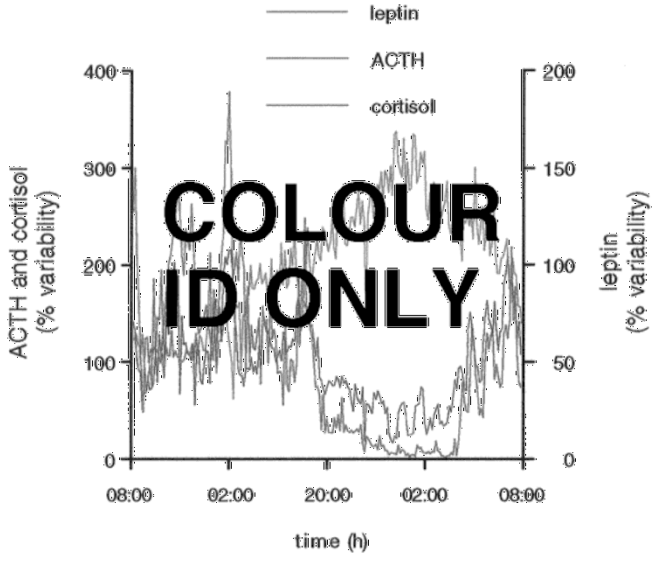

Figure 1 Simultaneous fluctuations in leptin, ACTH and cortisol levels in one healthy young man, studied for 24 h with sampling every 7 min for 207 simultaneous measurements of leptin (green), ACTH (blue) and cortisol (red). Each measurement is expressed as variability, defined as % of individual 24-h averages, using the formula: variability at time t = (hormone level at time t per 24-h individual average level) $\times$ 100.[7] Note the inverse relationship between the rhythms of leptin and ACTH/cortisol.

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assessed by rapid sampling. Rapid fluctuations in plasma levels of leptin are inversely related to those of ACTH and cortisol. This cannot be accounted for on the basis of glucocorticoid suppression of leptin, and may therefore be due to the acute effects of leptin on corticotropin-releasing hormone (CRH) production. Leptin treatment of mice substantially blunts the stress-induced rise in ACTH and corticosterone; moreover, leptin acutely inhibits hypoglycemia-induced CRH secretion by perifused rat hypothalami.[9] CRH not only regulates hypothalamic-pituitary-function, but also influences the levels of behavioral arousal.[10–13] Therefore, leptin-mediated alterations in the secretion or actions of CHR[14] might represent a mechanism by which a highly pulsatile peripheral signal of nutritional status, such as leptin, could modulate endocrine function and behavior.[8] A key function of the CNS is therefore regulated by a peripheral pulsatile signal.

Leptin affects the functioning of the hypothalamo-pituitary-gonadal axis. A recent study has shown that leptin, at very low concentrations, stimulated LHRH release from hypothalamic explants and LH release from anterior pituitary *in vitro* and *in vivo*. These data indicate that leptin plays an important role in controlling gonadotropin secretion by stimulatory actions in the hypothalamus and pituitary.[15] Leptin has also been shown to act in the ovary.[16]

Leptin administration affects reproduction: infertile homozygous female *OB/OB* mice can be treated by repeated administration of only recombinant human leptin, which corrects their sterility, and results in ovulation, pregnancy and parturition.[17] Moreover, normal prepubertal female mice injected with leptin reproduce up to 9 days earlier than controls and show earlier maturation of the reproductive tract.[18] These results suggest that leptin acts as a signal triggering puberty, and support the hypothesis that fat accumulation enhances maturation of the reproductive tract. Köpp's data in this issue of *Molecular Psychiatry*[2] advance this concept and lead to the conclusion that adequate levels of leptin are required not only for the maturation of reproductive function, but also for the maintenance of normal menstrual function in humans, possibly because of its actions at the level of the hypothalamus,[15] pituitary,[15] and ovary.[16]

Leptin is a part of a complex molecular network that controls food intake. Food intake is regulated by peripheral metabolic signals, including gastrointestinal hormones, as well as by the central nervous system, which integrates physiological signals, environmental clues, and conditioned (learned) behavior.[19] In the hypothalamus, leptin interacts with several other hormones that regulate food intake, such as neuropeptide Y (NPY) and corticotropin-releasing hormone (CRH).[7] CRH suppresses food intake, while NPY is a potent stimulator of food and water intake. *OB/OB* animals with a knockout of the NPY gene are deficient for both NPY and leptin. In the absence of NPY, *OB/OB* mice are less obese because of reduced food intake and increased energy expenditure, and are less severely affected by diabetes, sterility, and somatotropic defects. These results suggest that NPY is a central effector of leptin deficiency.[20] Additionally, two other new hormones have been shown to modulate food intake: urocortin, that binds with high affinity to the CRF_2 receptors, suppresses food intake,[21] and melanin-concentrating hormone (MCH), which is localized in the zona incerta and in the lateral hypothalamus, stimulates food intake after intracerebroventricular injection.[22] The interactions among the central circuitries that mediate the effects of leptin, NPY, urocortin, CRH, MCH, and classical neurotransmitters that modulate food intake and reward, such as serotonin, norepinephrine, and dopamine, represent a new frontier of investigation, integrating genetics, endocrinology, metabolism, molecular biology, neuroscience, behavioral science, and psychiatry.[23] The hypothesis that alterations in those circuitries contribute to the pathophysiology of eating disorders should certainly be tested.

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