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

Jeffrey I. Mechanick*,†, Shan Zhao‡, W. Timothy Garvey§,‖

New York, NY, USA; Redondo Beach, CA, USA; and Birmingham, AL, USA

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,

Dr. Mechanick has received honoraria from Abbott Nutrition International for program development. Dr. Garvey has received consulting fees from Novo Nordisk, Eisai, Janssen, Vivus, Takeda, AstraZeneca, Alexion, and Merck. Dr. Zhao reports no relationships that could be construed as a conflict of interest.

From the *Division of Cardiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; †Division of Endocrinology, Diabetes, and Bone Disease, Icahn School of Medicine at Mount Sinai, New York, NY, USA; ‡Basepaws Inc., Redondo Beach, CA, USA; §Department of Nutritional Sciences and Diabetes Research Center, University of Alabama at Birmingham, Birmingham, AL, USA; and the ‖Geriatric Research Education and Clinical Center, Birmingham Veterans Affairs Medical Center, Birmingham, AL, USA. Correspondence: J. I. Mechanick (jeffrey.mechanick@mountsinai.org).

GLOBAL HEART

VOL. 13, NO. 2, 2018
ISSN 2211-8160/$36.00.
https://doi.org/10.1016/j.gheart.2017.10.003

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

human adipose tissue mass, leptin resistance primarily involves reduction of energy intake (i.e., decreased appetite and food consumption).

The hyperleptinemia that accompanies human obesity is predictably the result of a primary defect in leptin receptor (LepR) signaling and/or downstream effector systems that impair hormone action. LepR is primarily found in the cytoplasm; high receptor specificity is conferred by constitutive internalization of membrane-bound receptors coupled with multiple regulatory steps controlling recycling rates and ectodomain shedding [46]. LepR trafficking is regulated in part by endospanin 1 (from alternative splicing of the *db* gene) and the ubiquitin ligase ring finger protein 41 [46,47]. Another contributor to hyperleptinemia is saturation of blood brain barrier (BBB) transporters, which are up-regulated by epinephrine, glucose, ethanol, and insulin, and down-regulated by triglycerides [48-50]. Moreover, tanycytes (specialized glial cells) regulate BBB plasticity via nutrient-dependent release of vascular endothelial growth factor A [51].

Leptin is a 4-helix bundle cytokine that binds to LepR, a single membrane spanning class-1 cytokine receptor with multiple isoforms resulting from alternative splicing [37,52,53]. Among the 6 LepR isoforms (secreted, short, and long forms), the long-form LepRb is unique by having a large intracellular domain with putative Janus kinase/signal transducer and activator of transcription (JAK/STAT) binding sites, conferring strong intracellular signal transduction and responses [52,54]. The secreted LepRe form does not exert an intracellular signal, but it serve as a plasma leptin-binding protein [55]. The short LepRa, -c, -d, and -f forms exert weak intracellular signal transduction and transfer leptin through the BBB to the hypothalamus [52,56].

LEPTIN EFFECTS ON THE BRAIN

Generally speaking, energy stores (represented as adiposity) are regulated by a classic negative feedback loop, wherein increased leptin from adipose tissue acts in the hypothalamus to inhibit appetite and increase metabolic rate, leading to a reduction in adiposity. This is accomplished through changes in leptin production, leptin action, and modulating signals, particularly those leading to a leptin-resistance state. Over time, these processes, left unchecked, can evolve into an ABCD state of excess energy storage: a contemporary diagnostic framework to identify obesity in less-stigmatizing, but more pathophysiologically relevant terms of fat mass, fat distribution, and adipocyte function [9]. Key drivers in the context of ABCD and leptin include food overconsumption (driven by both environmental factors and pathophysiological hormonal regulation), insulin resistance, leptin resistance, and inflammation. Contributory drivers include mood and behavior, various abnormalities in intermediary metabolism, physical inactivity, abnormal sleep, and certain eating patterns. The mechanisms by which all these drivers interact can be represented on a molecular scale.

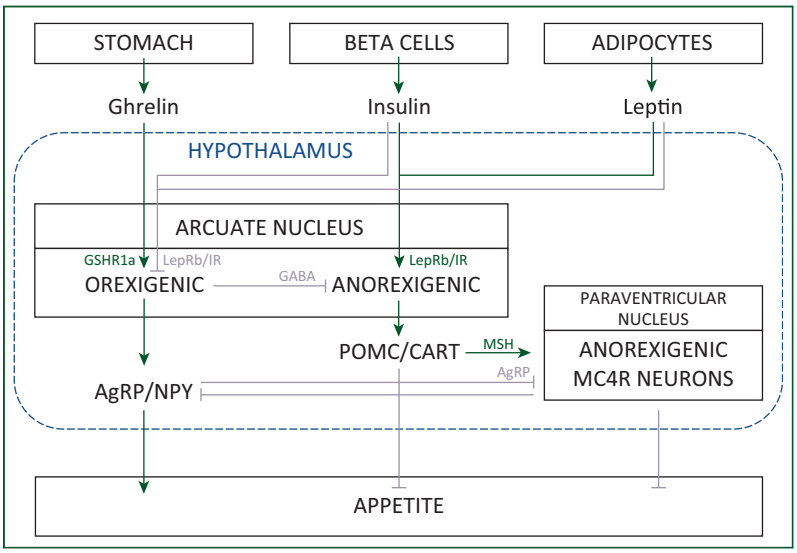

FIGURE 1. Leptin actions in key hypothalamic nuclei. Green arrows indicate stimulation; purple lines indicate inhibition. AgRP, agouti gene-related protein; CART, cocaine- and amphetamine-related transcript; GABA, γ-aminobutyric acid; GSHR1a, growth hormone secretagogue receptor 1a; IR, insulin receptor; LepRb, leptin receptor b; MC4R, melanocortin 4 receptor; MSH, melanocyte-stimulating hormone; NPY, neuropeptide Y; POMC, pro-opiomelanocortin.

The principal targets of leptin are in various hypothalamic regions: arcuate nucleus (ARC); dorsomedial nucleus; lateral hypothalamic area; medial basal hypothalamus; paraventricular nucleus (PVN); periventricular nucleus; supraoptic nucleus; and ventromedial nucleus of the hypothalamus. In the ARC nucleus of the hypothalamus, there are 2 functionally distinct leptin-dependent neuronal populations involved with appetite and projecting to other hypothalamic and limbic system areas:

1. Anorexigenic. These neurons express pro-opiomelanocortin (POMC) and cocaine- and amphetamine-related transcript (CART) and are stimulated by leptin to secrete α-melanocyte-stimulating hormone, which binds surface melanocortin 4 receptor on PVN neurons. This initiates anorexigenic neurotransmission to higher cortical centers. POMC/CART neurons are also stimulated by other anorexigenic hormones, such as insulin, amylin, glucagon-like peptide 1 (GLP-1), and peptide YY (PYY) to amplify the anorexigenic effect.
2. Orexigenic. These neurons express agouti gene-related protein (AgRP) and neuropeptide Y (NPY) and are stimulated by ghrelin to release NPY, which binds cognate receptors on PVN neurons to promulgate orexigenic neurotransmission to higher cortical centers. AgRP is also released by these neurons and then acts on POMC/CART neurons to inhibit α-melanocyte-stimulating hormone release and amplify the orexigenic effect. Importantly, leptin inhibits release of both NPY and AgRP, which, when

combined with leptin-stimulated POMC/CART neurons, even further amplifies this anorexigenic effect.

Overall, leptin provides strong integrative metabolic input to the core feeding neuraxis, primarily at the level of the ARC: leptin activates anorexigenic POMC/CART; inhibits orexigenic AgRP/NPY; opposes ghrelin signaling; synergizes with insulin signaling; and subsequently modulates PVN anorexigenic melanocortin 4 receptor neurons (Figure 1) [57].

However, leptin also affects the mesolimbic dopaminergic reward/motivation system, which is responsible for locomotor activity, food-seeking behavior, and drug-seeking behavior [58]. LepRb expressing neurons in the ventromedial nucleus of the hypothalamus express steroidogenic factor 1 and pituitary adenyl cyclase activating protein that mediate weight gain with high-fat diets through effects on compensatory increases in energy expenditure [59]. Ventromedial nucleus of the hypothalamus, in addition to ARC LepR neurons, also influence glucose homeostasis [60]. Moreover, LepR-positive lateral hypothalamic area neurons, mediating cognitive and arousal inputs, project to the mesolimbic system subpopulation containing neurotensin, which inhibits neighboring hypocretin (orexin)- and galanin-expressing neurons [61]. Significantly, this leptin-dependent lateral hypothalamic area -mesolimbic network modulates the hypothalamic-pituitary-adrenal stress response [62].

Leptin also activates neuronal centers in the brainstem. This includes the dorsal motor nucleus of the vagus nerve and the nucleus tractus solitarius, which receive interoceptive satiety signals from the gastrointestinal tract (such as GLP-1 and cholecystokinin modulation of vagal afferent neurons) [63,64]. Other regions such as the caudal brain stem also express LepR and contribute to the inhibitory effect of leptin on food intake [65]. Based on functional magnetic resonance imaging, leptin may be responsible for integration and enhanced functional connectivity of these various neural pathways involved with food cues and weight maintenance [66]. Evidence also indicates that leptin action in the brain stem may help regulate autonomic nervous system activity [67] and may contribute to baroreflex suppression during aging [68].

LEPTIN SIGNAL TRANSDUCTION IN THE BRAIN

There are several key pathways for LepRb signal transduction with crosstalk among biochemical and molecular markers, adaptor proteins, and other regulatory mechanisms (Figure 2). The principal pathway is JAK/STAT [52,69-71]; however, leptin action involves many other interdigitating pathways that modulate the LepRb-JAK/STAT-POMC/AgRP/NPY axis.

JAK2 tyrosine kinase phosphorylates LepRb (via Tyr1138), leading to STAT1/3/5/6 activation and most importantly, STAT3 dimerization [52,72,73]. Other JAK-mediated pathways include protein tyrosine phosphatase, nonreceptor type 1/11, mitogen-activated protein kinase—extracellular signal-regulated kinases (ERK), growth factor receptor-bound protein 2 (via Tyr985), Src homology-2 domain B1 adaptor protein (SH2B1) (via Tyr813 and Tyr985), and insulin receptor substrate (IRS)—phosphoinositide 3-kinase (PI3K)—protein kinase B—forkhead box protein 01 [52,73-77]. In addition, rho kinase 1 activates JAK2 and consequently increases STAT3 and forkhead box protein 01 activation [78]. Factors in these pathways (e.g., forkhead box protein 01, ERK, and STAT3) translocate to the nucleus, bind deoxyribonucleic acid, and influence target genes (e.g., AgRP, POMC, and NPY) that modulate food consumption, energy homeostasis, and even fertility, growth, and glucose metabolism [52,79,80]. Leptin also inhibits 5′ adenosine monophosphate-activated protein kinase (AMPK) (an important factor that regulates insulin secretion), leading to decreased appetite [81]. Physiologically, AMPK is influenced by upstream liver kinase B1, Ca^{++}/calmodulin-dependent protein kinase β, and energy/fuel (adenosine monophosphate—adenosine triphosphate ratio) signals (activated by fasting; deactivated by feeding), but AMPK is also inhibited by leptin-induced mechanistic target of rapamycin/S6 kinase signaling [82-85]. Leptin also increases *SOCS3* gene expression via LepRb Tyr1138, which through negative feedback, inhibits leptin-STAT3 signaling and fine-tunes this important hypothalamic network [52,86]. Hypothalamic leptin-STAT3 signaling is also modulated by low-density lipoprotein receptor-related protein 1 and 2, which mediate leptin-LepR complex endocytosis [52,87,88]. Although there is another POMC neuron population in the nucleus tractus solitarius, there is no demonstrable leptin-STAT3 signaling in this population [89].

IRS and PI3K are molecular components of an important hypothalamic pathway involving insulin receptor signal transduction and mediation of acute leptin effects. Specifically, leptin increases PI3K signaling in POMC neurons (producing an anorectic effect via α-melanocyte-stimulating hormone) and decreases PI3K signaling in AgRP neurons (also producing an anorectic effect via a decreased orectic effect of AgRP) [52,80,90]. SH2B1 increases JAK2-mediated IRS phosphorylation and PI3K activity, thus integrating the physiological messages from leptin and insulin [74,91,92]. Moreover, leptin and adiponectin act synergistically through PI3K activation, independent of AMPK, to activate ARC POMC neurons [93]. Other factors that modulate hypothalamic leptin signaling and affect energy balance and fat mass are the tumor suppressor phosphate and tensin homolog [94] and ciliary gene products: Bardet-Beidel syndrome proteins forming the Bardet-Beidel syndrome complex and retinitis pigmentosa guanosine triphosphatase regulator interacting protein 1 like (regulated by cut-line homeobox 1 and the *FTO* gene) [95-97]. It is very interesting that primary hypothalamic cilia sense metabolic signals and also that leptin promotes ciliary elongation via intraflagellar transport gene transcription and F-actin rearrangement [98].

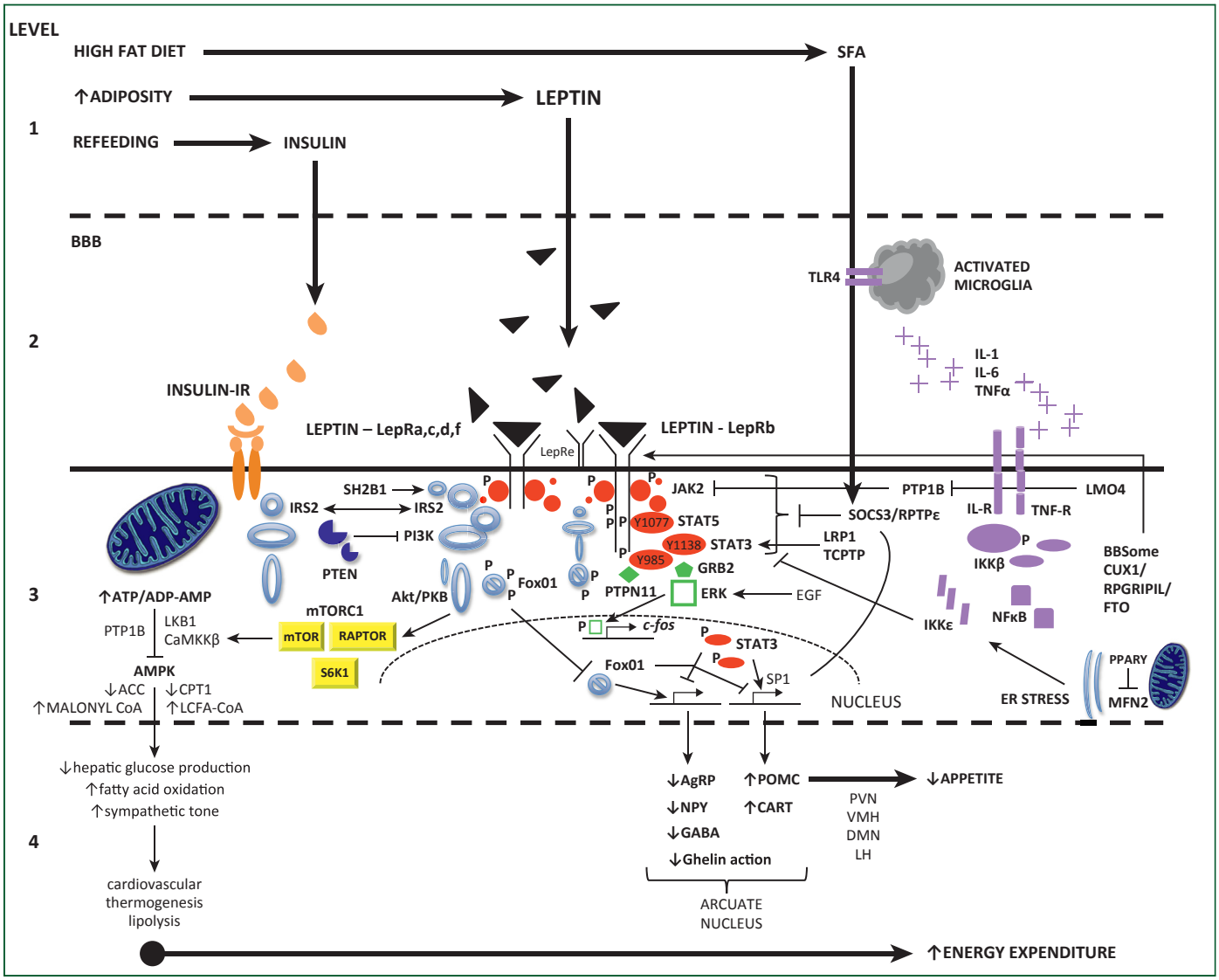

FIGURE 2. Four functional levels and multiple key hypothalamic ARC pathways for LepR signaling. Level 1—clinical circumstances and systemic circulation; level 2—circulating signals gaining entry to the central nervous system; level 3—hypothalamic arcuate nucleus LepR signaling and other regulatory factors; and level 4—central nervous system and peripheral and clinical sequelae. Afferent pathways are incoming with respect to the LepR. Efferent pathways are outgoing with respect to the LepR. Various colors of adaptor proteins indicate signaling pathways, which are described in text. ACC, acetyl-CoA carboxylase; Akt, protein kinase B; ADP, adenosine diphosphate; AMP, adenosine monophosphate; AMPK, 5′ adenosine monophosphate-activated protein kinase; ATP, adenosine triphosphate; BBB, blood brain barrier; BBSome, Bardet-Biedl syndrome complex; CaMKKβ, Ca^{++}/calmodulin-dependent protein kinase kinase β; CoA, coenzyme A; CPT1, carnitine/palmitoyl-transferase 1; CUX1, cut-line homeobox 1; DMN, dorsomedial nucleus; EGF, epidermal growth factor; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinases; Fox01, forkhead box protein 01; FTO, fat mass and obesity-associated protein; GRB2, growth factor receptor-bound protein 2; IKK, inhibitor of κ-light-chain enhancer of activated B kinase; IL, interleukin; IRS2, insulin receptor substrate 2; JAK2, Janus kinase 2; LCFA, long-chain fatty acid; LH, lateral hypothalamus; LKB1, liver kinase B1; LMO4, LIM domain only 4; LRP1, low-density lipoprotein receptor-related protein 1; MFN, mitofusin; mTORC1, mechanistic target of rapamycin complex (complex 1) 1; NFκB, nuclear factor κ-light-chain enhancer of activated B cells; P, phosphate; PI3K, phosphoinositide 3-kinase; PKB, protein kinase B; PPARγ, peroxisome proliferator-activated receptor γ; PTEN, phosphatase and tensin homolog; PTP, protein tyrosine phosphatase; PTPN11, protein tyrosine phosphatase, nonreceptor type 11; PVN, paraventricular nucleus; RPGRIPIL, retinitis pigmentosa guanosine triphosphatase regulator interacting protein-1 like; RPTPε, receptor-like protein tyrosine phosphatase ε; S6K1, S6 kinase 1; SFA, saturated fatty acid; SH2B1, Src homology-2 domain B1 adaptor protein; SOCS3, suppressor of cytokine signaling 3; SP1, specificity protein 1; STAT, signal transducer and activator of transcription; TCPTP, T cell protein tyrosine phosphatase; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor α; VMH, ventromedial nucleus of the hypothalamus; Y985, tyrosine-985 motif; Y1077, tyrosine-1077 motif; Y1138, tyrosine-1138 motif; other abbreviations as in Figure 1.

TABLE 2. Peripheral effects of leptin

Tissue	Effect	Reference
Adipocyte	↑ Insulin sensitivity (antilipolysis; beiging)	[143]
	↑ Oxygen consumption, thermogenesis, UCP1 and UCP2	[37,144]
Adrenal	↓ Cortisol	[37]
Bone	↑ Marrow adipogenesis via LepR on mesenchymal stromal cells; ↑ PTH	[145,146]
	↓ Osteoblastogenesis	
Immunity	↑ Shift T helper to T_h1 and T_h17 responses (↑ autoimmunity)	[147,148]
Intestine	↑ Fructose/butyrate absorption	[149]
	↓ Glucose/galactose/amino acid absorption	[149,150]
Kidney	↑ Albuminuria via ↑ TGFβ1—AMPK and ↓ megalin; ↑ CKD	[151,152]
	↓ eGFR	[153]
Liver	↓ Gluconeogenesis	[154]
Muscle	↑ UCP2 and UCP3, fatty acid oxidation	[37]
Pancreas	↑ UCP2, fatty acid oxidation	[37]
	↓ Insulin	[37]
Skeletal muscle	↑ Increased insulin sensitivity (glucose uptake/oxidation)	[155]
Tumor biology	↑ Endothelial cell proliferation and transformation via VEGFR/Notch	[156]

↑, increased; ↓, decreased; AMPK, 5′ adenosine monophosphate-activated protein kinase; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LepR, leptin receptor; PTH, parathyroid hormone; TGFβ1, transforming growth factor β1; UCP, uncoupling protein; VEGFR, vascular endothelial growth factor receptor.

The above-mentioned principal leptin signaling pathways are further modulated by yet another layer of complexity. Various signal transduction pathways and their respective adaptor proteins are itemized next that, in aggregate, produce varying degrees of leptin resistance:

- Protein tyrosine phosphatases (PTP):
  - PTP-1B in ARC, dorsomedial nucleus, and ventromedial nucleus of the hypothalamus via JAK2/STAT3 and α2-AMPK signaling; inhibited by SH2B1, LIM domain only 4, and certain cholesterol metabolites;
  - Receptor-like PTPε via negative feedback with leptin and JAK2; and
  - T-cell PTP via STAT3, SH2B1, and phosphate and tensin homolog signaling [91,99-104].
- Inhibitor of κ-light-chain enhancer of B kinase—-nuclear factor κ-light-chain enhancer of activated B cells signaling: in the medial basal hypothalamus and in response to inflammatory cytokines (e.g., interleukin 1 and 6 and tumor necrosis factor α) resulting from lipopolysaccharide or saturated fatty acid interactions with Toll-like receptor 4 in activated hypothalamic microglia, leading to
  - discordant effects: obesity-promoting; leptin-resistant; insulin-resistant; and obesity-inhibiting effects in AgRP (orexigenic) neurons;
  - leptin sensitivity in POMC (anorexigenic) neurons; and
  - decreased food consumption from decreased AMPK activity [105-109].
- Mitochondria-endoplasmic reticulum disruption: in POMC neurons and produces endoplasmic reticulum stress, associated with insulin- and leptin-resistance (increased disruption with peroxisome proliferator-activated receptor γ; decreased disruption with mitofusin 1 and 2 [in POMC but not AgRP neurons]) [110].
- Unfolded protein response signal molecules: protein kinase R-like endoplasmic reticulum kinase, inositol-requiring enzyme 1, spliced form of X-box binding protein 1s, glucose-regulated/binding immunoglobulin protein 78, and CCAAT-enhancer-binding protein homology protein; resolves the effects of endoplasmic reticulum stress on STAT/protein kinase B/LepR and insulin receptor pathways [106,111-115].
- Golgi apparatus: negative regulation of post-translational processing of LepR by leptin receptor overlapping transcript exon 2; leptin receptor overlapping transcript also regulates growth hormone receptors and is inversely related with type 2 diabetes [116].
- c-Jun N-terminal kinase signaling pathway and protein kinase θ: in ARC AgRP/NPY and other dorsomedial hypothalamic neurons; both of which impair insulin receptor and LepR signaling [107,117].
- Cyclic adenosine monophosphate—exchange proteins directly activated by cyclic adenosine monophosphate—Ras-related protein 1 cascade: impairs STAT3 and S6 kinase signaling via suppressor of cytokine signaling 3 and PTP1B-inducing leptin resistance in POMC neurons [118,119].

Many of these discordant effects in leptin signal pathways, with some overactive and others underactive, can account for obesity-related complications, such as hypertension [120].

Leptin promotes satiety through direct effects on appetite suppression, but also exerts indirect effects on hedonic responses to feeding [121] and synergistic effects with other gastrointestinal hormones, such as cholecystokinin,

TABLE 3. Cardiovascular relationships of leptin

Effect	Reference
Atherosclerotic plaque burden	[159]
Cardioprotective effects	[160-163]
Cardiovascular disease marker	[164,165]
Endothelial dysfunction	[166]
Hypertension	[167,168]
Left ventricular diastolic dysfunction	[169]
Low-density lipoprotein receptor—decreased expression	[170]

Clinical correlates of leptin used for the adipokine-cardiovascular network are provided in Mechanick et al. [6].

PYY (via the NPY receptor) and GLP-1, centrally and peripherally [122-126]. In fact, a negative feedback loop is suggested by leptin-mediated potentiation of peripheral insulinotropic GLP-1 effects [126] and decreased leptin levels after GLP-1 administration [123] (though in humans, liraglutide [a GLP-1 receptor agonist] blunts the leptin decline with weight loss) [127]. Furthermore, leptin exerts additional direct and indirect ameliorating actions on dysfunctional hypothalamic-pituitary-gonadal, -somatotropic, -adrenal, and -thyroid axes [128].

Although it is clear that leptin is a critical component in a matrix of molecular interactions regulating metabolism, leptin also appears to play a central role in the formation of these interacting networks during growth and development. For example, leptin has been shown to alter development of hypothalamic pathways during fetal development [129,130]. Neonatal leptin is a neurotrophic factor that specifically promotes development of projections from the ARC to the PVN in the hypothalamus [130]. These neuronal pathways regulate feeding circuits that determine the set point around which satiety hormones regulate body weight and are primarily formed during neonatal life [131]. Intriguingly, recent reports suggest that neonatal ghrelin signaling also contributes to early organization of these critical feeding circuits [132]. These early-life effects of leptin can affect body composition and lead to the development of central resistance to leptin and insulin signaling in later life [133-139]. In a similar manner, leptin exerts a trophic effect on the gonadal-hypothalamic-pituitary axis helping to regulate dynamic relationships among gonadotropins and sex steroids, ovulation, and the onset of puberty [140-142].

PERIPHERAL AND CARDIOVASCULAR EFFECTS OF LEPTIN

Leptin has a host of actions on a variety of tissues other than the brain and hypothalamus (Table 2) [37,143-156]. For example, leptin decreases ectopic fat, increases adipocyte insulin sensitivity and is antilipolytic, induces adipocyte beiging via PYY/NPY, increases myocyte insulin sensitivity via insulin-like growth factor binding protein 2, reduces hepatic gluconeogenesis, and when secreted by gastric chief cells, interacts with intestinal LepR cells to reduce glucose absorption (via protein kinase C−p38 mitogen-activated protein kinase−PI3K−ERK activation) [150,157,158]. These peripheral effects also participate in networked interactions that influence hypothalamic signaling.

Among these peripheral actions, leptin also has important effects on the cardiovascular system (Table 3) [6,159-170]. However, due to networking effects and an evidence base primarily derived from observational associations instead of causal demonstrations, it is not clear whether leptin is a major, or even minor driver of metabolic syndrome or CVD, or whether it is simply a marker [6,164,165]. Endothelial dysfunction is associated with disturbances in leptin physiology. For instance, leptin is positively associated with soluble intercellular adhesion molecule 1 and soluble vascular cell adhesion molecule 1 elevations, possibly through f-actin, protein kinase B/glycogen synthase kinase 3β, and β-catenin pathways [166]. Thus, increased levels of leptin with chronic kidney disease may explain subsequent development of endothelial dysfunction. Elevated leptin expression in aortic root/coronary artery perivascular adipose tissue was

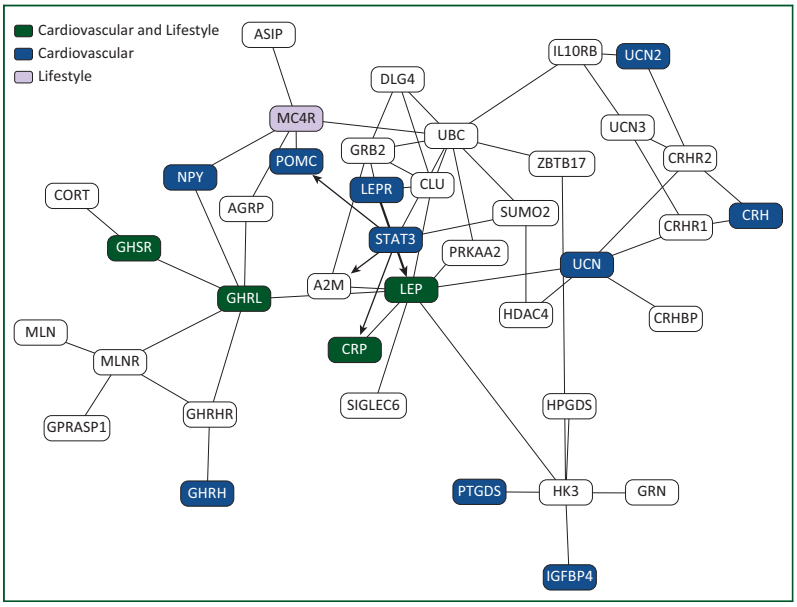

FIGURE 3. The leptin-cardiovascular-lifestyle subnetwork. Enriched leptin influence subnetwork from the human interactome with lifestyle only, cardiovascular only, and both cardiovascular- and lifestyle-related genes labeled in purple, blue, and green, respectively. Genes were associated with cardiovascular and lifestyle through the GeneRIF database [177]. They were enriched based on preferential downstream influences as described in the text. All node labels are gene symbols. Arrows denote a directed relationship; lines denote an interaction.

TABLE 4. Potential network effects of targeting leptin

Ranking	Symptom	Score	Ranking	Symptom	Score
1	Emaciation	12.61	11	Intestinal hemorrhage	1.08
2	Loss of appetite	11.32	12	Chronic fatigue syndrome	0.68
3	Underweight	2.29	13	Delirium	0.62
4	Failure to thrive	2.06	14	Cachexia	0.47
5	Cramp	1.92	15	Systemic infection	0.47
6	Sleep disturbance	1.91	16	Joint pain	0.47
7	Decreased appetite	1.84	17	Wasting	0.45
8	Vascular necrosis	1.36	18	Knee pain	0.33
9	Insomnia	1.30	19	Abnormal behavior	0.32
10	Chest pain	1.17	20	Anorexia	0.32

Ranked listing of symptoms based on network effects of targeting leptin from the human interactome. Symptoms were based on the Symptoms Ontology database from University of Maryland [178]. Symptoms were associated to genes through the GeneRIF database [177] and enriched based on preferential downstream influences as described in the text.

TABLE 5. Leptin therapy in clinical conditions

Clinical Condition	Role of Leptin [Reference]
Congenital leptin deficiency	Rare, but consider in childhood obesity; metreleptin* decreases appetite and fat mass [197]
Dementia	Inferential effects of leptin on neural plasticity [198]
Depression	Leptin may modulate antidepressant therapy [199]
Diabetes, type-2	Mild A_{1c} improvements independent of weight loss, with saturable leptin signaling pathways [200]
Hypothalamic amenorrhea	Metreleptin treatment in this hypoleptinemic state restores menstruation, improves bone formation, and normalizes estrogen, thyroid hormone, and IGF-1 levels [201]
Lipodystrophy†	Metreleptin treatment in this hypoleptinemic state improves insulin sensitivity, dyslipidemia, and reduced central fat mass [202]
Nonalcoholic fatty liver disease	Inferential effects of leptin on insulin action and the metabolic syndrome [203]
Obesity	Metreleptin with/without pramlintide for prevention of weight regain [204,205]
Rabson-Mendenhall syndrome	Insulin receptor mutation and extreme insulin resistance; metreleptin improves A_{1c} via weight loss [206]

IGF-1, insulin growth factor 1.

*Metreleptin is a methionyl human leptin; Myalept (Aegerion Pharmaceuticals, Cambridge, MA, USA) is only US Food and Drug Administration—approved—under risk evaluation and mitigation strategies—for nonhuman immunodeficiency virus generalized lipodystrophy and compassionate use with congenital leptin deficiency.

†Lipodystrophy is a rare condition with absent to low body fat, low leptin levels, increased appetite, and ectopic lipid storage in muscle/liver, with serum hyperlipidemia and type 2 diabetes.

associated with angiogenesis and inflammation and may contribute to atherosclerotic plaque burden [159]. Leptin is also associated with elevated sympathetic nervous system activity and hypertension [167], left ventricular diastolic dysfunction in patients with coronary artery disease supporting the relationship of obesity with congestive heart failure [169], and reductions of the low-density lipoprotein receptor via the protein convertase subtilisin/kexin type 9 pathway [170]. The relationship of leptin with hypertension appears to be highly complex with current hypotheses focusing on stretch-induced vascular smooth muscle hypertrophy involving crosstalk among leptin synthesis, rho/rho kinase, Ca^{2+}/calcineurin/nuclear factor of activated T cells, and ERK1 and ERK2 pathways [168].

On the other hand, the longitudinal MESA (Multi-Ethnic Study of Atherosclerosis) demonstrated a protective effect of leptin on left ventricular structure and function [171]. In specific studies, leptin is negatively associated with cardiac ischemia, reperfusion injury, cardiac hypertrophy, and cardiac lipotoxicity, together supporting a cardioprotective effect [160-163].

ANALYSIS OF THE LEPTIN-CARDIOVASCULAR-LIFESTYLE SUBNETWORK

Network analysis offers a different way to understand the effects of targeting genes and proteins within a complex array of interactions, in contrast to an approach that informally considers many different findings from medical publications [172]. Network analysis is hypothesis-generating and has been used to better understand arrhythmias [173], drug side effects [174], cancer [175], obesity [5], diabetes [5], and CVD [176]. New information derived from network analysis can then be translated into enhanced recommendations for clinical decision making.

By coupling network analysis with database text mining (e.g., GeneRIF [177]), genes can be associated with specific terms, such as "cardiovascular" and "lifestyle." In our previous adipokine-cardiovascular-lifestyle analysis, certain proteins within the human interactome network were identified that differentially traversed a random walk from leptin [6,174]. These same proteins can now be ranked based on their degree of difference, with the top 40 proteins selected for a subnetwork and labeled by their GeneRIF association with "cardiovascular," "lifestyle," or both terms (Figure 3) [177].

It is particularly noteworthy that network analysis, using the Fisher exact test, verified existing knowledge of the role for leptin and also demonstrated that both "cardiovascular" ($p = 1.74 \times 10^{-10}$) and "lifestyle" ($p = 1.97 \times 10^{-6}$) were significantly enriched in the leptin subnetwork. Since "cardiovascular" and "lifestyle" also had significant overlaps within the leptin subnetwork ($p = 0.0425$), leptin targeting may be accomplished through lifestyle modifications. Furthermore, other proteins—hexokinase 3, urocortins, clusterin, and sialic acid-binding immunoglobulin-like lectin 6—were identified as promising targets for regulating the biological effects of leptin.

To explore potentially unrecognized but desirable clinical outcomes from leptin targeting, the Symptoms Ontology database [178] was used to identify specific symptoms relating to any human disease, and GeneRIF [177] was used to associate these symptoms with specific genes. Network analysis was applied again to identify and then rank symptoms that were differentially regulated by leptin according to degree of involvement (Table 4) [177,178].

Symptoms related to weight change and general eating disorders were strongly associated with the leptin subnetwork. Other associations included vascular necrosis symptoms and chronic fatigue syndrome, which have been previously reported with respect to mechanisms [179,180], as well as chest pain and anorexia, for which mechanisms have not been well defined. However, in the case of chest pain, C-reactive protein, platelet glycoprotein VI, albumin, and pentraxin-3 emerged as particularly interesting associated proteins. In the case of anorexia, ghrelin, obestatin prepropeptide, LepR, NPY, and corticotropin-releasing factor receptor-1 were attractive mechanistic components.

CLINICAL TRANSLATION FOR OBESITY AND CARDIOMETABOLIC RISK MITIGATION

The principal clinical context of leptin pathophysiology is the prevention of weight regain in patients with

overweight/obesity and cardiometabolic risk who are successfully losing weight. Though serum sampling of leptin provides a common metric of physiology, pulsatility variables may be more predictive of eating disorders [181]. Leptin resistance, characterized by inadequate suppression of appetite despite elevated leptin levels (compared with lean or weight loss-maintaining counterparts), is a critical therapeutic target and can involve decreased access of leptin to relevant hypothalamic nuclei, impaired LepR expression or function, and abnormal leptin signaling [182]. Leptin resistance is associated with low-fructose, high-fat, and leucine-replete eating patterns [183,184]. In contrast, "paleolithic" eating patterns have been noted to decrease leptin levels in association with weight loss [185]. Besides LepR and certain nutritional modulators of leptin physiology, epigenetic mechanisms involving lifestyle variables have also gained recognition as therapeutic targets. Examples include deoxyribonucleic acid hypermethylation of the leptin promoter [186], hypermethylation of the POMC promoter [187], and hypomethylation of the NPY promoter [188], each predicting responses to calorie-restricted diets and the implication of fetal metabolic programming [189]. Endocrine disruptors in the environment also affect leptin levels and possibly leptin sensitivity: for example, bisphenol A, a synthetic xenoestrogen, is positively associated with leptin levels [190].

The timing of eating and energy expenditure has been linked with outcomes with weight loss strategies, possibly based on circadian misalignment of leptin or ghrelin. However, Garaulet et al. [191] found no association of these hormones with early versus late eating patterns. Extended morning fasting was studied by Chowdhury et al. [192] and found to be associated with incomplete energy compensation and lower leptin levels (decreased satiety) at lunchtime; however, consuming a carbohydrate-rich breakfast paradoxically abolished ghrelin suppression (increased appetite), possibly due to a decreased insulin response with the second meal (lunch). This is a significant finding that involves leptin and implies that afternoon appetite is unaffected by morning feeding patterns [192]. In addition, meal size is mediated by leptin by increasing inhibitory feedback of gastric load on the nucleus tractus solitarius [193]. However, the pace at which a meal is consumed does not appear to be related to leptin (though eating slowly is associated with an increased thermic effect of food, lower nonesterified fatty acids, and high adiponectin levels) [194].

Ghrelin exhibits orexigenic activity but was also found to increase cue-induced urge to consume alcohol [195]. In a prospective, randomized, double-blind proof-of-concept study, Haass-Koffler et al. [196] showed that ghrelin-induced effects on alcohol consumption were mediated by inhibition of leptin levels. These data implicate leptin targeting as a plausible strategy to combat alcohol dependence.

There are several clinical states and syndromes that prominently include leptin signaling and/or benefit from leptin (as metreleptin) therapy (Table 5) [197-206]. In subjects with obesity, both intranasal [207] and subcutaneous [208] leptin administration were associated with decreased body weight. In general, however, the weight loss response to subcutaneously injected leptin in humans with obesity has been quite modest [200,209], in part reflecting leptin resistance. More robust reductions in body weight may require the combined pharmacological targeting of multiple regulatory pathways. For example, combined treatment with metreleptin and pramlintide (an amylin analog) produced significantly greater weight loss than either agent alone [210]. On the other hand, as a single agent, metreleptin improves insulin sensitivity and glucose tolerance and reduces serum triglycerides and hepatic steatosis in patients with generalized lipodystrophy [211]. In addition, patients with congenital leptin deficiency (lacking biologically active leptin due to genetic mutations) respond dramatically to exogenous leptin with improvements in obesity, hypogonadism, immune function, and metabolism [212]. Thus, single-agent leptin exerts impressive therapeutic effects in patients lacking leptin whether due to involution of fat tissue or genetic deletion.

High-energy eating patterns inhibit BBB leptin transport, giving rise to hyperleptinemia and decreased hypothalamic leptin signaling [213]. This increases NPY-mediated events that lead to increased appetite, hyperphagia, fat accrual, insulin resistance, hyperinsulinemia, diabetes, and metabolic syndrome [214]. Thus, a single intracerebroventricular injection in rodents of a non-immunogenic recombinant adenoassociated viral vector that encodes the leptin gene into discrete hypothalamic nuclei was associated with increased leptin expression, suppressed NPY gene expression, and amelioration of high-fat diet—induced hyperinsulinemia and fat accrual [215-217]. Future leptin interventions will be based on these and other pre-clinical studies.

Other potential mechanisms that can increase hypothalamic leptin include augmenting BBB leptin transport, particularly through the use of leptin mimetics in leptin-resistant states [218-221]. Alternatively, leptin can be more effective when used with leptin-sensitizing molecules, such as amylin, cholecystokinin, or GLP1 [222-224]. Inhibitors of leptin signaling via PTP1B have also been studied using thiazolidinediones and trodusquemine [225,226]. Ericson et al. [227] screened compounds and discovered that inhibitors of the ataxia telangiectasia and Rad3-related protein, a checkpoint kinase, increased leptin-induced STAT3 activity, possibly through decreased suppressor of cytokine signaling 3 negative feedback. In short, the use of these newer pharmacologic technologies could, at the very least, synergize with other medications, therapeutic eating patterns, and behavioral techniques (e.g., mindful eating) for patients with obesity and/or other cardiometabolic risk factors.

SUMMARY

The obesity epidemic is understood in terms of genetic predisposition, pathophysiology, and a contextualization based on CVD risk, the built environment, and ethnocultural behaviors, across local, national, and global scales. This paper focuses on an integrative pathophysiological aspect that has great potential as a therapeutic target for cardiologists. Functionally, leptin is a critical hormone in the network-based modulation of body weight, body composition, appetite, and energy balance, primarily at the hypothalamic level. But leptin also has pleiotropic effects on the brain and peripheral organs that remain unclear.

Key messages that are relevant to the cardiologist are:

- Leptin is primarily produced/secreted by adipocytes and acts on the hypothalamus to suppress appetite and increase energy expenditure.
- Experimental evidence in animals and humans supports the central role of leptin in the control of adiposity and other cardiometabolic risk factors.
- Clinical translation of results from network analysis of complex leptin-mediated physiological and signaling relationships supports the role for lifestyle and pharmacotherapeutic targeting to improve cardiovascular health.
- Emergent mechanistic components of leptin networks include hexokinase 3, urocortins, clusterin, sialic acid-binding immunoglobulin-like lectin 6, C-reactive protein, platelet glycoprotein VI, albumin, pentraxin 3, ghrelin, obestatin prepropeptide, LepR, NPY, and corticotropin-releasing factor receptor 1. These molecules may have roles in the clinical management of obesity and CVD as diagnostic markers and/or therapeutic targets.
- Emergent symptoms associated with leptin physiology include weight change, eating disorders, vascular necrosis, chronic fatigue, and chest pain.
- Successful leptin-targeted therapies are reported for lipodystrophy and leptin deficiency but are still investigational for leptin resistance, obesity, and other chronic diseases.
- Network analysis of leptin physiology is a valuable hypothesis-generating research tool for those interested in preventive cardiology.

On a global scale, successful leptin-targeting with lifestyle and pharmaceuticals must take into account various transcultural factors, such as attitudes toward health, eating patterns, socioeconomic challenges, and resource availability. Underdeveloped nations and those with economic transitions can demonstrate different obesity phenotypes. Moving forward, the precise effects of leptin on the cardiovascular system, food-seeking behaviors, and cardiometabolic health, especially among various populations with economic, demographic, and other transitions, merits further basic, translational, and clinical outcomes research.

REFERENCES

1. Yatsuya H, Li Y, Hilawe EH, et al. Global trend in overweight and obesity and its association with cardiovascular disease incidence. Circ J 2014;78:2807–18.
2. Gregg EW, Shaw JE. Global health effects of overweight and obesity. N Engl J Med 2017;377:80–1.
3. Castillo JJ, Hazlett ZS, Orlando RA, Garver WS. A global evolutionary and metabolic analysis of human obesity gene risk variants. Gene 2017;627:412–9.
4. Zobel EH, Hansen TW, Rossing P, von Scholten BJ. Global changes in food supply and the obesity epidemic. Curr Obes Rep 2016;5:449–55.
5. Lee KH, Park SW, Ye SM, et al. Relationships between dietary habits and allostatic load index in metabolic syndrome patients. Korean J Fam Med 2013;34:334–46.
6. Mechanick JI, Zhao S, Garvey WT. The adipokine-cardiovascular-lifestyle network: translation to clinical practice. J Am Coll Cardiol 2016;68:1785–803.
7. Friedman JM. Leptin and the regulation of body weight. Keio J Med 2011;60:1–9.
8. Gaston KJ, Chown SL, Calosi P, et al. Macrophysiology: a conceptual reunification. Am Nat 2009;174:595–612.
9. Garvey WT, Garber AJ, Mechanick JI, et al. American Association of Clinical Endocrinologists and American College of Endocrinology position statement on the 2014 advanced framework for a new diagnosis of obesity as a chronic disease. Endocr Pract 2014;20:977–89.
10. Fernando E, Razak F, Lear SA, Anand SS. Cardiovascular disease in South Asian migrants. Can J Cardiol 2015;31:1139–50.
11. Liu P, Shi H, Liu R, et al. Lack of association between LEPR Q223R polymorphisms and cancer susceptibility: evidence from a meta-analysis. J BUON 2014;19:855–62.
12. Leonard WR, Sorensen MV, Mosher MJ, Spitsyn V, Comuzzie AG. Reduced fat oxidation and obesity risks among the Buryat of Southern Siberia. Am J Hum Biol 2009;21:664–70.
13. Esteghamati A, Khalilzadeh O, Ashraf H, et al. Physical activity is correlated with serum leptin independent of obesity: results of the national surveillance of risk factors of noncommunicable diseases in Iran (SuRFNCD-2007). Metabolism 2010;59:1730–5.
14. Akter S, Pham NM, Nanri A, et al. Association of serum leptin and ghrelin with depressive symptoms in a Japanese working population: a cross-sectional study. BMC Psychiatry 2014;14:203.
15. Kashino I, Nanri A, Kurotani K, et al. Association of dietary patterns with serum adipokines among Japanese: a cross-sectional study. Nutr J 2015;14:58.
16. Haraguchi A, Hayashida N, Kamasaki T, et al. Uptake of aortic 18F-FDG is correlated with low-density lipoprotein cholesterol and leptin in a general population. PLoS One 2014;9:e111990.
17. Kimura Y, Pham NM, Yasuda K, et al. Association of adulthood weight gain with circulating adipokine and insulin resistance in the Japanese population. Eur J Clin Nutr 2015;69:462–6.
18. Petrášová D, Bertková I, Petrášová M, et al. Biomarkers associated with obesity and overweight in the Roma population residing in Eastern Slovakia. Cent Eur J Public Health 2014;22:S18–21.
19. Friedlander Y, Li G, Fornage M, et al. Candidate molecular pathway genes related to appetite regulatory neural network, adipocyte homeostasis and obesity: results from the CARDIA study. Ann Hum Genet 2010;74:387–98.
20. Atiase Y, Farni K, Plange-Rhule J, et al. A comparison of indices of glucose metabolism in five black populations: data from modeling the epidemiologic transition study (METS). BMC Public Health 2015;15:895.
21. Darling AM, McDonald CR, Conroy AL, et al. Angiogenic and inflammatory biomarkers in midpregnancy and small-for-gestational-age outcomes in Tanzania. Am J Obstet Gynecol 2014;211:509.e1–8.
22. Brown SA, Kouzekanani K, García AA, Orlander PR, Hanis CL. Diabetes self-management and leptin in Mexican Americans with type 2 diabetes: the Starr County border health initiative. Diabetes Educ 2013;39:820–7.

23. Cansell C, Luquet S. Triglyceride sensing in the reward circuitry: a new insight in feeding behaviour regulation. Biochimie 2016;120: 75–80.
24. O'Rourke RW. Metabolic thrift and the genetic basis of human obesity. Ann Surg 2014;259:642–8.
25. Garland T, Zhao M, Saltzman W. Hormones and the evolution of complex traits: insights from artificial selection on behavior. Integr Comp Biol 2016;56:207–24.
26. Cui MY, Hu CK, Pelletier C, et al. Ancient origins and evolutionary conservation of intracellular and neural signaling pathways engaged by the leptin receptor. Endocrinology 2014;155:4202–14.
27. Londraville RL, Macotela Y, Duff RJ, Easterling MR, Liu Q, Crespi EJ. Comparative endocrinology of leptin: assessing function in a phylogenetic context. Gen Comp Endocrinol 2014;203:146–57.
28. Denver RJ, Bonett RM, Boorse GC. Evolution of leptin structure and function. Neuroendocrinology 2011;94:21–38.
29. Ingalls AM, Dickie MM, Snell GD. Obese, a new mutation in the house mouse. J Hered 1950;41:317–8.
30. Hummel KP, Dickie MM, Coleman DL. Diabetes, a new mutation in the mouse. Science 1966;153:1127–8.
31. Coleman DL, Hummel KP. Effects of parabiosis of normal with genetically diabetic mice. Am J Physiol 1969;217:1298–304.
32. Coleman DL. Effects of parabiosis of obese with diabetes and normal mice. Diabetologia 1973;9:294–8.
33. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature 1994;372:425–32.
34. Hoggard N, Mercer JG, Rayner DV, Moar K, Trayhurn P, Williams LM. Localization of leptin receptor mRNA splice variants in murine peripheral tissues by RT-PCR and in situ hybridization. Biochem Biophys Res Commun 1997;232:383–7.
35. Bado A, Levasseur S, Attoub S, et al. The stomach is a source of leptin. Nature 1998;394:790–3.
36. Farooqi IS, Jebb SA, Langmack G, et al. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. N Engl J Med 1999;341:879–84.
37. Houseknecht KL, Portocarrero CP. Leptin and its receptors: regulators of whole-body energy homeostasis. Domest Anim Endocrinol 1998;15:457–75.
38. Matarese G, Moschos S, Mantzoros CS. Leptin in immunology. J Immunol 2005;174:3137–42.
39. Huynh FK, Levi J, Denroche HC, et al. Disruption of hepatic leptin signaling protects mice from age- and diet-related glucose intolerance. Diabetes 2010;59:3032–40.
40. Cohen P, Zhao C, Cai X, et al. Selective deletion of leptin receptor in neurons leads to obesity. J Clin Invest 2001;108:1113–21.
41. Licinio J, Mantzoros C, Negrão AB, et al. Human leptin levels are pulsatile and inversely related to pituitary-adrenal function. Nat Med 1997;3:575–9.
42. Sinha MK, Sturis J, Ohannesian J, et al. Ultradian oscillations of leptin secretion in humans. Biochem Biophys Res Commun 1996; 228:733–8.
43. Cooper JA, Polonsky KS, Schoeller DA. Serum leptin levels in obese males during over- and underfeeding. Obesity (Silver Spring) 2009; 17:2149–54.
44. Chin-Chance C, Polonsky KS, Schoeller DA. Twenty-four-hour leptin levels respond to cumulative short-term energy imbalance and predict subsequent intake. J Clin Endocrinol Metab 2000;85: 2685–91.
45. Kennedy A, Gettys TW, Watson P, et al. The metabolic significance of leptin in humans: gender-based differences in relationship to adiposity, insulin sensitivity, and energy expenditure. J Clin Endocrinol Metab 1997;82:1293–300.
46. De Ceuninck L, Wauman J, Masschaele D, Peelman F, Tavernier J. Reciprocal cross-regulation between RNF41 and USP8 controls cytokine receptor sorting and processing. J Cell Sci 2013;126: 3770–81.
47. Couturier C, Sarkis C, Séron K, et al. Silencing of OB-RGRP in mouse hypothalamic arcuate nucleus increases leptin receptor signaling and prevents diet-induced obesity. Proc Natl Acad Sci U S A 2007; 104:19476–81.
48. Burguera B, Couce ME, Curran GL, et al. Obesity is associated with a decreased leptin transport across the blood-brain barrier in rats. Diabetes 2000;49:1219–23.
49. Banks WA, King BM, Rossiter KN, Olson RD, Olson GA, Kastin AJ. Obesity-inducing lesions of the central nervous system alter leptin uptake by the blood-brain barrier. Life Sci 2001;69:2765–73.
50. Banks WA, Coon AB, Robinson SM, et al. Triglycerides induce leptin resistance at the blood-brain barrier. Diabetes 2004;53:1253–60.
51. Langlet F, Levin BE, Luquet S, et al. Tanycytic VEGF-A boosts blood-hypothalamus barrier plasticity and access of metabolic signals to the arcuate nucleus in response to fasting. Cell Metab 2013;17: 607–17.
52. Kwon O, Kim KW, Kim M-S. Leptin signalling pathways in hypothalamic neurons. Cell Mol Life Sci 2016;73:1457–77.
53. Tartaglia LA, Dembski M, Weng X, et al. Identification and expression cloning of a leptin receptor, OB-R. Cell 1995;83:1263–71.
54. Fong TM, Huang RR, Tota MR, et al. Localization of leptin binding domain in the leptin receptor. Mol Pharmacol 1998;53:234–40.
55. Sun Q, van Dam RM, Meigs JB, Franco OH, Mantzoros CS, Hu FB. Leptin and soluble leptin receptor levels in plasma and risk of type 2 diabetes in U.S. women: a prospective study. Diabetes 2010;59: 611–8.
56. Bjørbaek C, Elmquist JK, Michl P, et al. Expression of leptin receptor isoforms in rat brain microvessels. Endocrinology 1998;139: 3485–91.
57. Schwartz GJ, Zeltser LM. Functional organization of neuronal and humoral signals regulating feeding behavior. Annu Rev Nutr 2013; 33:1–21.
58. Fulton S, Pissios P, Manchon RP, et al. Leptin regulation of the mesoaccumbens dopamine pathway. Neuron 2006;51:811–22.
59. Hawke Z, Ivanov TR, Bechtold DA, Dhillon H, Lowell BB, Luckman SM. PACAP neurons in the hypothalamic ventromedial nucleus are targets of central leptin signaling. J Neurosci 2009;29: 14828–35.
60. Meek TH, Matsen ME, Dorfman MD, et al. Leptin action in the ventromedial hypothalamic nucleus is sufficient, but not necessary, to normalize diabetic hyperglycemia. Endocrinology 2013;154: 3067–76.
61. Goforth PB, Leinninger GM, Patterson CM, Satin LS, Myers MG. Leptin acts via lateral hypothalamic area neurotensin neurons to inhibit orexin neurons by multiple GABA-independent mechanisms. J Neurosci 2014;34:11405–15.
62. Bonnavion P, Jackson AC, Carter ME, de Lecea L. Antagonistic interplay between hypocretin and leptin in the lateral hypothalamus regulates stress responses. Nat Commun 2015;6:6266.
63. Huo L, Maeng L, Bjørbaek C, Grill HJ. Leptin and the control of food intake: neurons in the nucleus of the solitary tract are activated by both gastric distension and leptin. Endocrinology 2007;148: 2189–97.
64. Ronveaux CC, Tomé D, Raybould HE. Glucagon-like peptide 1 interacts with ghrelin and leptin to regulate glucose metabolism and food intake through vagal afferent neuron signaling. J Nutr 2015; 145:672–80.
65. Grill HJ, Schwartz MW, Kaplan JM, Foxhall JS, Breininger J, Baskin DG. Evidence that the caudal brainstem is a target for the inhibitory effect of leptin on food intake. Endocrinology 2002;143: 239–46.
66. Hinkle W, Cordell M, Leibel R, Rosenbaum M, Hirsch J. Effects of reduced weight maintenance and leptin repletion on functional connectivity of the hypothalamus in obese humans. PLoS One 2013; 8:e59114.
67. Hosoi T, Kawagishi T, Okuma Y, Tanaka J, Nomura Y. Brain stem is a direct target for leptin's action in the central nervous system. Endocrinology 2002;143:3498–504.
68. Arnold AC, Diz DI. Endogenous leptin contributes to baroreflex suppression within the solitary tract nucleus of aged rats. Am J Physiol Heart Circ Physiol 2014;307:H1539–46.

69. Münzberg H, Huo L, Nillni EA, Hollenberg AN, Bjørbaek C. Role of signal transducer and activator of transcription 3 in regulation of hypothalamic proopiomelanocortin gene expression by leptin. Endocrinology 2003;144:2121–31.
70. Varela L, Horvath TL. Leptin and insulin pathways in POMC and AgRP neurons that modulate energy balance and glucose homeostasis. EMBO Rep 2012;13:1079–86.
71. Joly-Amado A, Denis RGP, Castel J, et al. Hypothalamic AgRP-neurons control peripheral substrate utilization and nutrient partitioning. EMBO J 2012;31:4276–88.
72. Akira S. Functional roles of STAT family proteins: lessons from knockout mice. Stem Cells 1999;17:138–46.
73. Banks AS, Davis SM, Bates SH, Myers MG. Activation of downstream signals by the long form of the leptin receptor. J Biol Chem 2000; 275:14563–72.
74. Bjørbaek C, Buchholz RM, Davis SM, et al. Divergent roles of SHP-2 in ERK activation by leptin receptors. J Biol Chem 2001;276: 4747–55.
75. Tups A, Stöhr S, Helwig M, et al. Seasonal leptin resistance is associated with impaired signalling via JAK2-STAT3 but not ERK, possibly mediated by reduced hypothalamic GRB2 protein. J Comp Physiol B 2012;182:553–67.
76. Kim KW, Donato J, Berglund ED, et al. FOXO1 in the ventromedial hypothalamus regulates energy balance. J Clin Invest 2012;122: 2578–89.
77. Takahashi Y, Okimura Y, Mizuno I, et al. Leptin induces mitogen-activated protein kinase-dependent proliferation of C3H10T1/2 cells. J Biol Chem 1997;272:12897–900.
78. Huang H, Kong D, Byun KH, et al. Rho-kinase regulates energy balance by targeting hypothalamic leptin receptor signaling. Nat Neurosci 2012;15:1391–8.
79. Withers DJ, Gutierrez JS, Towery H, et al. Disruption of IRS-2 causes type 2 diabetes in mice. Nature 1998;391:900–4.
80. Xu AW, Kaelin CB, Takeda K, Akira S, Schwartz MW, Barsh GS. PI3K integrates the action of insulin and leptin on hypothalamic neurons. J Clin Invest 2005;115:951–8.
81. Minokoshi Y, Alquier T, Furukawa N, et al. AMP-kinase regulates food intake by responding to hormonal and nutrient signals in the hypothalamus. Nature 2004;428:569–74.
82. Hawley SA, Boudeau J, Reid JL, et al. Complexes between the LKB1 tumor suppressor, STRAD alpha/beta and MO25 alpha/beta are upstream kinases in the AMP-activated protein kinase cascade. J Biol 2003;2:28.
83. Racioppi L, Means AR. Calcium/calmodulin-dependent protein kinase kinase 2: roles in signaling and pathophysiology. J Biol Chem 2012;287:31658–65.
84. Dagon Y, Hur E, Zheng B, Wellenstein K, Cantley LC, Kahn BB. p70S6 kinase phosphorylates AMPK on serine 491 to mediate leptin's effect on food intake. Cell Metab 2012;16:104–12.
85. Cota D, Proulx K, Smith KAB, et al. Hypothalamic mTOR signaling regulates food intake. Science 2006;312:927–30.
86. Bjørbaek C, Elmquist JK, Frantz JD, Shoelson SE, Flier JS. Identification of SOCS-3 as a potential mediator of central leptin resistance. Mol Cell 1998;1:619–25.
87. Liu Q, Zhang J, Zerbinatti C, et al. Lipoprotein receptor LRP1 regulates leptin signaling and energy homeostasis in the adult central nervous system. PLoS Biol 2011;9:e1000575.
88. Gil SY, Youn B-S, Byun K, et al. Clusterin and LRP2 are critical components of the hypothalamic feeding regulatory pathway. Nat Commun 2013;4:1862.
89. Huo L, Grill HJ, Bjørbaek C. Divergent regulation of proopiomelanocortin neurons by leptin in the nucleus of the solitary tract and in the arcuate hypothalamic nucleus. Diabetes 2006;55:567–73.
90. Niswender KD, Baskin DG, Schwartz MW. Insulin and its evolving partnership with leptin in the hypothalamic control of energy homeostasis. Trends Endocrinol Metab 2004;15:362–9.
91. Ren D, Li M, Duan C, Rui L. Identification of SH2-B as a key regulator of leptin sensitivity, energy balance, and body weight in mice. Cell Metab 2005;2:95–104.
92. Duan C, Li M, Rui L. SH2-B promotes insulin receptor substrate 1 (IRS1)- and IRS2-mediated activation of the phosphatidylinositol 3-kinase pathway in response to leptin. J Biol Chem 2004;279: 43684–91.
93. Sun J, Gao Y, Yao T, et al. Adiponectin potentiates the acute effects of leptin in arcuate Pomc neurons. Mol Metab 2016;5:882–91.
94. Backer JM, Myers MG, Shoelson SE, et al. Phosphatidylinositol 3′-kinase is activated by association with IRS-1 during insulin stimulation. EMBO J 1992;11:3469–79.
95. Nachury MV, Loktev AV, Zhang Q, et al. A core complex of BBS proteins cooperates with the GTPase Rab8 to promote ciliary membrane biogenesis. Cell 2007;129:1201–13.
96. Stratigopoulos G, LeDuc CA, Cremona ML, Chung WK, Leibel RL. Cut-like homeobox 1 (CUX1) regulates expression of the fat mass and obesity-associated and retinitis pigmentosa GTPase regulator-interacting protein-1-like (RPGRIP1L) genes and coordinates leptin receptor signaling. J Biol Chem 2011;286:2155–70.
97. Frayling TM, Timpson NJ, Weedon MN, et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science 2007;316:889–94.
98. Kang GM, Han YM, Ko HW, et al. Leptin elongates hypothalamic neuronal cilia via transcriptional regulation and actin destabilization. J Biol Chem 2015;290:18146–55.
99. Zabolotny JM, Bence-Hanulec KK, Stricker-Krongrad A, et al. PTP1B regulates leptin signal transduction in vivo. Dev Cell 2002;2: 489–95.
100. Xue B, Pulinilkunnil T, Murano I, et al. Neuronal protein tyrosine phosphatase 1B deficiency results in inhibition of hypothalamic AMPK and isoform-specific activation of AMPK in peripheral tissues. Mol Cell Biol 2009;29:4563–73.
101. Chen H-H, Schock SC, Xu J, Safarpour F, Thompson CS, Stewart AFR. Extracellular ATP-dependent upregulation of the transcription cofactor LMO4 promotes neuron survival from hypoxia. Exp Cell Res 2007;313:3106–16.
102. Rousso-Noori L, Knobler H, Levy-Apter E, et al. Protein tyrosine phosphatase epsilon affects body weight by downregulating leptin signaling in a phosphorylation-dependent manner. Cell Metab 2011; 13:562–72.
103. Loh K, Fukushima A, Zhang X, et al. Elevated hypothalamic TCPTP in obesity contributes to cellular leptin resistance. Cell Metab 2011;14: 684–99.
104. St-Pierre J, Tremblay ML. Modulation of leptin resistance by protein tyrosine phosphatases. Cell Metab 2012;15:292–7.
105. De Souza CT, Araujo EP, Bordin S, et al. Consumption of a fat-rich diet activates a proinflammatory response and induces insulin resistance in the hypothalamus. Endocrinology 2005;146:4192–9.
106. Zhang X, Zhang G, Zhang H, Karin M, Bai H, Cai D. Hypothalamic IKKbeta/NF-kappaB and ER stress link overnutrition to energy imbalance and obesity. Cell 2008;135:61–73.
107. Tsaousidou E, Paeger L, Belgardt BF, et al. Distinct roles for JNK and IKK activation in agouti-related peptide neurons in the development of obesity and insulin resistance. Cell Rep 2014;9:1495–506.
108. Jang P-G, Namkoong C, Kang GM, et al. NF-kappaB activation in hypothalamic pro-opiomelanocortin neurons is essential in illness- and leptin-induced anorexia. J Biol Chem 2010;285:9706–15.
109. Shi X, Wang X, Li Q, et al. Nuclear factor κB (NF-κB) suppresses food intake and energy expenditure in mice by directly activating the Pomc promoter. Diabetologia 2013;56:925–36.
110. Dietrich MO, Liu Z-W, Horvath TL. Mitochondrial dynamics controlled by mitofusins regulate AgRP neuronal activity and diet-induced obesity. Cell 2013;155:188–99.
111. Milanski M, Degasperi G, Coope A, et al. Saturated fatty acids produce an inflammatory response predominantly through the activation of TLR4 signaling in hypothalamus: implications for the pathogenesis of obesity. J Neurosci 2009;29:359–70.
112. Ropelle ER, Flores MB, Cintra DE, et al. IL-6 and IL-10 anti-inflammatory activity links exercise to hypothalamic insulin and leptin sensitivity through IKKbeta and ER stress inhibition. PLoS Biol 2010; 8:e1000465.

113. Ozcan L, Ergin AS, Lu A, et al. Endoplasmic reticulum stress plays a central role in development of leptin resistance. Cell Metab 2009;9:35–51.
114. Won JC, Jang P-G, Namkoong C, et al. Central administration of an endoplasmic reticulum stress inducer inhibits the anorexigenic effects of leptin and insulin. Obesity (Silver Spring) 2009;17:1861–5.
115. Williams KW, Liu T, Kong X, et al. Xbp1s in Pomc neurons connects ER stress with energy balance and glucose homeostasis. Cell Metab 2014;20:471–82.
116. Jeon J-P, Shim S-M, Nam H-Y, et al. Copy number variation at leptin receptor gene locus associated with metabolic traits and the risk of type 2 diabetes mellitus. BMC Genomics 2010;11:426.
117. Benoit SC, Kemp CJ, Elias CF, et al. Palmitic acid mediates hypothalamic insulin resistance by altering PKC-theta subcellular localization in rodents. J Clin Invest 2009;119:2577–89.
118. Fukuda M, Williams KW, Gautron L, Elmquist JK. Induction of leptin resistance by activation of cAMP-Epac signaling. Cell Metab 2011;13:331–9.
119. De Rooij J, Zwartkruis FJ, Verheijen MH, et al. Epac is a Rap1 guanine-nucleotide-exchange factor directly activated by cyclic AMP. Nature 1998;396:474–7.
120. Mark AL. Selective leptin resistance revisited. Am J Physiol Regul Integr Comp Physiol 2013;305:R566–81.
121. Farr OM, Fiorenza C, Papageorgiou P, et al. Leptin therapy alters appetite and neural responses to food stimuli in brain areas of leptin-sensitive subjects without altering brain structure. J Clin Endocrinol Metab 2014;99:E2529–38.
122. Heldsinger A, Grabauskas G, Song I, Owyang C. Synergistic interaction between leptin and cholecystokinin in the rat nodose ganglia is mediated by PI3K and STAT3 signaling pathways: implications for leptin as a regulator of short term satiety. J Biol Chem 2011;286:11707–15.
123. Clemmensen C, Chabenne J, Finan B, et al. GLP-1/glucagon coagonism restores leptin responsiveness in obese mice chronically maintained on an obesogenic diet. Diabetes 2014;63:1422–7.
124. Matson CA, Reid DF, Cannon TA, Ritter RC. Cholecystokinin and leptin act synergistically to reduce body weight. Am J Physiol Regul Integr Comp Physiol 2000;278:R882–90.
125. Unniappan S, Kieffer TJ. Leptin extends the anorectic effects of chronic PYY(3-36) administration in ad libitum-fed rats. Am J Physiol Regul Integr Comp Physiol 2008;295:R51–8.
126. Sakai T, Kusakabe T, Ebihara K, et al. Leptin restores the insulinotropic effect of exenatide in a mouse model of type 2 diabetes with increased adiposity induced by streptozotocin and high-fat diet. Am J Physiol Endocrinol Metab 2014;307:E712–9.
127. Iepsen EW, Lundgren J, Dirksen C, et al. Treatment with a GLP-1 receptor agonist diminishes the decrease in free plasma leptin during maintenance of weight loss. Int J Obes (Lond) 2015;39:834–41.
128. Khan SM, Hamnvik O-PR, Brinkoetter M, Mantzoros CS. Leptin as a modulator of neuroendocrine function in humans. Yonsei Med J 2012;53:671–9.
129. Persson B, Westgren M, Celsi G, Nord E, Ortqvist E. Leptin concentrations in cord blood in normal newborn infants and offspring of diabetic mothers. Horm Metab Res 1999;31:467–71.
130. Westgate JA, Lindsay RS, Beattie J, et al. Hyperinsulinemia in cord blood in mothers with type 2 diabetes and gestational diabetes mellitus in New Zealand. Diabetes Care 2006;29:1345–50.
131. Bouret SG, Simerly RB. Development of leptin-sensitive circuits. J Neuroendocrinol 2007;19:575–82.
132. Steculorum SM, Collden G, Coupe B, et al. Neonatal ghrelin programs development of hypothalamic feeding circuits. J Clin Invest 2015;125:846–58.
133. Higgins MF, Russell NM, Brazil DP, Firth RG, McAuliffe FM. Fetal and maternal leptin in pre-gestational diabetic pregnancy. Int J Gynaecol Obstet 2013;120:169–72.
134. Bush NC, Chandler-Laney PC, Rouse DJ, Granger WM, Oster RA, Gower BA. Higher maternal gestational glucose concentration is associated with lower offspring insulin sensitivity and altered beta-cell function. J Clin Endocrinol Metab 2011;96:E803–9.
135. Bouret SG, Simerly RB. Developmental programming of hypothalamic feeding circuits. Clin Genet 2006;70:295–301.
136. Bouret SG. Early life origins of obesity: role of hypothalamic programming. J Pediatr Gastroenterol Nutr 2009;48(Suppl 1):S31–8.
137. Stein LJ, Dorsa DM, Baskin DG, Figlewicz DP, Porte D, Woods SC. Reduced effect of experimental peripheral hyperinsulinemia to elevate cerebrospinal fluid insulin concentrations of obese Zucker rats. Endocrinology 1987;121:1611–5.
138. Isganaitis E, Lustig RH. Fast food, central nervous system insulin resistance, and obesity. Arterioscler Thromb Vasc Biol 2005;25:2451–62.
139. Lustig RH. The "skinny" on childhood obesity: how our Western environment starves kids' brains. Pediatr Ann 2006;35:898–902. 905—7.
140. Mantzoros CS, Flier JS, Rogol AD. A longitudinal assessment of hormonal and physical alterations during normal puberty in boys. V. Rising leptin levels may signal the onset of puberty. J Clin Endocrinol Metab 1997;82:1066–70.
141. Licinio J, Negrão AB, Mantzoros C, et al. Synchronicity of frequently sampled, 24-h concentrations of circulating leptin, luteinizing hormone, and estradiol in healthy women. Proc Natl Acad Sci U S A 1998;95:2541–6.
142. Ahima RS, Saper CB, Flier JS, Elmquist JK. Leptin regulation of neuroendocrine systems. Front Neuroendocrinol 2000;21:263–307.
143. Siegrist-Kaiser CA, Pauli V, Juge-Aubry CE, et al. Direct effects of leptin on brown and white adipose tissue. J Clin Invest 1997;100:2858–64.
144. Marti A, Novo FJ, Martinez-Anso E, Zaratiegui M, Aguado M, Martinez JA. Leptin gene transfer into muscle increases lipolysis and oxygen consumption in white fat tissue in ob/ob mice. Biochem Biophys Res Commun 1998;246:859–62.
145. Yue R, Zhou BO, Shimada IS, Zhao Z, Morrison SJ. Leptin receptor promotes adipogenesis and reduces osteogenesis by regulating mesenchymal stromal cells in adult bone marrow. Cell Stem Cell 2016;18:782–96.
146. Hoang D, Broer N, Sosa JA, et al. Leptin is produced by parathyroid glands and stimulates parathyroid hormone secretion. Ann Surg 2017;266:1075–83.
147. Babaei A, Zarkesh-Esfahani SH, Bahrami E, Ross RJ. Restricted leptin antagonism as a therapeutic approach to treatment of autoimmune diseases. Hormones (Athens) 2011;10:16–26.
148. Moraes-Vieira PMM, Larocca RA, Bassi EJ, et al. Leptin deficiency impairs maturation of dendritic cells and enhances induction of regulatory T and Th17 cells. Eur J Immunol 2014;44:794–806.
149. Sáinz N, Barrenetxe J, Moreno-Aliaga MJ, Martínez JA. Leptin resistance and diet-induced obesity: central and peripheral actions of leptin. Metabolism 2015;64:35–46.
150. El-Zein O, Kreydiyyeh SI. Leptin inhibits glucose intestinal absorption via PKC, p38MAPK, PI3K and MEK/ERK. PLoS One 2013;8:e83360.
151. Briffa JF, Grinfeld E, Mathai ML, Poronnik P, McAinch AJ, Hryciw DH. Acute leptin exposure reduces megalin expression and upregulates TGFβ1 in cultured renal proximal tubule cells. Mol Cell Endocrinol 2015;401:25–34.
152. Lim CC, Teo BW, Tai ES, et al. Elevated serum leptin, adiponectin and leptin to adiponectin ratio is associated with chronic kidney disease in Asian adults. PLoS One 2015;10:e0122009.
153. Pedone C, Roshanravan B, Scarlata S, Patel KV, Ferrucci L, Incalzi RA. Longitudinal association between serum leptin concentration and glomerular filtration rate in humans. PLoS One 2015;10:e0117828.
154. Perry RJ, Zhang X-M, Zhang D, et al. Leptin reverses diabetes by suppression of the hypothalamic-pituitary-adrenal axis. Nat Med 2014;20:759–63.
155. Ceddia RB, William WN, Curi R. Comparing effects of leptin and insulin on glucose metabolism in skeletal muscle: evidence for an effect of leptin on glucose uptake and decarboxylation. Int J Obes Relat Metab Disord 1999;23:75–82.
156. Lanier V, Gillespie C, Leffers M, et al. Leptin-induced transphosphorylation of vascular endothelial growth factor receptor increases Notch and stimulates endothelial cell angiogenic transformation. Int J Biochem Cell Biol 2016;79:139–50.

157. Serradeil-Le Gal C, Lafontan M, Raufaste D, et al. Characterization of NPY receptors controlling lipolysis and leptin secretion in human adipocytes. FEBS Lett 2000;475:150–6.
158. Yau SW, Henry BA, Russo VC, et al. Leptin enhances insulin sensitivity by direct and sympathetic nervous system regulation of muscle IGFBP-2 expression: evidence from nonrodent models. Endocrinology 2014;155:2133–43.
159. Drosos I, Chalikias G, Pavlaki M, et al. Differences between perivascular adipose tissue surrounding the heart and the internal mammary artery: possible role for the leptin-inflammation-fibrosis-hypoxia axis. Clin Res Cardiol 2016;105:887–900.
160. Sweeney G. Cardiovascular effects of leptin. Nat Rev Cardiol 2010;7:22–9.
161. Antonopoulos AS, Antoniades C, Tousoulis D. Unravelling the "adipokine paradox": when the classic proatherogenic adipokine leptin is deemed the beneficial one. Int J Cardiol 2015;197:125–7.
162. Boumaiza I, Omezzine A, Rejeb J, et al. Relationship between leptin G2548A and leptin receptor Q223R gene polymorphisms and obesity and metabolic syndrome risk in Tunisian volunteers. Genet Test Mol Biomarkers 2012;16:726–33.
163. Wannamethee SG, Shaper AG, Whincup PH, Lennon L, Papacosta O, Sattar N. The obesity paradox in men with coronary heart disease and heart failure: the role of muscle mass and leptin. Int J Cardiol 2014;171:49–55.
164. Jamar G, Caranti DA, de Cassia Cesar H, Masquio DCL, Bandoni DH, Pisani LP. Leptin as a cardiovascular risk marker in metabolically healthy obese: hyperleptinemia in metabolically healthy obese. Appetite 2017;108:477–82.
165. Montazerifar F, Bolouri A, Paghalea RS, Mahani MK, Karajibani M. Obesity, serum resistin and leptin levels linked to coronary artery disease. Arq Bras Cardiol 2016;107:348–53.
166. Ding N, Liu B, Song J, et al. Leptin promotes endothelial dysfunction in chronic kidney disease through AKT/GSK3β and β-catenin signals. Biochem Biophys Res Commun 2016;480:544–51.
167. Simonds SE, Pryor JT, Cowley MA. Does leptin cause an increase in blood pressure in animals and humans? Curr Opin Nephrol Hypertens 2017;26:20–5.
168. Soudani N, Ghantous CM, Farhat Z, Shebaby WN, Zibara K, Zeidan A. Calcineurin/NFAT activation-dependence of leptin synthesis and vascular growth in response to mechanical stretch. Front Physiol 2016;7:433.
169. Puurunen VP, Lepojärvi ES, Piira OP, et al. High plasma leptin levels are associated with impaired diastolic function in patients with coronary artery disease. Peptides 2016;84:17–21.
170. Du Y, Li S, Cui C-J, Zhang Y, Yang S-H, Li J-J. Leptin decreases the expression of low-density lipoprotein receptor via PCSK9 pathway: linking dyslipidemia with obesity. J Transl Med 2016;14:276.
171. Sharma S, Colangelo LA, Allison MA, et al. Association of serum leptin with future left ventricular structure and function: the Multi-Ethnic Study of Atherosclerosis (MESA). Int J Cardiol 2015;193:64–8.
172. Zhao S, Iyengar R. Systems pharmacology: network analysis to identify multiscale mechanisms of drug action. Annu Rev Pharmacol Toxicol 2012;52:505–21.
173. Berger SI, Ma'ayan A, Iyengar R. Systems pharmacology of arrhythmias. Sci Signal 2010;3:ra30.
174. Zhao S, Nishimura T, Chen Y, et al. Systems pharmacology of adverse event mitigation by drug combinations. Sci Transl Med 2013;5:206ra140.
175. Kreeger PK, Lauffenburger DA. Cancer systems biology: a network modeling perspective. Carcinogenesis 2010;31:2–8.
176. Meng Q, Mäkinen V-P, Luk H, Yang X. Systems biology approaches and applications in obesity, diabetes, and cardiovascular diseases. Curr Cardiovasc Risk Rep 2013;7:73–83.
177. Jimeno-Yepes AJ, Sticco J, Mork JG, Aronson AR. GeneRIF indexing: sentence selection based on machine learning. BMC Bioinformatics 2013;14:171. Available at: http://bmcbioinformatics.biomedcentral.com/articles/10.1186/1471-2105-14-171. Accessed November 19, 2016.
178. Anon. Symptom Ontology Wiki. Available at: http://symptomontologywiki.igs.umaryland.edu/mediawiki/index.php/Main_Page. Accessed January 1, 2016.
179. Stringer EA, Baker KS, Carroll IR, et al. Daily cytokine fluctuations, driven by leptin, are associated with fatigue severity in chronic fatigue syndrome: evidence of inflammatory pathology. J Transl Med 2013;11:93.
180. Zhou L, Jang KY, Moon YJ, et al. Leptin ameliorates ischemic necrosis of the femoral head in rats with obesity induced by a high-fat diet. Sci Rep 2015;5:9397. Available at: http://www.nature.com/articles/srep09397. Accessed November 19, 2016.
181. Baskaran C, Eddy KT, Miller KK, Meenaghan E, Misra M, Lawson EA. Leptin secretory dynamics and associated disordered eating psychopathology across the weight spectrum. Eur J Endocrinol 2016;174:503–12.
182. Crujeiras AB, Carreira MC, Cabia B, Andrade S, Amil M, Casanueva FF. Leptin resistance in obesity: an epigenetic landscape. Life Sci 2015;140:57–63.
183. Haring SJ, Harris RBS. The relation between dietary fructose, dietary fat and leptin responsiveness in rats. Physiol Behav 2011;104:914–22.
184. Zhang Q, Liu B, Cheng Y, et al. Leptin signaling is required for leucine deprivation-enhanced energy expenditure. J Biol Chem 2014;289:1779–87.
185. Fontes-Villalba M, Lindeberg S, Granfeldt Y, et al. Palaeolithic diet decreases fasting plasma leptin concentrations more than a diabetes diet in patients with type 2 diabetes: a randomised cross-over trial. Cardiovasc Diabetol 2016;15:80.
186. Cordero P, Campion J, Milagro FI, et al. Leptin and TNF-alpha promoter methylation levels measured by MSP could predict the response to a low-calorie diet. J Physiol Biochem 2011;67:463–70.
187. Marco A, Kisliouk T, Weller A, Meiri N. High fat diet induces hypermethylation of the hypothalamic Pomc promoter and obesity in post-weaning rats. Psychoneuroendocrinology 2013;38:2844–53.
188. Plagemann A, Harder T, Brunn M, et al. Hypothalamic proopiomelanocortin promoter methylation becomes altered by early overfeeding: an epigenetic model of obesity and the metabolic syndrome. J Physiol 2009;587:4963–76.
189. Allard C, Desgagné V, Patenaude J, et al. Mendelian randomization supports causality between maternal hyperglycemia and epigenetic regulation of leptin gene in newborns. Epigenetics 2015;10:342–51.
190. Rönn M, Lind L, Örberg J, et al. Bisphenol A is related to circulating levels of adiponectin, leptin and ghrelin, but not to fat mass or fat distribution in humans. Chemosphere 2014;112:42–8.
191. Garaulet M, Gómez-Abellán P, Alburquerque-Béjar JJ, Lee Y-C, Ordovás JM, Scheer FA. Timing of food intake predicts weight loss effectiveness. Int J Obes (Lond) 2013;37:604–11.
192. Chowdhury EA, Richardson JD, Tsintzas K, Thompson D, Betts JA. Carbohydrate-rich breakfast attenuates glycaemic, insulinaemic and ghrelin response to ad libitum lunch relative to morning fasting in lean adults. Br J Nutr 2015;114:98–107.
193. Moran TH, Aja S, Ladenheim EE. Leptin modulation of peripheral controls of meal size. Physiol Behav 2006;89:511–6.
194. Reddy NL, Peng C, Carreira MC, et al. Enhanced thermic effect of food, postprandial NEFA suppression and raised adiponectin in obese women who eat slowly. Clin Endocrinol (Oxf) 2015;82:831–7.
195. Leggio L, Zywiak WH, Fricchione SR, et al. Intravenous ghrelin administration increases alcohol craving in alcohol-dependent heavy drinkers: a preliminary investigation. Biol Psychiatry 2014;76:734–41.
196. Haass-Koffler CL, Aoun EG, Swift RM, de la Monte SM, Kenna GA, Leggio L. Leptin levels are reduced by intravenous ghrelin administration and correlated with cue-induced alcohol craving. Transl Psychiatry 2015;5:e646.
197. Wabitsch M, Funcke J-B, Lennerz B, et al. Biologically inactive leptin and early-onset extreme obesity. N Engl J Med 2015;372:48–54.
198. Paz-Filho GJ. The effects of leptin replacement on neural plasticity. Neural Plast 2016;2016:1–8.

199. Fava M, Ramey T, Pickering E, Kinrys G, Boyer S, Altstiel L. A randomized, double-blind, placebo-controlled phase 2 study of the augmentation of a nicotinic acetylcholine receptor partial agonist in depression: is there a relationship to leptin levels? J Clin Psychopharmacol 2015;35:51–6.

200. Moon H-S, Matarese G, Brennan AM, et al. Efficacy of metreleptin in obese patients with type 2 diabetes: cellular and molecular pathways underlying leptin tolerance. Diabetes 2011;60:1647–56.

201. Audi L, Mantzoros CS, Vidal-Puig A, Vargas D, Gussinye M, Carrascosa A. Leptin in relation to resumption of menses in women with anorexia nervosa. Mol Psychiatry 1998;3:544–7.

202. Moon H-S, Dalamaga M, Kim S-Y, et al. Leptin's role in lipodystrophic and nonlipodystrophic insulin-resistant and diabetic individuals. Endocr Rev 2013;34:377–412.

203. Procaccini C, Galgani M, De Rosa V, et al. Leptin: the prototypic adipocytokine and its role in NAFLD. Curr Pharm Des 2010;16:1902–12.

204. Moon H-S, Chamberland JP, Diakopoulos KN, et al. Leptin and amylin act in an additive manner to activate overlapping signaling pathways in peripheral tissues: in vitro and ex vivo studies in humans. Diabetes Care 2011;34:132–8.

205. Rosenbaum M, Goldsmith R, Bloomfield D, et al. Low-dose leptin reverses skeletal muscle, autonomic, and neuroendocrine adaptations to maintenance of reduced weight. J Clin Invest 2005;115:3579–86.

206. Brown RJ, Cochran E, Gorden P. Metreleptin improves blood glucose in patients with insulin receptor mutations. J Clin Endocrinol Metab 2013;98:E1749–56.

207. Schulz C, Paulus K, Lehnert H. Central nervous and metabolic effects of intranasally applied leptin. Endocrinology 2004;145:2696–701.

208. Freemark M. Pharmacotherapy of childhood obesity: an evidence-based, conceptual approach. Diabetes Care 2007;30:395–402.

209. Heymsfield SB, Greenberg AS, Fujioka K, et al. Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial. JAMA 1999;282:1568–75.

210. Ravussin E, Smith SR, Mitchell JA, et al. Enhanced weight loss with pramlintide/metreleptin: an integrated neurohormonal approach to obesity pharmacotherapy. Obesity (Silver Spring) 2009;17:1736–43.

211. Oral EA, Simha V, Ruiz E, et al. Leptin-replacement therapy for lipodystrophy. N Engl J Med 2002;346:570–8.

212. Paz-Filho G, Mastronardi CA, Licinio J. Leptin treatment: facts and expectations. Metabolism 2015;64:146–56.

213. Banks WA, Farr SA, Morley JE. The effects of high fat diets on the blood-brain barrier transport of leptin: failure or adaptation? Physiol Behav 2006;88:244–8.

214. Kalra SP. Central leptin insufficiency syndrome: an interactive etiology for obesity, metabolic and neural diseases and for designing new therapeutic interventions. Peptides 2008;29:127–38.

215. Dhillon H, Kalra S, Prima V, et al. Central leptin gene therapy suppresses body weight gain, adiposity and serum insulin without affecting food consumption in normal rats: a long-term study. Regul Pept 2001;99:69–77.

216. Boghossian S, Dube MG, Torto R, Kalra PS, Kalra SP. Hypothalamic clamp on insulin release by leptin-transgene expression. Peptides 2006;27:3245–54.

217. Dhillon H, Ge Y, Minter RM, et al. Long-term differential modulation of genes encoding orexigenic and anorexigenic peptides by leptin delivered by rAAV vector in ob/ob mice: relationship with body weight change. Regul Pept 2000;92:97–105.

218. Kalra SP. Disruption in the leptin-NPY link underlies the pandemic of diabetes and metabolic syndrome: new therapeutic approaches. Nutrition 2008;24:820–6.

219. Kraynov V, Putnam AMAH, Knudsen N, Pinkstaff J, Myler H, Sullivan L. Modified Leptin Polypeptides and Their Uses. Available at: https://www.google.com/patents/EP2247743A4?cl=en; 2011. Accessed November 18, 2017.

220. Grasso P, Lee DW, Leinung MC. Leptin-Related Peptides. Available at: https://www.google.ch/patents/US7208572; 2007. Accessed November 18, 2017.

221. Grasso P, Rozhavskaya-Arena M, Leinung MC, Lee DW. [D-LEU-4]-OB3, a synthetic leptin agonist, improves hyperglycemic control in C57BL/6J ob/ob mice. Regul Pept 2001;101:123–9.

222. Trevaskis JL, Coffey T, Cole R, et al. Amylin-mediated restoration of leptin responsiveness in diet-induced obesity: magnitude and mechanisms. Endocrinology 2008;149:5679–87.

223. Trevaskis JL, Turek VF, Griffin PS, Wittmer C, Parkes DG, Roth JD. Multi-hormonal weight loss combinations in diet-induced obese rats: therapeutic potential of cholecystokinin? Physiol Behav 2010;100:187–95.

224. Williams DL, Baskin DG, Schwartz MW. Leptin regulation of the anorexic response to glucagon-like peptide-1 receptor stimulation. Diabetes 2006;55:3387–93.

225. Bhattarai BR, Kafle B, Hwang J-S, et al. Novel thiazolidinedione derivatives with anti-obesity effects: dual action as PTP1B inhibitors and PPAR-γ activators. Bioorg Med Chem Lett 2010;20:6758–63.

226. Lantz KA, Hart SGE, Planey SL, et al. Inhibition of PTP1B by trodusquemine (MSI-1436) causes fat-specific weight loss in diet-induced obese mice. Obesity (Silver Spring) 2010;18:1516–23.

227. Ericson E, Wennberg Huldt C, Strömstedt M, Brodin P. A novel role of the checkpoint kinase ATR in leptin signaling. Mol Cell Endocrinol 2015;412:257–64.