Review

Role of leptin in energy-deprivation states: normal human physiology and clinical implications for hypothalamic amenorrhoea and anorexia nervosa

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Leptin is an adipocyte-secreted hormone that plays a key part in energy homoeostasis. Advances in leptin physiology have established that the main role of this hormone is to signal energy availability in energy-deficient states. Studies in animals and human beings have shown that low concentrations of leptin are fully or partly responsible for starvation-induced changes in neuroendocrine axes, including low reproductive, thyroid, and insulin-like growth factor (IGF) hormones. Disease states such as exercise-induced hypothalamic amenorrhoea and anorexia nervosa are also associated with low concentrations of leptin and a similar spectrum of neuroendocrine abnormalities. We have recently shown in an interventional, proof-of-concept study that leptin can restore ovulatory menstrual cycles and improve reproductive, thyroid, and IGF hormones and bone markers in hypothalamic amenorrhoea. Further studies are warranted to establish the safety and effectiveness of leptin for the infertility and osteoporosis associated with hypothalamic amenorrhoea, and to clarify its role in anorexia nervosa.

Introduction

In 1994, the discovery of leptin fundamentally changed our perspective of adipose tissue from that of an inert energy store to a true endocrine organ that secretes metabolically active hormones. Leptin was identified as the hormone whose absence resulted in morbid obesity in the *ob/ob* mouse,[1] thus acquiring its name from the Greek word "leptos" (thin). Although initially hopes were high that leptin would prove important in the pathophysiology and thus treatment of human obesity, early studies quickly showed that human obesity is generally not associated with leptin deficiency due to a leptin gene defect,[2] a finding not altogether surprising in view of the complex, multifactorial nature of obesity. It was also soon realised, however, that leptin might be more important at the other end of the energy homoeostasis spectrum—ie, energy deprivation rather than obesity. In this context, studies in mice[3] and also in people[4] have shown that leptin has a role in the neuroendocrine adaptation to starvation, which includes changes in hormone concentrations that probably have a protective effect. These findings are clinically relevant for common disease states associated with low leptin concentrations and neuroendocrine abnormalities—ie, energy-deficient states such as exercise-induced amenorrhoea, non-athletic forms of hypothalamic amenorrhoea, and anorexia nervosa. We review the role of leptin in neuroendocrine function, the reproductive and other neuroendocrine abnormalities associated with these energy-deficient conditions, and the evidence that low leptin concentrations could play a part in their pathophysiology and potentially their treatment. We also discuss the clinical relevance of these syndromes with respect to effect on fertility and skeletal health.

Search strategy and selection criteria

We searched MEDLINE for articles relating "leptin" to "hypothalamic-pituitary-peripheral axes", "neuroendocrine function", "hypothalamic amenorrhea", "exercise-induced amenorrhea", and "anorexia nervosa", with emphasis on articles on human beings.

Leptin physiology

Leptin is a 167 aminoacid protein product of the *ob* gene that was discovered in 1994 through positional cloning in the *ob/ob* obese mouse, a model of morbid obesity resulting from absence of leptin due to a gene mutation.[1] The tertiary structure of leptin suggests that it belongs to the cytokine family. Leptin is expressed mainly in white adipose tissue, but also in stomach, placenta, and the mammary gland.[5] Leptin circulates in the serum in a free form or bound to leptin-binding proteins, and the sum of free and bound leptin (ie, total leptin) is the generally accepted standard of measurement. Like other hormones, leptin is secreted in a pulsatile way and has a substantial diurnal variation with an increase of about 50% in the late evening and early morning hours that might be related to an intrinsic circadian component, meal timing, and the sleep-wake cycle.[6–8] Leptin concentrations correlate with the amount of fat mass, with higher amounts in more obese people (figure 1).[2] Although the amount of fat is an important determinant of leptin concentrations, other factors are also relevant, including sex, adipose tissue-specific factors such as adipocyte size and visceral versus subcutaneous fat distribution, other hormones (eg, insulin, glucocorticoids) and cytokines (eg, tumour necrosis factor α, interleukin 1).[6,9–11] Importantly, women have higher leptin concentrations than men even after