Leptin, An Adipokine With Central Importance in the Global Obesity Problem

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ABSTRACT

Leptin has central importance in the global obesity and cardiovascular disease problem. Leptin is principally secreted by adipocytes and acts in the hypothalamus to suppress appetite and food intake, increase energy expenditure, and regulate body weight. Based on clinical translation of specific and networked actions, leptin affects the cardiovascular system and may be a marker and driver of cardiometabolic risk factors with interventions that are actionable by cardiologists. Leptin subnetwork analysis demonstrates a statistically significant role for ethnoculturally and socioeconomically appropriate lifestyle intervention in cardiovascular disease. Emergent mechanistic components and potential diagnostic or therapeutic targets include hexokinase 3, urocortins, clusterin, sialic acid-binding immunoglobulin-like lectin 6, C-reactive protein, platelet glycoprotein VI, albumin, pentraxin 3, ghrelin, obestatin prepropeptide, leptin receptor, neuropeptide Y, and corticotropin-releasing factor receptor 1. Emergent associated symptoms include weight change, eating disorders, vascular necrosis, chronic fatigue, and chest pain. Leptin-targeted therapies are reported for lipodystrophy and leptin deficiency, but they are investigational for leptin resistance, obesity, and other chronic diseases.

Obesity and cardiovascular disease (CVD) are global problems that are intertwined with high levels of complexity [1]. Using the GBD (Global Burden of Disease) study data, more than two-thirds of deaths in patients with overweight/obesity were due to CVD [2]. Successful strategies to decipher key mechanistic drivers of obesity and tactics for management based on molecular targeting generally parse out genetic and environmental risk factors. The findings of Castillo et al. [3] affirm this interaction between genetics and the environment, wherein selection patterns for certain obesity gene risk variants depend on the ambient obesogenic environment (based on comparisons between ancestral hunter-gatherers before migration from Africa versus agriculturalists after migration from Africa). Key environmental components of the obesity problem across the globe and influenced-by-ethnocultural factors include food supply and stressors (particularly in economically disadvantaged populations), governing allostatic load and behavior [4,5]. Thus, food-seeking behavior is a principal determinant of body composition and consequent cardiometabolic risk.

Leptin is a central physiological component of food-seeking behavior and will be discussed in the context of the global obesity epidemic and prevention of CVD. Hence, the strategy of this review is to present a physiological model of food consumption and leptin signaling, primarily based on experimental results from animal studies, and an interpretation using network analysis of complex relationships. Results of this network analysis will be translated in the context of cardiometabolic risk to enrich complicated clinical decision making when confronted with different geographic and ethnocultural presentations of obesity.

LEPTIN BASICS

In the context of cardiometabolic risk, food consumption plays a critical role that needs to be teased out from a complex network of interactions, feedback loops, varying time scales, and subtle endpoints. Among the numerous players, leptin stands out as among the most important and deserving of focused analysis. Leptin figures prominently in an adipocyte-cardiovascular-lifestyle network [6] and merits more detailed analysis, especially as it relates to appetite and energy balance. In a plenary lecture, Dr. Jeffrey Friedman—first to identify the leptin gene in 1994—commented that "mutations in leptin or other components of the neural circuit controlling body weight account for ≈ 10−15% of morbid human obesity" [7].

Evolutionary biology helps the understanding of complex pathophysiology, particularly feeding behaviors. On a macrophysiological scale [8], humans evolved in an adverse environment with scarce food and a metabolic imperative for efficiency, consequently developing an up-regulated appetite during periods of starvation. However, across the globe, leptin physiology varies as different environments have exerted different evolutionary pressures on obesity gene risk variants. Though most surveillance studies draw correlative information using body mass index (BMI), this anthropometric has many flaws, which have led to proposals for new diagnostic terms, such as adiposity-based chronic disease (ABCD) [9]. For example,

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TABLE 1. Major historical events in leptin research

Date [Reference]	Event
1950 [29]	*ob/ob* (*Lep*^{ob}) mouse: obese, hyperphagia, mild diabetes symptoms
1966 [30]	*db/db* (*Lepr*^{db}) mouse: obese, hyperphagia, severe diabetes symptoms
1969 [31], 1973 [32]	Murine leptin deficiency (*ob/ob*) and resistance (*db/db*)
1994 [33]	Leptin cloned and found to be produced in white adipose tissue
1997 [34]	Leptin expressed in many tissues
1998 [35]	Leptin produced by chief cells in stomach
1999 [36]	Beneficial effects of leptin therapy to child with congenital leptin deficiency
2001 [37]	Primary neuronal leptin targets identified
2005 [38]	Pleiotropic effect on immune system
2010 [39]	Other peripheral leptin targets identified

in Southeast Asians, there are higher leptin levels for a given BMI (presumed to reflect a "leptin-resistant" state) compared with other ethnicities [10]. In another study on Asians, leptin receptor polymorphisms are associated with cancer susceptibility (dominant genetic model) [11]. In the Buryat (a Mongol subpopulation of Southern Siberia), leptin is associated with reduced fat oxidation [12]. In Iran, Esteghamati et al. [13] found inverse relationships between leptin and physical activity, independent of adiposity. In Japanese women with higher depression scores, compared with those with lower depression scores, leptin levels were lower [14]. In another study of Japanese subjects (men and women), leptin was inversely related to the consumption of a Westernized breakfast pattern (increased confectionaries, bread, milk, and yoghurt, with lower rice and alcohol content) [15]. Also, leptin is elevated in Japanese adults with early atherosclerosis (by aortic fluorodeoxyglucose F 18 uptake [16]) and in those who gain weight independently of BMI [17]. In Europe, among the Romani subpopulation in Eastern Slovakia, leptin levels were positively correlated with BMI [18]. In elderly Italians, leptin was associated with cognitive decline [19]. In the CARDIA (Coronary Artery Risk Development in Young Adults) study, various associations were identified among adipokine gene variants and obesity-related phenotypes, with the most prominent involving the *LEP* gene in African Americans [20]. In the METS (Modeling the Epidemiologic Transition Study) of 5 cohorts of African descent in various levels of epidemiologic transition (rural Ghana, periurban South Africa, the Seychelles, urban Jamaica, and metropolitan Chicago, IL, USA), leptin was not correlated with indices of glucose metabolism [21]. However, in Tanzanian pregnant women, low leptin levels (leptin is also produced by the placenta) were associated with intrauterine growth restriction [21]. In an impoverished Mexican American community in Starr County, TX, USA, with uncontrolled type 2 diabetes, lifestyle changes (healthy eating, weight loss, and physical activity) did not have a significant overall effect on leptin [22].

Food consumption is determined by goal-directed behaviors based on pleasure/reward, especially in terms of "learning," "liking," and "wanting," and mediated in large part by mesolimbic dopaminergic neurotransmission and hypothalamic triglyceride sensing [23]. The endocrine system has been implicated in a variety of evolutionary theories of obesity, including the thrifty gene, drifty gene, and thrifty phenotype hypotheses [24]. Hormones are well suited to mediate both behavioral and physiological components of energy balance, but this also implicates unwanted, maladaptive, or nonadaptive functions that are "dragged along" as pleiotropic gene actions coevolve [25]. Leptin is a pleiotropic stress-responsive hormone serving as an ancient anorexigen, immunomodulator, and growth factor, with signaling pathways and neural substrates conserved over 350 million years, having a key physiologic role during starvation, and now situated as a central player in cardiometabolic networking research [6,26-28].

In short, governed by a physiological set point ("adipostat"), rising leptin levels decrease energy intake, increase energy use, and result in decreased energy stores, or adiposity. Inversely, reductions in circulating leptin augment caloric intake and diminish energy expenditure, resulting in positive energy balance. Despite natural and intuitive extrapolations that leptin would be a useful anti-obesity medication, accumulating scientific knowledge over time has led to a more detailed model of leptin signaling and clinical targeting (Table 1) [29-39]. The majority of knowledge about the molecular actions of leptin derives from animal studies. Although there are substantial differences between rodent and human leptin physiology, leptin is primarily expressed in white adipose tissue [33], acts primarily in the central nervous system [40], and has pleiotropic effects in all species.

Leptin levels exhibit a nocturnal peak and multiple smaller ultradian pulses over 24 h [41,42]. During periods of overfeeding or underfeeding, diurnal leptin levels will rise and fall, reflecting the cumulative energy balance over a period of several days [43,44]. Thus, leptin regulates energy intake in response to cumulative alterations in energy balance and not in a manner that acutely affects caloric intake or satiety within the course of single meals.

Serum leptin levels increase with progressive obesity in both men and women. For any given measure of obesity, leptin levels are higher in women than in men, perhaps reflecting a higher percentage of body fat in female subjects. However, there appear to be additional sex-specific effects because leptin levels increase at a more rapid rate in female subjects as a function of increasing BMI or percentage of body fat [45]. Because higher leptin levels physiologically act to reduce adipose mass, the increase in leptin levels with progressive obesity reflects a state of leptin resistance. But unlike rodents, there is no clear relationship between circulating leptin levels and energy expenditure in humans [45]. Therefore, in the regulation of