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Novel pathways regulating neuroendocrine function, energy homeostasis and metabolism in humans

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Abstract

The discovery of leptin, an adipocyte-secreted hormone, set the stage for unraveling the mechanisms dictating energy homeostasis, revealing adipose tissue as an endocrine system that regulates appetite and body weight. Fluctuating leptin levels provide molecular signals to the brain regarding available energy reserves modulating energy homeostasis and neuroendocrine response in states of leptin deficiency and to a lesser extent in hyperleptinemic states. While leptin replacement therapy fails to provide substantial benefit in common obesity, it is an effective treatment for congenital leptin deficiency and states of acquired leptin deficiency such as lipodystrophy. Current evidence suggests that regulation of eating behavior in humans is not limited to homeostatic mechanisms and that the reward, attention, memory and emotion systems are involved, participating in a complex central nervous system network. It is critical to study these systems for the treatment of typical obesity. Although progress has been made, further studies are required to unravel the physiology, pathophysiology and neurobehavioral mechanisms underlying potential treatments for weight-related problems in humans.

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Under stable environmental conditions, body weight is under homeostatic control, maintained relatively constant around a set-operating point (1). This weight stability is observed over short and prolonged periods of time (2). The energy homeostatic system is a complex

array of central nervous system (CNS) circuitry actively integrating peripheral metabolic feedback signals of either energy abundance or deficit and is much more complicated in humans than in rodents or other animals (1). According to these signals, adaptive changes to

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appetite and energy expenditure maintain body weight around this setpoint (3) (Fig. 1).

One such peripheral signal is leptin. Adipocyte-derived leptin is a feedback signal regulating energy intake and expenditure in mice and lean humans (4). In states of acute energy deficit and/or low body fat mass or leanness, low leptin levels trigger the hypothalamus to increase appetite and decrease energy expenditure in mice (5) and in humans. Our published and unpublished observations in humans indicate that although energy intake may be decreased in response to leptin, energy expenditure is not appreciably altered (6, 7). Although it might be assumed that in states of energy abundance such as obesity, leptin would be equally effective in defending the energy balance by increasing energy expenditure and decreasing appetite, this is typically not the case (8, 9). Other peripheral and/or CNS systems may be enacted to maintain the body weight setpoint (8, 9).

In terms of CNS mechanisms, human studies implicate several cortical and subcortical networks in the eating process, implying that appetite is regulated by higher cognitive functions such as cognitive control, memory, attention and emotions, as well as the reward system (10, 11). Other peripheral signals such as gastrointestinal, adipose tissue and skeletal muscle-derived peptides and hormones (e.g. GLP-1, gastric inhibitory peptide (GIP), adiponectin) also represent feedback signals regarding current energy status (12, 13, 14). Here, we begin discussing

leptin as a well-studied peripheral signal and its role in leanness before discussing typical obesity, which is a state of leptin tolerance or resistance, and the other peripheral/central mechanisms that may be at play in regulating body weight with a focus on human physiology.

Leptin biology

Adipose tissue, once considered to be an inert triglyceride storage organ, may now represent its largest endocrine organ. Circulating leptin, the prototypical adipocyte-derived hormone (15), constitutes a molecular signal to the CNS regarding the currently available amount of energy stored in adipose tissue and acute nutritional status, the circulating concentration of which is directly proportional to total body fat mass (16). Beyond being a longer-term energy signal, abrupt changes in caloric consumption are also reflected by circulating levels of leptin (17). Food restriction results in a sharp decline of leptin levels, at a greater level than would be expected from changes in fat mass, indicating its overall involvement in energy balance and metabolism (17, 18). Leptin also has a circadian rhythm, reaching its maximum level during the early nocturnal sleep period (19).

Leptin receptors are almost ubiquitously expressed in human tissues, highlighting the diversity of its impact on the human body ranging from reproduction to immunity (20). The leptin–leptin receptor complex activates several intracellular signaling pathways such

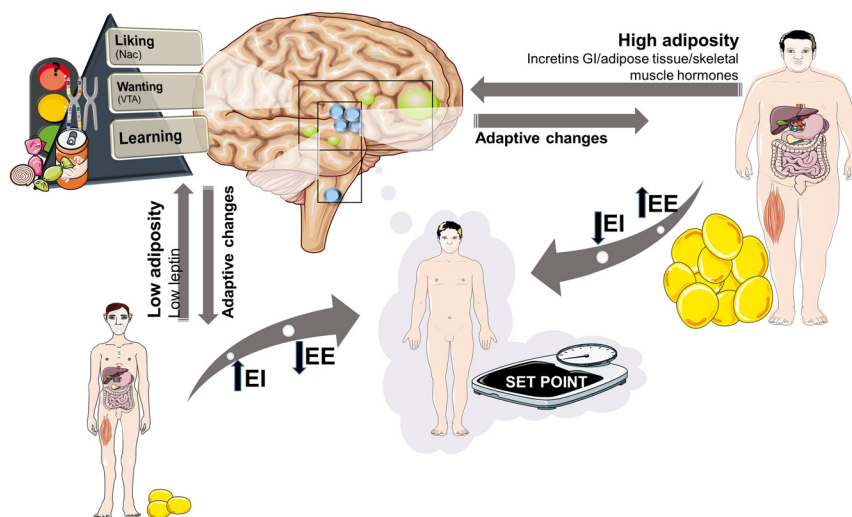


Figure 1

Body weight is determined by a set point, which is individualized based on genetics, hormonal input and neurocognitive changes. When body weight goes above or below this set point, there are certain mechanisms (hormones, energy intake (EI), energy expenditure (EE), brain changes) that will bring body weight back to this point. Treatments now attempt to alter this set point by altering these inputs. Some of the illustrations used have been downloaded from Servier Medical Art Database which provides these illustrations through the Creative Commons license (<https://creativecommons.org/licenses/by/3.0/>).

as Janus kinase 2-signal transducer and activator of transcription 3 (JAK2-STAT3) (21, 22, 23), insulin receptor substrate (IRS)-phosphatidylinositol 3 kinase (PI3K) (24), SH2-containing protein tyrosine phosphatase 2 (SHP2)-mitogen-activated protein kinase (MAPK) (25) and 5' adenosine monophosphate activated protein kinase (AMPK) – acetyl-CoA carboxylase (ACC) (26). The aforementioned molecular signaling pathways regulate energy homeostasis, anorectic/orexigenic pathways, glucose and fatty acid metabolism, insulin secretion and activation of cellular proliferation pathways (21, 24, 27, 28).

Central actions

In rat models, leptin receptors are expressed throughout the CNS, in the hypothalamus as well as in cortex, midbrain and hindbrain (29, 30, 31). Within the hypothalamus, a subpopulation of hypothalamic neurons in the arcuate nucleus (ARC) project outside the blood–brain barrier, exhibiting increased accessibility and sensitivity to circulating leptin (32). Two types of leptin receptor-expressing neurons in the ARC, neuropeptide Y (NPY)/agouti-related protein (AgRP) neurons and cocaine- and amphetamine-regulated transcript (CART)/pro-opiomelanocortin (POMC) are responsible for the synthesis of neurotransmitters promoting orexigenic or anorexigenic states, respectively (33, 34, 35, 36, 37, 38, 39). Thus, in states of positive energy balance and higher body fat, the subsequently elevated levels of leptin stimulate the POMC/CART neurons (inhibiting energy intake and promote energy expenditure), while the AgRP/NPY neurons are suppressed (inhibiting energy intake by suppressing appetite) (35, 38). As anticipated, in states of energy deprivation and low body fat levels, low levels of leptin results in the opposite aforementioned trends (40). These data, largely derived from mice, have not yet been confirmed in humans and thus relevant human trials are expected with great anticipation.

Our knowledge regarding the specific regions where leptin acts in the CNS is primarily based on behavioral, cognitive and physiology studies in rodents, the brains and metabolism of which are different than in humans. However, the utilization of continuously evolving neurocognitive and neuroimaging techniques, such as MRI, which allow investigators to noninvasively study brain structure and activation in humans (41). Morphologically, congenital leptin deficiency leads

to atrophy of gray matter in regions responsible for the regulation of eating in adults, that reverses with leptin administration (42, 43). In addition, leptin administration affects food-reward and homeostatic related brain regions (43, 44). On the other hand, acquired hypoleptinemia in three female patients was not associated with structural brain differences neither pre nor post leptin treatment (45). In these same patients, short-term administration of leptin increased the activation of cortical areas responsible for decision-related evaluative processes while fasting, when food is expected to be more salient (45). With long-term leptin administration, areas related to food saliency and reward processing in response to visual food stimuli were decreased (45). Hypothalamic activity was also investigated, and, with metreleptin, administration paradoxically increases when viewing food compared to controls at baseline, however, decreases after 24 weeks of metreleptin use in comparison to controls (45). This increased sensitivity to leptin may be explained as a response to chronic leptin deficiency with upregulation of leptin receptors and eventually corrects with leptin repletion (45). Additionally, a decrease in the functional connectivity of the hypothalamus with midcingulate, somatosensory and insular cortices was observed after metreleptin therapy in these women, suggesting a decreased saliency of food images (45). This is opposite to patterns observed in patients with obesity that lose weight and then are given leptin at a dose to return leptin to pre-weight loss levels (46). These trends suggest the complexity of leptin's interaction may depend on the initial etiology, but regardless, may help dictate feeding behavior (45). Whether and how leptin alters body weight and fat mass in lean (leptin-sensitive) vs obese (leptin-tolerant) humans remains to a certain extent unknown, and ongoing human studies along these lines are anticipated with great interest.

Leptin - regulation of neuroendocrine axis

The long active leptin receptor isoform is primarily expressed in the hypothalamus including nuclei involved in the regulation of energy balance (47, 48). This location places leptin in position to communicate energy balance but also to influence hypothalamus–pituitary–endocrine organ axes (49). As outlined below, this influence can vary between axes, species and etiology of leptin biology and dysregulation.

Hypothalamus–pituitary–adrenal (HPA) axis

The hormones contributing to this pathway include corticotropin-releasing hormone (CRH) causing adrenocorticotrophic hormone (ACTH) release, which in turn stimulates the adrenal gland to release hormones. Leptin and its receptor are both expressed within the hypothalamus and the pituitary gland, while only the leptin receptor is expressed in the adrenal gland (29, 30, 50, 51). *In vitro* studies demonstrate a direct relation of CRH secretion and leptin administration, a phenomenon also witnessed in lean rats after an 18-h fast (52, 53). In acutely starved mice, the stress response HPA axis activation diminishes with leptin administration, which has not been seen in small-scale studies of lean humans (5, 7, 54). Non-randomized investigations of congenital leptin deficiency do not indicate significant impairment of this axis (55, 56, 57). In our large randomized, placebo-controlled trial, leptin administration in women with hypothalamic amenorrhea induced statistically significant decreases in cortisol levels (58). In a similar manner, we demonstrate that fluctuations in circulating leptin levels inversely relate to those in ACTH and cortisol in healthy men (19). It appears that unlike rodent studies in which the effect is more profound, leptin affects the human HPA axis to a small extent and can be detected in larger, randomized studies.

Hypothalamus–pituitary–thyroid (HPT) axis

The HPT axis begins with thyrotropin-releasing hormone (TRH) inducing production of thyroid-stimulating hormone (TSH) which then stimulates assembly of thyroxine (T4) within the thyroid gland. Like TSH, leptin release exhibits a pulsatile pattern and circadian rhythm that becomes disrupted in deficiency (59). Leptin stimulates rat pro-thyrotropin-releasing hormone (proTRH) gene expression, which produces mature TRH (60, 61). Ob/ob mice display striking features consistent with congenital hypothyroidism that contrasts children with congenital leptin deficiency with normal thyroid function tests (TFTs) (56, 57, 62). Fasting-induced hypoleptinemia depresses T4 levels in rats, and this effect is ameliorated by leptin administration (5, 63). To investigate effects leptin has on TSH changes in men and women after acute caloric deprivation, we performed two studies. In lean men but not lean women, leptin administration blunts the decrease of TSH in response to fasting-induced hypoleptinemia (7, 54). Comparing

these results, leptin levels in the lean women studied did not reach the same magnitude as the men and thus, may suggest a threshold which leptin exerts an effect on the HPT axis (7, 54). Leptin may regulate human TSH secretion at higher levels; however, its role in downstream HPT hormone levels may be variable (6, 27, 64). The HPT axis also exhibits variable responses to leptin administration between relative acute hypoleptinemia and complete deficiency (6, 27, 64). Collectively, these data suggest hypoleptinemia downregulates the HPT axis and leptin replacement restores its function uniformly in rodent models; however, this trend is not consistently observed in human models where the effect of leptin to regulate thyroid hormones is rather limited.

Hypothalamus–pituitary–growth hormone (HPGH) axis

This axis begins with growth hormone-releasing hormone (GHRH) causing growth hormone (GH) production at the pituitary, which interacts with the liver, increasing insulin-like growth factor 1 (IGF-1) production. IGF-1 is associated with at least six IGF-binding proteins (IGFBP1–6), which can hinder and/or promote IGF-1 actions; thus, it is important not only to understand the levels of IGF-1 in total or active forms but also to understand the levels of the IGFBPs. GH and IGF-1 play key roles in body composition as well as growth where they increase muscle growth and lipolysis in adipose tissue, leading to weight loss and a leaner physique (65). Fasting-induced hypoleptinemia in rats inhibits GH secretion that reverses with leptin administration (66). Patients with congenital leptin deficiency present with normal linear growth during childhood; however, final adult height is decreased due to absent, sex hormone-driven, pubertal growth spurt (56, 57, 67). In contrast to rodents, humans with fasting-induced hypoleptinemia demonstrate increases in GH pulsatility, enhancement of GH secretion and total GH production and decreased IGF-1 levels and increased IGFBP3 (68, 69, 70). Total levels of IGFBP1, 4 and 6 did not show changes with leptin (70). Leptin administration restores IGF-1 levels in men but not women; however, no amelioration of GH pulsatility is observed in either sex (7, 54, 70). The same is true for states of acquired leptin deficiency, such as hypothalamic amenorrhea and anorexia nervosa (71, 72, 73). The varying IGF-1 response to leptin administration between our studies in men and women may again highlight a threshold for leptin action on

this axis (56, 57). Our group hypothesized that leptin may not directly be involved with GHRH-mediated GH secretion, but rather GH-associated IGF-1 secretion and its binding proteins (70). Aside from those mentioned above, other IGFBPs (total and/or intact) remain to be investigated to unravel the complex relationship between leptin and the HPGH axis in humans and these studies are underway.

Hypothalamus–pituitary–gonadal (HPG) axis

The hypothalamic component of this axis is gonadotropin-releasing hormone (GnRH) which stimulates the pituitary's gonadotropes to produce luteinizing (LH) and follicle-stimulating hormones (FSHs) which interact with sex-specific gonadal structures to produce androgens or estrogens. Human reproductive biology demands substantial energy investments and, therefore, is tightly associated with energy balance (74). In rodent models, leptin demonstrates profound influence over reproductive processes including puberty and ovulation by acting as a gatekeeper, permitting progression when adequate energy reserve exists (75, 76, 77, 78, 79, 80). Humans with congenital leptin deficiency display a similar reproductive phenotype of hypogonadotropic hypogonadism with axis function restoration after leptin treatment despite absent leptin receptors on GnRH-secreting neurons (56, 57, 81, 82, 83). It has been suggested that leptin does not directly act upon GnRH neurons but rather interacts with neurons afferent to them, such as AGP/NPY, POMC, and arcuate nucleus neurons expressing kisspeptin, bradykinin and dynorphin via KiSS-1 neurons (83, 84, 85, 86).

Disruptions in LH pulsatility and decreases in testosterone levels occur during fasting-induced hypoleptinemia in lean men, while in lean women LH peak frequency decreases, and in both cases, leptin restores to baseline with leptin administration (7, 54, 87). Women experiencing chronic energy deprivation may develop hypothalamic amenorrhea related to a severe decline in leptin levels, which is amendable to leptin administration. Women with chronic hypoleptinemia caused by hypothalamic amenorrhea have dysfunctional HPG function which is restored with leptin therapy (88, 89). Thus, leptin strongly influences the HPG axis in humans, and this physiological function has important pathophysiological and potentially therapeutic implications.

Hypoleptinemic states

Lipodystrophy: the case of lack of adipose tissue and low leptin

Lipodystrophy can be broadly categorized into generalized or partial forms and can be congenital or acquired. Generalized lipodystrophy indicates whole body subcutaneous adipose tissue loss while partial lipodystrophy describes local loss and redistribution of this tissue (90). While lipodystrophy is considered rare, objective diagnostic criteria are not yet established, often requiring long-term follow-up for confirmation (91). Conversely, acquired forms are more common and are often seen in patients receiving highly active antiretroviral therapy with a prevalence ranging from 13 to 70% (92, 93).

Complication severity with lipodystrophy, including abnormal glucose (insulin resistance, diabetes), hypertriglyceridemia and nonalcoholic fatty liver disease, correlates with the amount of adipose tissue loss and highlights the importance of adipose tissue as an active endocrine organ (93, 94).

Patients with lipodystrophy can also present with neuroendocrine axis abnormalities. While pubertal development is appropriate, these patients still have attenuated LH response to luteinizing hormone-releasing hormone, irregular menses and amenorrhea, all of which can be corrected with leptin treatment (80, 95). The thyroid, adrenal and GH axes do not exhibit profound dysfunctions, and leptin treatment only significantly increases IGF-1 levels (95, 96).

The first studies investigating recombinant human methionyl leptin (metreleptin) as a replacement therapy in lipodystrophy demonstrate dramatic improvement in most metabolic abnormalities, including insulin resistance (80). Given the observed potential development of leptin-neutralizing antibodies, the US Food and Drug Administration approved metreleptin in 2014 for the treatment of congenital and acquired generalized lipodystrophy, and in Japan, it is approved for all types of lipodystrophy by the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) (97). Studies, which supported the approval of metreleptin for lipodystrophy treatment have been open-label in design with small sample sizes (80, 98, 99, 100, 101). Results from much-needed ongoing RCTs will more clearly evaluate metreleptin's safety, efficacy and cost-effectiveness (90).

Hypothalamic amenorrhea

Hypothalamic amenorrhea (HA) represents a chronic energy-deficient state associated with excessive energy expenditure, decreased caloric consumption or excessive stress causing infertility, neuroendocrine abnormalities and osteoporosis (89). Independent of body fat, exercise intensity is inversely related to serum estradiol and directly related to leptin levels (102). Amenorrheic athletes display lower leptin levels than their eumenorrheic counterparts (103).

The dysregulation of ovulatory function results from an absent LH surge, a consequence of impaired pulsatile secretion of GnRH (88). Other hormones, the activin-follistatin system, have been implicated as a largely leptin-independent system that also modulates the HPG axis during acute and chronic hypoleptinemic states (104). Hormones of this system include activin A, activin B, follistatin and follistatin-like 3 (FSTL3) of which all, excluding follistatin, decrease in response to states of energy deprivation with subsequent downregulation of the HPG axis through interactions with the pituitary gland and the gonads to decrease follicular growth, hormone production, Sertoli cell proliferation and germ cell development (104, 105, 106). The development of HA in chronic energy-deficient states illustrates impairment of the HPG axis; however, it appears each of the hypothalamic axes are affected as an adaptive mechanism for homeostatic maintenance. Activation of the HPA axis occurs in response to this stress, identified by increasing levels of CRH, ACTH, cortisol and increased adrenal sensitivity to ACTH (107, 108). Conversely, suppression of the HPT axis occurs with low-normal TRH, decreased T3 and increased reverse T3 (88). Despite increased 24-h GH levels, basal IGF-1 concentration is significantly decreased (70, 109), but the exact effect on free IGF-1, IGFBPs, and total vs intact components of the IGF axis remains to be fully elucidated.

Our group's proof-of-concept pilot study and subsequent randomized, placebo-controlled trial assessing leptin as a possible treatment of for HA demonstrated that leptin resulted in recovery of menstruation and improved neuroendocrine dysfunction with increased FT3 levels, IGF1:IGFBP3 ratio and decreased cortisol levels (5, 6, 54, 70, 73). Regarding the activin-follistatin system, leptin administration improved only levels of activin B, again reinforcing the leptin-independent nature of this system (104). These results illustrate that chronic hypoleptinemia influences neuroendocrine abnormalities associated with HA primarily in the HPG, HPT, HPA and to a lesser extent

the hypothalamic–pituitary–GH axis (6) – the effect on which remains to be fully elucidated by ongoing studies.

Another consequence of ovulatory dysfunction and decreased estrogen levels in HA is impairments in bone health. In these models, leptin acts to positively regulate bone metabolism (110). Leptin treatment for 4 weeks in HA women results in increased markers of bone formation which remained significantly elevated during the study period without significant effects on bone resorption markers (6, 73). Two-year metreleptin treatment significantly increases bone mineral density at the lumbar spine by 4–6% (58). Intact parathyroid hormone (iPTH) and receptor activator of nuclear factor kappa-B ligand (RANKL) to osteoprotegerin (OPG) ratio levels were significantly decreased after 36 weeks of leptin treatment (111). These trends of iPTH and RANKL:OPG are postulated in being beneficial to bone metabolism (111, 112, 113).

According to the 2017 Endocrine Society Clinical Practice guidelines, leptin is not recommended for the improvement of bone metabolism or fertility treatment in adolescents and women with functional HA. The small yet significant weight loss, development of leptin antibodies during treatment with the currently available compound and alternative therapeutic options such as cognitive behavioral therapy limit the use of the current formulation of leptin as a treatment for HA (97, 114, 115). We have shown, however, that with leptin dose adjustments one could avoid weight loss while still maintaining the desired hormonal (6) and metabolic and bone metabolism outcomes (58) without any decreases in lean body mass (116). In other words, when achieved leptin levels remain within a range of physiological leptin levels, neuroendocrine abnormalities and fertility are restored, and weight loss occurs only when leptin levels increase above the upper physiological level. Moreover, the weight lost was primarily fat mass whereas lean mass remained unchanged or increased. Larger studies for longer study periods with careful metabolic monitoring and dose adjustments need to be conducted so as safety and efficacy could be assessed (114). Moreover, investigations into alternative leptin analogs not triggering anti-leptin antibodies could potentially alleviate immunogenic concerns.

Common obesity

Obesity is a worldwide health problem directly related to leading causes of preventable death including

cardiovascular disease, type 2 diabetes and cancer (3). In an effort to address the complexity of this chronic medical problem, obesity has been declared as a disease by several scientific organizations (3).

Evidence from adoption, twin and family studies estimate heritability of BMI between 40 and 70%, highlighting the role of genetic contribution in obesity (117). Seventy-nine syndromes associated with obesity are reported in the literature with a substantial portion following Mendelian patterns of inheritance stressing the role genetics has in obesity (118). The most common cause of monogenic obesity results from mutations in the leptin–melanocortin pathway encoding the MC4R receptor (119). However, these mutations account for less than 10% extreme obesity cases (3). Genome-wide association studies support a polygenic nature for common obesity by identifying hundreds of SNPs associated with this pathology (120). Modifiable epigenetic changes from *in utero* and postnatal exposures have also been associated with obesity and may be targets to prevent future adverse metabolic outcomes (121). Looking at this modifiable factor, two pregnancy cohorts suggested that maternal adherence to a Mediterranean diet in early stages of pregnancy resulted in lower child adiposity and improved cardiometabolic outcomes (122).

Environmental factors related to diet, food intake and physical activity have also been linked to obesity. Larger portions of low-nutrient, high-caloric, palatable food consumed at irregular meal patterns by sedentary individuals are all factors promoting obesity (123). With the use of functional MRI (fMRI), internal factors including post-prandial decreased activation in reward-related putamen and salience- and reward-related insula in fasting subjects with obesity and prediabetes are hypothesized to underlie caloric intake, which leads to these conditions (124). Altogether, these environmental and central mechanisms in combination with genetic, epigenetic and other mechanisms create a complex disease in need of effective therapies.

Following observations of dramatic weight reducing effects of leptin administration in rodents and humans with congenital leptin deficiency, leptin was assumed to be an anti-obesity hormone (125). Although the discovery of leptin generated hopes of successfully treating obesity, results from clinical trials in typical obesity demonstrate significant weight loss only with supraphysiologic doses not well tolerated, thus limiting its application as an anti-obesity medication in clinical practice (126, 127). While leptin treatment alone may not be feasible in typical obesity, other effective medications have been

developed. However, downstream effectors of leptin may still be effective at treating obesity, and some, such as melanocortin receptor agonists, are currently being investigated for their potential use in obesity (128, 129, 130, 131).

Pointed investigation of pharmaceutical targets for obesity treatment largely distills from observational peripheral hormone changes following bariatric surgery (132). These hormones include, but are not limited to, leptin, gastrin, ghrelin, cholecystokinin, GLP-1, oxyntomodulin, GIP and peptide YY (PYY) (133, 134). Many of these molecules have been (GLP-1 as liraglutide) or are being developed (oxyntomodulin, GIP, etc.) for the treatment of obesity. Other medications approved for obesity target the brain directly, instead of the periphery, to alter appetite (e.g. lorcaserin, phentermine/topiramate, bupropion/naltrexone).

Liraglutide is a GLP-1 receptor agonist that acts peripherally and centrally to induce weight loss through its interplay with POMC/CART and AgRP/NPY neurons while also displaying interaction with cortical areas in mice (135). Our group identified presence of GLP-1 receptors in the hypothalamus, medulla and parietal cortex of humans (136). In rodent models, GLP-1 suppresses the excitatory input destined for the mesolimbic dopamine neurons of reward pathways causing decreases in food intake (137). This pathway highlights just one of the many neural circuits where GLP-1 acts; however, there is minimal interaction with cortical centers in rodents (138). In humans, there appears to be additional GLP-1 action more peripherally in cortical areas of the CNS, as we recently demonstrated. We performed a randomized, controlled trial to demonstrate that GLP-1 receptors are expressed in several brain areas including the parietal cortex (136). Liraglutide treatment decreases brain activation of this and similar cortical areas, and therefore, the attention and reward networks, in response to highly desirable food cues (136). Interestingly, the amplification of fasting-induced hypoleptinemia in response to liraglutide treatment, increased activation of reward-related brain regions and decreased activation of attention-related brain areas (11). This highlights the compensatory role of low leptin levels in appetite and provides a theoretical rationale for combination therapies of GLP-1 with leptin analogs (11).

Lorcaserin is a medication which acts centrally as a 5-hydroxytryptamine 2C (5HT2C) receptor agonist possibly through stimulation of POMC neurons (139, 140). Our group demonstrated in a RCT that lorcaserin decreased food cue activation of brain networks associated with attention and saliency, again, highlighting more

interactions with cortical systems in humans (10, 11). In contrast to rodent studies with lorcaserin, hypothalamic activation was not observed and highlights interspecies differences of brain complexity/function (10, 141). Our study further determined that baseline activation of the amygdala (a component of the emotional/limbic system) was directly correlated to weight loss success with lorcaserin, suggesting it decreases food intake by decreasing the emotional significance of highly palatable food cues (10). Future research will continue to delineate the brain areas which are impacted by anti-obesity therapies. Defining the brain areas in which different medications work to treat obesity work in humans, using fMRI and/or PET imaging, can lead to the elucidation of underlying mechanisms in humans, which have brains very different from the brains in rodents that have served as the experimental model to date, and thus, could lead to effective single or combination therapies leveraging complementary mechanisms.

Conclusions

Ultimately, experimental data from rodents generate hypotheses and provide mechanisms that may or may not directly translate to human physiology, making it difficult to directly translate hypotheses raised by studies in rodents into findings and data in humans indicating the necessity for novel translational methods and efforts that would be performed in an ethical manner but apparently overcoming the inconsistencies associated with historical methods. Rapid advancement and availability of neuroimaging, such as fMRI, PET scans or other novel techniques, allow for in-depth investigation of the neurophysiological underpinnings of weight balance in human brains, and in the future, may help further elucidate pathways responsible for weight regulation and obesity. Treating underlying pathology with novel medical therapies to address the problem of dysregulated energy homeostasis proves daunting given the complexity of pathways contributing to the body's response toward energy balance.

While metreleptin shows clear evidence of efficacy for treating obesity and leptin-deficient states, the side effect profile and immunogenicity of the currently available formulation limits widespread use and endorsement for disease states other than complete leptin deficiency. Further investigation into compounding leptin with other substances for synergistic and/or development of novel compounds with less immunogenic effects are ongoing.

Ultimately, in order to further investigate leptin's role in the future, more RCTs with greater number of participants and thus power are needed and appropriate use of databases as well as real-world trials and/or the leverage of patient registries worldwide may prove to be more effective.

Appetite and body weight regulation in humans is complicated, involving the integration of massive amounts of data reflecting the status of our internal and external environments. A seemingly infinite interplay of hormones, receptors, neurons and cells all coordinate to shape our body and its response in an ever-changing environment. Analysis of these data will require a combination of efforts of scientists working not only in human physiology and therapeutics but also in biology and neurosciences and the vast amounts of data to be collected would require novel mathematical modeling for their analysis and reduction to practice in order for us to be able to provide tangible benefits to suffering humans in the not so distant future (142, 143).

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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