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Leptin and the endocrine control of energy balance

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The discovery of leptin changed the view of adipose tissue from that of a passive vessel that stores fat to that of a dynamic endocrine organ that actively regulates behaviour and metabolism. Secreted by adipose tissue, leptin functions as an afferent signal in a negative feedback loop, acting primarily on neurons in the hypothalamus and regulating feeding and many other functions. The leptin endocrine system serves a critical evolutionary function by maintaining the relative constancy of adipose tissue mass, thereby protecting individuals from the risks associated with being too thin (starvation and infertility) or too obese (predation). In this Review, the biology of leptin is summarized, and a conceptual framework is established for studying the pathogenesis of obesity, which, analogously to diabetes, can result from either leptin hyposecretion or leptin resistance. Herein, these two states are distinguished with the terms 'type 1 obesity' and 'type 2 obesity': type 1 obesity describes a subset of obese individuals with low endogenous plasma leptin levels who respond to leptin therapy, whereas type 2 obesity describes most obese individuals, who are leptin resistant but might respond to leptin therapy in combination with other drugs, such as leptin sensitizers.

Historical considerations

A large body of evidence dating to Lavoisier has shown that the same laws that govern chemical and physical processes in inanimate systems also apply to bioenergetics in living organisms[1]. The second law of thermodynamics states that energy within a system must be conserved and that any change must result from either a change in the energy input to, or output from, that system. Thus, among mammals, in which energy is stored primarily as energy-rich triglycerides (9 kilocalories per gram) in adipose tissue, any change in weight (fat mass) must necessarily be a result of changes in energy input (food intake) and/or energy expenditure. For weight to remain stable in a living organism, energy input thus must be precisely balanced against energy output over long periods of time.

When food is readily available, adult humans maintain a remarkably stable weight while consuming approximately 1 million kilocalories each year[2]. Collectively, these findings have long suggested the existence of a biologic mechanism indexing food intake to energy expenditure to maintain the stability of weight and adipose tissue mass[3,4]. Maintaining the stability of energy stored in adipose tissue is also essential for survival, because lower levels of body fat have deleterious consequences by increasing the risk of starvation during periods of food insecurity or famine, as well as decreasing fertility and immune function; in contrast, a higher adipose tissue mass increases the risk of predation[5–8].

It had thus been postulated that nutritional state, probably from a fat-derived signal, is sensed to maintain homeostasis of adipose tissue mass[4]. However, the identification of the molecular components of this putative system has proven elusive, owing in part to the intrinsic difficulty in applying biochemical methods to identify signals that physiologically regulate food intake or energy expenditure in vivo. This difficulty is further compounded by the ability of many factors to decrease food intake by non-specifically eliciting an aversive (non-physiologic) response, including nausea and other unpleasant sensations.

Clues from genetic models of obesity

A clue as to the identity of the factors that regulate energy balance was provided by the identification of the recessive mouse obese (*ob*) mutation in 1950 (ref. [9]) and the subsequent identification of the diabetes (*db*) spontaneous mutation, both of which cause mice to develop massive obesity and show identical phenotypes on the same genetic background[10,11]. A similar phenotype also develops in genetically obese rats carrying the fatty (*fa*) mutation[12]. These fully penetrant recessive mutations cause extreme obesity and insulin-resistant diabetes as part of a complex syndrome including a broad set of unusual abnormalities not generally observed among obese humans, including infertility, immune alterations and hypothermia[13]. The explanation for this unusual constellation of abnormalities is explained in further detail below.

The extreme obesity of these mutants resembles that in animals with lesions of the ventromedial hypothalamus (VMH), thus suggesting that the encoded gene products might interact with this brain region, although whether the lesion also affects neurons in adjacent nuclei or fibbers of passage was unclear[14]. A possible function of this brain region was first suggested in the late 1950s in studies using parabiosis (a surgical union of two animals, resulting in chronic blood exchange) between wild-type and VMH-lesioned rats. In these experiments, the paired wild-type animals showed decreased food intake and a substantial loss of fat mass, whereas the phenotype of the lesioned animals was unchanged[15]. This observation suggested that animals with hypothalamic lesions overproduce a blood-borne signal that normally decreases weight, but, because of the lesion, they cannot respond. The lesion was further suggested to lead to a compensatory increase in the level of humoral factor, thus resulting in weight loss in the paired animal with a normal hypothalamus.

Later studies showed that, similarly to the results after parabiosis of animals with hypothalamic lesions, wild-type mice parabiosed to *db* mice, and wild type rats parabiosed to *fa*/*fa* rats also lost large amounts of weight, thus suggesting that these gene products might be expressed in the hypothalamus[11,16,17]. Finally, similarly to wild-type mice, *ob* mice parabiosed to *db* mice lost copious amounts of weight, thus indicating that they respond normally to the elevated levels of the putative humoral factor circulating in *db* mice. This finding suggested that *ob* mice carry a mutation in the humoral factor[11,18]. In aggregate, these results, derived from several different laboratories over the course of multiple decades, led to an internally consistent hypothesis that *ob* mice are obese because they do not

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produce a hormone that regulates food intake and body weight; *db* mice and *fa* rats are obese because they do not express the receptor for that factor; and finally, the receptor should be expressed in the hypothalamus. However, despite intensive research, the identity of the putative hormone and its site of expression were unknown until the *ob* gene was identified[19]. As described below, subsequent studies confirmed that all elements of this hypothesis are largely correct.

Identification of leptin and its receptor

The *ob* gene was identified in 1994 through positional cloning and shown to be expressed in adipose tissue as a secreted ~14-kDa polypeptide[19]. In agreement with the aforementioned hypothesis, the gene product circulates in plasma in normal animals, and its levels are elevated in *db* mice and decrease after weight loss[20,21]. Administration of the hormone, named leptin, was found to significantly decrease body weight and adipose tissue mass in *ob* mice and wild-type animals, but to have no discernible effect in *db* animals[22–24]. In contrast to weight loss after dieting, leptin had no effect on decreasing lean mass. These and subsequent data from animals have established that leptin levels increase when fat mass increases, thereby suppressing food intake, whereas weight loss leads to a decrease in leptin levels and a consequent increase in food intake. This mechanism maintains homeostatic control of adipose tissue mass within a relatively narrow range, thus serving an important evolutionary function. Although the effects of leptin treatment in humans have been less well studied, the available evidence suggests that leptin serves the same function in humans (described below).

Subsequent studies have shown that this new hormone acts primarily on a cytokine family receptor encoded by the *db* gene expressed in discrete neural populations in the hypothalamus and elsewhere in the brain[25–28] (Fig. 1). Several splice variants of the leptin receptor exist. All but one of the different mutant strains of *db* mice and *fa* rats carry null mutations that affect all of the splice variants[26,27,29]. However, the original *db* strain, maintained on the C57BLKS genetic background, has an unusual mutation affecting only one of the splice variants, ObRb, while leaving the function of the other forms unaltered[26,27]. The ObRb isoform has a long cytoplasmic region containing multiple motifs required for signal transduction, whereas the other isoforms do not. In addition, whereas the other splice variants are expressed in many tissues, ObRb is highly enriched in the hypothalamus[26,30]. Because the phenotype of this mutant is identical to those of animals with null mutations, these findings provided initial evidence that leptin acts primarily in the hypothalamus. In agreement with this hypothesis, plasma levels of leptin increase after hypothalamic lesions, and low doses of intracerebroventricular leptin replicate the effects of much higher doses of peripheral leptin[21,31]. A brain-specific knockout of the leptin receptor leads to obesity, whereas brain-specific expression of the leptin receptor suppresses obesity in *db* mice[32,33]. Leptin is thus unusual in that it is the only peptide hormone whose principal site of action is in the brain. The only site outside the central nervous system for which a direct effect of leptin has been confirmed is on immune cells[34–36].

Leptin signal transduction. The leptin receptor is a member of the JAK–Stat family, and leptin-receptor signalling activates the JAK2 kinase, which phosphorylates and activates the Stat3 transcription factor in the hypothalamus as well as in immune cells, but has much weaker effects in other tissues[30,37]. A point mutation in the Stat3-binding site of the leptin receptor results in recapitulation of much of the obesity of *db* mice, as does brain-specific knockout of JAK2 and Stat3, thus establishing the importance of this signal-transduction pathway[38–40], although roles for several other signal transduction pathways have also been suggested[41–43]. Leptin also activates the regulatory proteins SOCS3 and PTP1b, both of which diminish leptin signaling[44–47] (Fig. 2). A mutation of the SOCS3-binding site on the leptin receptor potentiates leptin action, as does a SOCS3 knockout[44,47].

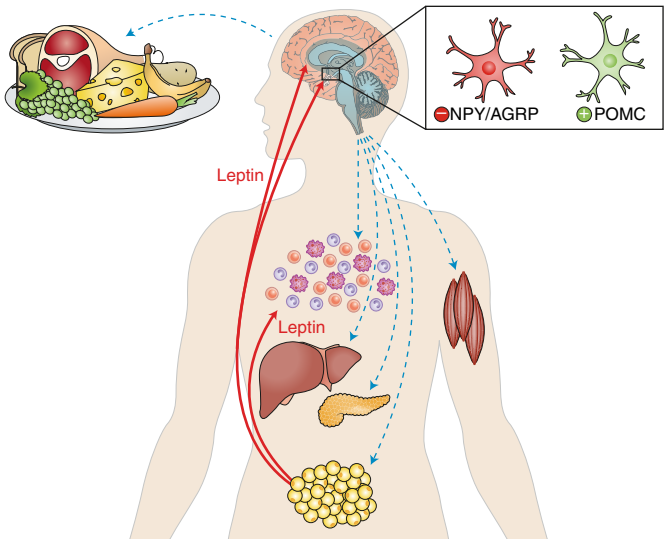

Fig. 1 | Leptin loop and target tissues. Leptin is the afferent signal in a negative feedback loop that maintains homeostatic control of adipose tissue mass and links changes in energy stores to a set of adaptive physiologic responses. Leptin is secreted by adipose tissue and regulates food intake, metabolism and numerous other physiologic processes. The signalling form of the leptin receptor (LepRb) is expressed primarily in the brain, and most of leptin's effects on end organs are indirect via the central nervous system. Leptin also regulates immune function via the central nervous system and also acts directly on immune cells, which also express high levels of LepRb. Leptin regulates the activity of key neural populations in the arcuate nucleus of the hypothalamus, where it inhibits orexigenic NPY/AGRP neurons while stimulating anorexigenic POMC neurons. Leptin also acts on other brain regions and regulates behaviour, metabolism, thermogenesis, the neuroendocrine axis, immune function and many other physiologic processes.

A negative feedback loop regulating adipose tissue mass

Leptin modulates food intake and body weight largely, although not exclusively, by stimulating pro-opiomelanocortin (POMC) neurons and inhibiting neuropeptide Y and Agouti-related protein (NPY/AGRP) neurons in the arcuate nucleus of the hypothalamus[48–51]. This brain region is adjacent to the median eminence, a circumventricular organ with a porous blood–brain barrier. An earlier study of mice with leptin-receptor knockout in POMC neurons provided evidence that these neurons diminish food intake and body weight after leptin treatment[52]. However, a recent report showing that a CRISPR knockout of the leptin receptor in AGRP neurons causes massive obesity suggests that this neural population is the principal target mediating leptin's effects on energy balance[52]. However, mutations that disrupt melanocortin signalling in animals and humans cause leptin resistance and obesity, thus suggesting that they also mediate some of leptin's effects (described below and in refs. [53–56]). POMC neurons also regulate glucose metabolism in response to leptin independently of effects on body weight[52].

Leptin has been shown to acutely affect the firing rate of POMC and NPY/AGRP neurons in slice preparations via effects on specific ion channels, although it is not known how the leptin signal-transduction pathway alters the function of these channels or how leptin activates firing of some cells (POMC neurons) while inhibiting others (such as NPY/AGRP neurons)[57–59]. Leptin treatment of *ob* mice also elicits rapid and substantial plasticity of the synaptic inputs to NPY/AGRP and POMC neurons, with opposite effects on

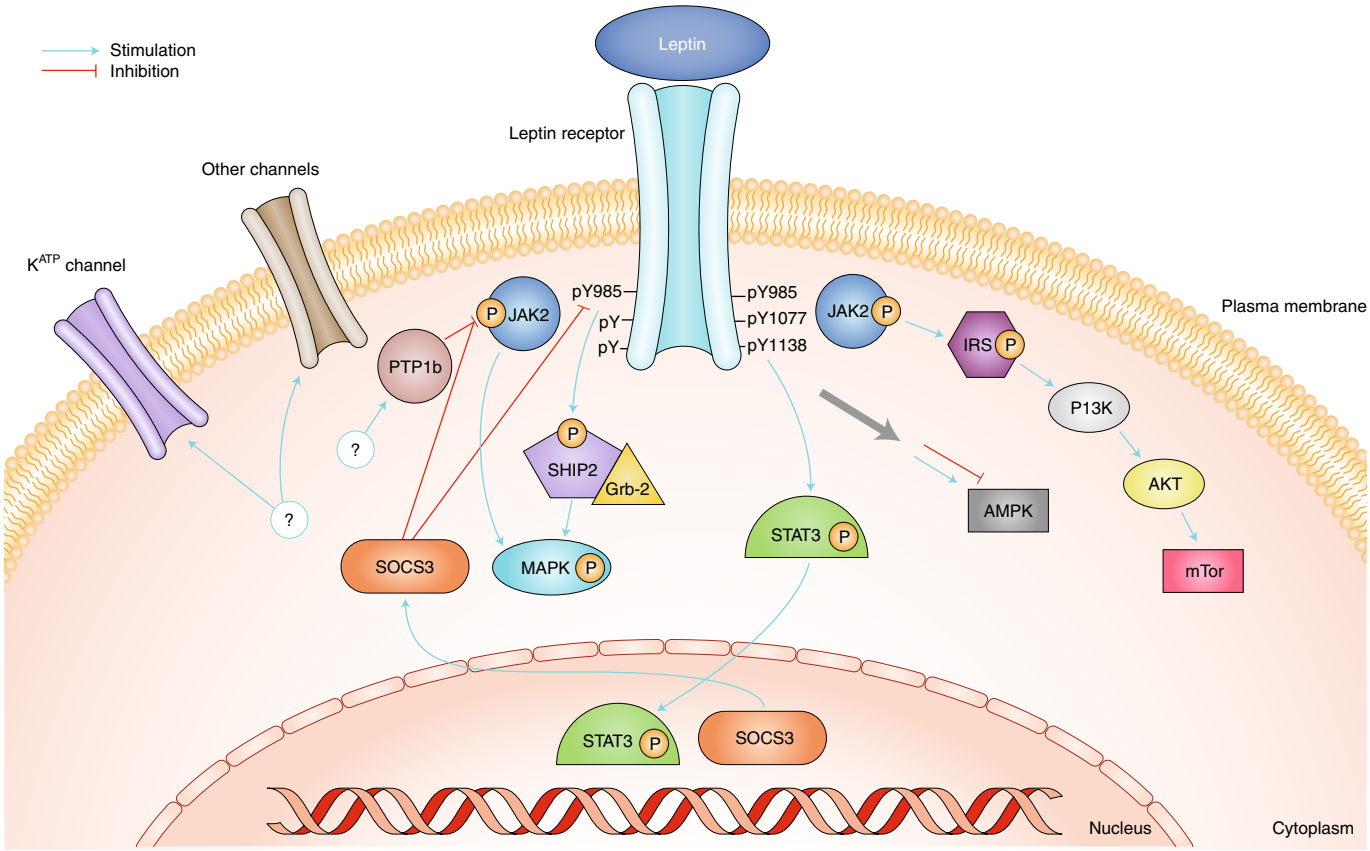

Fig. 2 | Leptin-receptor signalling. The leptin receptor is a cytokine family receptor. Leptin binding activates the JAK2 kinase, thus leading to the phosphorylation of three tyrosine residues on the C-terminal receptor intracellular domain. This phosphorylation leads to binding of Stat3 to Y1128; this residue is then phosphorylated, and SHP2 is subsequently activated and binds Y985. pStat3 increases expression of specific genes, whereas SHP2 activates the MAPK signal-transduction pathway. Stat3 induces the transcription of several genes, including *SOCS3*; SOCS3 in turn inhibits JAK2 and diminishes leptin signalling via interactions with Y985. Leptin signalling is also decreased by PTP1b, a phosphotyrosine phosphatase, although the factors regulating its activity in leptin-responsive neurons are unknown[148]. Several other signal-transduction pathways are activated by leptin, and, although inhibitors of these pathways have been shown to blunt some of leptin's actions, the cellular mechanisms controlling their activation in neurons have not been fully characterized. Leptin signalling in neurons has been reported to regulate neural activity in part by gating of a K^{ATP} channel, although the signal transduction regulating this and other channels has not been elucidated. Leptin has also been shown to regulate the synaptic inputs to NPY/AGRP and POMC neurons, although how leptin activates some neurons, such as POMC neurons, while inhibiting NPY/AGRP and other neural populations, remains unclear. AMPK, AMP kinase; mTor, mammalian target of rapamycin; PI3K, phosphatidylinositol 3,4,5-trisphosphate; SHIP2, PI3K 5-phosphatase 2; Grb-2, growth factor receptor-bound protein 2; AKT, RAC-alpha serine/threonine-protein kinase. Figure adapted from ref. [148], Faculty of 1000 Ltd.

each, and is also necessary for the development of a specific hypothalamic projection[60,61]. These neurons modulate food intake via numerous projections to other brain regions including the parabrachial nucleus, which conveys satiety signals and nausea, and the paraventricular nucleus of the hypothalamus[62,63]. When active, AGRP neurons convey a negative valence (that is, the unpleasant sensation of hunger), thereby augmenting the drive to eat. Ingestion of food alleviates this negative sensation by suppressing the activity of the NPY/AGRP neurons[64]. Leptin also modulates the activity of reward pathways and decreases food intake partially by decreasing the hedonic value of food[65]. Direct effects of leptin on higher centres have also been reported, including the hippocampus, where leptin appears to exert an antidepressant effect[66]. Numerous other neural populations also respond to leptin and mediate various aspects of leptin's diverse effects[67–73]. Overall, tracing of the neural pathways regulated by leptin has led to a detailed circuit map of the neural pathways that regulate feeding, which now encompasses the most detailed wiring diagram of any complex behavior[74].

One of the remaining questions is the mechanism by which leptin crosses the blood–brain barrier and subsequently acts on deeper structures. Approximately half of leptin's action is mediated by direct effects on dendrites close to the median eminence, which has a permeable blood–brain barrier[75]. Leptin can also cross the blood–brain barrier and is found in the cerebrospinal fluid[76]. Recent evidence suggests that leptin may be transported into the cerebrospinal fluid by tanycytes, although leptin might possibly also be transported across the vascular endothelium via a yet-unknown mechanism[77]. Although a recent report did not find the leptin receptor in tanycytes, the data do not exclude the possibility that other molecules might transport leptin, such as megalin, which transports leptin out of the renal tubules[78–80]

Perhaps the key unanswered question is how and where complex sensory and interoceptive information is processed by the brain to initiate feeding rather than other competing behaviours. In other words, how and where is the decision to eat made? In a classic set of papers, Tinbergen provided a conceptual basis for considering the hierarchy of the motor behaviours needed to complete a goal-directed behavior[81]. In 1906, Sherrington referred to the anatomic site at which the integrated movements of a reflex are controlled as the final common pathway[82,83]. Advances in neuroscience now

provide an opportunity to overlay specific circuits and neural populations on the ethologic framework provided by Tinbergen and the neurobiologic framework provided by Sherrington. Although the neural basis of most reflexes has been delineated, the sites at which the coordinated movements of feeding are controlled are only recently emerging[84]. An important advance has been the identification of neurons in the reticular formation and periaqueductal gray that are required for the control of the motor outputs required for feeding. On the basis of this information, together with findings from other studies identifying the primary nodes processing relevant sensory and interoceptive information[48], it should now be possible to link the relevant inputs and outputs and to establish the anatomic sites and neural mechanisms that control the initiation of feeding behaviour. Indeed, a circuit map for feeding in *Drosophila* linking sites of sensory input to sites of motor output has been constructed[85], and analogous studies aiming to link inputs and outputs in the mammalian brain are underway. The critical neural population responsible for the decision to eat should be the final node in the circuit that can activate the behaviour and satisfy the following criteria: (i) activation of the key neurons should lead to the initiation of the complete behaviour; (ii) these neurons should directly or indirectly receive relevant inputs and connect to the relevant motor outputs; (iii) these neurons should activate feeding even when other sites that inhibit feeding are also modulated; (iv) inhibiting these neurons should prevent feeding even if other sites that induce feeding are modulated; and (v) activating these neurons should extinguish competing behaviours. Broad advances in neuroscience have made the question of how and where behavioural decisions are made tractable and within reach.

Leptin and the adaptive response to starvation

In addition to increasing appetite, the absence of leptin in *ob* mice is associated with many physiologic changes including hypothermia, infertility, immune alterations, the insulin resistance of starvation and a euthyroid sick state, among many other changes not generally associated with obesity[13]. Instead, this set of physiologic changes is generally associated with starvation, thus suggesting that *ob* mice are obese because their brains interpret a low leptin level as a signal that the adipose tissue mass is dangerously low. For this reason, *ob* mice, while eating voraciously and showing a massive increase in weight, manifest a syndrome distinct from that generally associated with obesity. This observation initially suggested that leptin levels, in addition to inducing a state of positive energy balance to restore the lost weight, activates an adaptive 'starvation' response whose net effect is to conserve energy during times of privation. Consequently, leptin treatment corrects all the aforementioned abnormalities, including the reproductive defects in *ob* mice[86,87]. Leptin is also required for the normal onset of puberty[88,89]. In addition, leptin ameliorates the immune and neuroendocrine alterations that accompany food restriction, although the precise thresholds for these different responses appear to be subtly different[34,90]. Thus, in leptin-deficient animals, leptin has pleiotropic effects and provides a link between changes in nutritional state and physiologic responses in many (perhaps all) other physiologic systems.

Increases in leptin levels in mice or rats have the opposite effect on energy balance and lead to weight loss by decreasing food intake and suppressing the compensatory decrease in energy expenditure that is typically associated with dieting[22–24]. Overall, there is a graded decrease in fat mass in mice with incremental increases in leptin concentrations within the physiologic range, thus providing evidence that hyperleptinaemia in normally responsive animals restricts weight gain[31]. However, in contrast to treatment of leptin-deficient animals, increasing the physiologic leptin concentrations has few other discernible effects on other physiologic systems. The weight loss induced by leptin treatment is a result of lipolysis via activation of sympathetic efferent signalling and subsequent decreases in adipose tissue[91]. However, although analysis of the respiratory quotient indicates that lipids are being oxidized, the sites at which fat is burned have not been precisely determined[92].

In the leptin system, similarly to other endocrine systems, increasing leptin concentrations above the physiologic range in rodents decreases weight, and the dose–response curve of the effects of exogenous leptin on energy balance is not linear; in addition, a proportionately greater decrease in food intake and body weight is observed after treatment of animals with absent or low leptin levels compared with treatment of normal, lean animals. Thus the potency of leptin is greater when leptin levels are low, and a diminished response occurs as the levels approach the physiologic range or higher. In aggregate, the data indicate that leptin is a long-term signal that maintains homeostatic control of adipose tissue mass. Abundant evidence has also indicated that hormonal and neural signals from the gastrointestinal tract comprise a short-term system regulating hunger and satiety[93–95]. The brainstem is a primary site of action of these short-term signals, which interact extensively with leptin-activated circuits originating in the hypothalamus. Other signals might possibly also restrain weight gain when obesity develops, although their precise identity has not been determined[96,97]. Overall, these findings establish that leptin is a key means through which nutritional changes are sensed and elicit adaptive physiologic responses.

Leptin and the pathogenesis of obesity

Leptin deficiencies. The identification of the leptin endocrine system has provided a framework for understanding the pathogenesis of nutritional disorders including obesity and other forms of metabolic disease. In general, endocrine disorders can result from hormone deficiency (complete or partial) or hormone resistance. Rodents with a complete deficiency as a consequence of leptin mutations, as well as those with a partial deficiency, lose copious amounts of weight with leptin treatment[21–23,98]. In addition, animals with lipodystrophy—which have diminished leptin levels as a result of defects in adipose tissue differentiation that prevent fat-tissue formation—show marked metabolic improvements on leptin therapy as well as weight loss[99].

Another aetiology for diminished leptin expression has recently been identified in animals with a mutation in a fat-specific long non-coding RNA, LncOb[91]. On both chow and high-fat diets, the knockout mice show increased fat mass with decreased leptin levels, despite becoming more obese. The diet-induced-obese (DIO) LncOb mice also show significant weight loss after leptin treatment, thus suggesting that leptin can decrease weight in animals with a relative leptin deficiency[100]. Together, these findings indicate that leptin is an effective treatment in obese animals with complete or partial hormone deficiency, and, as illustrated by the phenotype of the LncOb-knockout mice, mutations that dysregulate leptin gene expression can result in a hypoleptinaemic, leptin-responsive form of obesity.

Leptin resistance in obesity. Most forms of obesity in animals are associated with high endogenous plasma leptin levels and a diminished response to exogenous hormone[20,31]. The normal plasma leptin concentration in animals (and humans) is ~5 ng ml^{-1}. DIO yellow agouti (A^y) and New Zealand obese mice are all highly hyperleptinaemic (levels range between approximately 25 and 100 ng ml^{-1}, and can be even higher) and show little or no response to peripheral leptin infusion[31]. This diminished response is in contrast to the aforementioned response of normal animals, in which leptin treatment at physiologic levels induces a dose-dependent decrease in food intake, adipose tissue mass and body weight. The finding that lean wild-type animals have lower leptin levels and lose weight on leptin therapy, whereas obese animals have high endogenous levels and do not, indicates that these obese animals are leptin resistant[31,101].

Table 1 | Experimental evidence that leptin resistance can cause obesity

Cause	Mechanism	Physiologic consequence	Reference
Obesity-causing mutations in feeding circuit	Melanocortin signalling is inhibited	Obesity, hyperleptinaemia, leptin insensitivity	102
Genetic mutations in *Socs3* and *PTP1b*	Socs3 and PTP1b inhibit leptin signalling, and receptor signalling is enhanced in animals with mutations	Prevention of dietary obesity in animals	44,45,47
Genetic mutation in leptin-receptor Y935	Socs3 binding is inhibited by mutation; leptin-receptor signalling is enhanced	Prevention of dietary obesity in animals	46
Treatment with leptin sensitizers (e.g., amylin, celastrol)	Leptin signalling is restored, and leptin resistance is reversed in obese animals	Weight reduction with amylin and celastrol alone; synergistic effects and increased weight loss in combination with leptin	108,109
Overexpression of Socs3	Stat3 phosphorylation and leptin-receptor signalling are decreased	Worsening of obesity, hyperleptinaemia and leptin resistance	47,103,104
Treatment with leptin-receptor antagonist	Leptin signalling is diminished through competitive inhibition	Increased weight in DIO mice	106
Chronically high plasma leptin levels	Chronic hyperleptinaemia leads to leptin insensitivity	Maintenance of leptin sensitivity in the absence of hyperleptinaemia, in animals on a high-fat diet	115

Most obese animals and people are hyperleptinaemic and do not respond to leptin treatment[20,21,31,136], thus suggesting that they are leptin resistant. Numerous additions lines of evidence support this conclusion.

Several independent lines of evidence support the conclusion that obesity can result from leptin resistance in animals and humans (described below), and that leptin signalling restrains weight gain in lean and obese animals. This evidence includes the finding that mutations in melanocortin pathways normally activated by leptin lead to obesity, hyperleptinaemia and a decreased response to leptin treatment[102] (Table 1). Several other lines of evidence suggest that leptin resistance leads to obesity (Table 1). First, mutations in SOCS3 and PTP1b, which normally shut off leptin signal transduction, enhance leptin signalling and prevent diet-induced obesity in animals fed a high-fat diet[44,45,47]. Second, in agreement with the previous observation, mice with a mutation in Y935 of the leptin receptor, a site of tyrosine phosphorylation in the intracellular domain and SOCS3 binding, are also resistant to diet-induced obesity and maintain leptin sensitivity. In contrast, elevated levels of SOCS3 are associated with decreased Stat3 phosphorylation and result in obesity, and SOCS3 overexpression in leptin-receptor neurons in transgenic mice leads to leptin resistance and obesity[46,103–105]. Third, extremely obese DIO mice whose weight has stabilized at ~50 g show significant weight gain after treatment with a leptin antagonist[106]. These data unequivocally establish that obese animals are still dependent on endogenous leptin for maintaining a stable (obese) weight and further suggest that leptin resistance resets the animals' weights at new higher levels. Fourth, cellular resistance to leptin has been confirmed in electrophysiologic recordings in normal and leptin-resistant cells. Leptin can induce electrophysiologic responses in POMC and AGRP neurons, and these responses are diminished in neurons in slice preparations derived from DIO (leptin-resistant) animals[57,107]. Fifth, the aforementioned LncOb-knockout mice, with diminished plasma leptin levels, respond to leptin, whereas wild-type DIO mice do not, thus indicating that the latter group (which have higher leptin levels) are leptin resistant, and the knockouts (with lower plasma leptin levels) are not[100]. However, the LncOb mice still lose weight on leptin therapy despite having higher plasma leptin levels than those wild-type mice fed a chow diet (but lower levels than those of wild-type DIO mice). This finding suggests that an inappropriately low plasma leptin level relative to adipose tissue mass determines the response to leptin therapy and that absolute plasma leptin levels may not be the most useful predictor of the leptin response. Sixth, although leptin may no longer activate Stat3 in obese animals, treatment with amylin, a pancreatic peptide, or celastrol, a small molecule that alleviates endoplasmic reticulum stress, restores leptin-mediated Stat3 phosphorylation. As a consequence, treatment with amylin or celastrol can lead to resensitizaton to leptin and can, alone or in combination with leptin, promote weight loss in DIO mice[108,109]. Combinations of leptin and other gut hormones show similar weight-reducing effects in DIO animals[110,111]. Seventh, although some of leptin's effects are lost in the leptin-resistant state, other effects of leptin are retained, thus suggesting that, similarly to insulin resistance, leptin resistance is selective[112]. Finally, *ob*/*ob* mice receiving a chronic leptin infusion that maintains plasma leptin levels in the physiologic range of 5 ng ml^{-1} still maintain leptin sensitivity when fed a high-fat diet. Thus, obese animals that cannot become hyperleptinaemic do not develop leptin resistance. This observation suggests that in some instances, as has also been observed for insulin, leptin resistance can be caused by compensatory down-regulation of the response to the endogenous hormone (that is, tachyphylaxis).

Mechanistic basis of leptin resistance

The precise mechanism through which hyperleptinaemia leads to leptin resistance is not known. However, induction of PTP1b and/or SOCS3 in cells expressing the leptin receptor, perhaps secondarily to hyperleptinaemia, is likely to contribute[44,45]. The causes of leptin resistance appear to be heterogeneous and, as mentioned, also include constitutive defects in the neural circuit downstream of leptin, such as in mice lacking the leptin receptor or mice with defects in melanocortin signalling, such as A^y or melanocortin 4 receptor–knockout mice[22,31]. Indeed, to date, all genes identified as Mendelian causes of obesity in humans are expressed in the central nervous system, and most are components of the neural circuit modulated by leptin. Decreased transport of leptin across the blood–brain barrier has also been suggested to contribute to leptin resistance both in DIO mice and in New Zealand obese mice, which lose weight after intracerebroventricular but not subcutaneous administration of the hormone[31,76]. These findings suggest the possibility that decreased transport across the blood–brain barrier, or a lowered V_{max}, could cause obesity, although definitive evidence supporting this possibility is lacking. Thus, the aetiology of leptin resistance is known in some individuals, including humans and animals with mutations in the neural circuit that responds to leptin to regulate feeding, whereas in other cases the aetiology is less clear.

This scenario is analogous to insulin resistance, whose pathogenesis in the general population is unclear but is known to be caused by discrete mutations in components of the insulin signal-transduction pathway[113,114].

The cause of leptin resistance in DIO is less clear, but in this case, hyperleptinaemia contributes[115]. Whereas C57BL/6J mice become obese on a high-fat diet, other mouse strains do not[52]. One possibility explaining these findings is that genetic differences among mouse strains and possibly humans may determine whether or not leptin resistance develops as weight is gained and leptin levels increase during times of surfeit. Leptin resistance could thus confer a survival advantage in environments in which starvation is the prevailing threat, whereas maintenance of leptin sensitivity would be selected for in circumstances in which predation is the greater danger (further discussion in 'Evolutionary considerations' below). Nonetheless, although the molecular pathogenesis of leptin resistance is known in some cases, the precise cause of leptin resistance in diet-induced obesity or obesity in the human population is largely unknown.

A more comprehensive understanding of the molecular mechanism responsible for the development of leptin resistance could provide a basis for new anti-obesity treatments, although this task will be challenging. It is worth remembering in this context that insulin resistance was first defined in the 1950s, yet the nature of the precise molecular defect in most people with type 2 diabetes is still largely unknown even though in vitro assays (insulin effects on liver, fat and muscle cells) and in vivo assays (insulin clamps) of insulin action are readily available. In contrast, similarly robust means for assaying leptin resistance are lacking. Moreover, leptin acts at a diverse set of neural targets, which display varying degrees of leptin resistance, thus amplifying the difficulty of establishing the identity of the leptin-resistant cell types and the molecular nature of the cellular 'block'[67,68].

Mapping of the sites of leptin resistance and the nature of the molecular defect could provide new approaches for treating metabolic disease by reversing leptin resistance through leptin sensitizers such as celastrol, or amylin and other gut peptides, which show potent weight-reducing effects in DIO mice when co-administered with leptin. Pre-treatment with either agent can restore leptin-mediated Stat3 phosphorylation, although the cellular and molecular mechanisms have not been determined[108,109]. An alternative approach is to modulate the activity of neurons downstream of the 'block'. Inhibition of GABAergic neurons in the dorsal raphe nucleus has recently been shown to significantly decrease food intake and body weight in *ob* and DIO mice, thus showing that this neural population is 'downstream' of the site of leptin resistance[116]. The development of pharmacologic agents that modulate the activity of these and other distal neurons could thus be of therapeutic value, providing a further rationale for intense efforts by many laboratories to map feeding circuits.

Leptin function in humans

Treatment of leptin deficiencies. The effects of leptin in humans, though not as intensively studied as in rodents, are consistent with the findings in mice. Although rarely seen, humans with leptin mutations have extreme obesity and lose copious amounts of weight on leptin therapy, primarily as a result of decreased food intake[117–119]. This response confirms a physiologic role of leptin in humans. Before leptin treatment, these people show constitutive activation of reward centres in the striatum and a general lack of food preference (similarly to starved individuals, they prefer all sources of calories nearly equally), and both of these responses are normalized by leptin therapy[120]. Leptin treatment of people with congenital leptin deficiency and obese people who have lost weight, in contrast to mice, does not induce a net increase in energy expenditure but instead blunts the decreased energy expenditure normally associated with weight loss[89,121]. Leptin also corrects the immunologic abnormalities evident in people with leptin mutations, which are similar[89] to the abnormalities associated with severe weight loss in mice and humans (not obesity). People with leptin mutations also appear to have an increased incidence of death from bacterial infections[122], thus raising the yet-untested possibility that leptin might support immune function in people with extremely low leptin levels, including in cancer cachexia, or chronic inflammation, both of which are associated with an increased risk of death from infectious disease.

Treatment of lipodystrophies. Leptin treatment also has robust effects in other patient populations with pathologically low leptin levels. Patients with complete or partial lipodystrophy and low endogenous levels of leptin show a marked improvement in several metabolic parameters after leptin therapy, including significant decreases in triglycerides, steatosis and haemoglobin A1c, as well as food intake[123]. On the basis of these results, leptin been approved as a treatment for lipodystrophy in the United States, the European Union and Japan. Leptin has also shown potential benefit in people with insulin-receptor mutations (Rabson–Mendenhall syndrome) and in animals with type 1 diabetes, although supporting data from human trials in people with type 1 diabetes are lacking[124,125]. The available data further suggest that the anti-diabetic effects of leptin are not solely a result of decreased food intake but that other mechanisms contribute, perhaps via effects on POMC neurons[104,126–128]. In lipodystrophic animals, the metabolic improvement is a result of actions on the brain, thus suggesting that leptin indirectly modulates the activity of autonomic outputs to pancreatic islets, liver, fat and muscle[129].

Treatment of hypothalamic amenorrhoea. In people with hypothalamic amenorrhea, an infertility syndrome associated with low endogenous leptin levels, leptin treatment can restore fertility. Some patients have even become pregnant during the treatment period[130,131]. In addition, low leptin[132] levels are predictive of amenorrhoea in underweight women, including people with eating disorders[132,133]. In those cases, leptin treatment also corrects or improves several neuroendocrine abnormalities, most of which are characteristic of the 'starved' state, including increased levels of insulin-like growth factor 1 and thyroid hormone[130]. Improvements in these abnormalities as a result of exogenous leptin treatment occur, although these individuals lose weight, thus confirming that leptin, not the fat mass itself, is the key signal that suppresses the starvation response. In a small study, leptin has also been shown to have significant beneficial effects on the premature osteoporosis often associated with this condition[134].

Leptin therapy and weight loss. The finding that people with a diverse set of conditions associated with low endogenous leptin levels lose weight on leptin therapy further confirms a physiologic role of the hormone in humans. In addition, low endogenous leptin levels have been found to be predictive of subsequent weight gain among a cohort of Pima Native Americans[135]. These findings raise the possibility that lean or even obese people with similarly low levels might lose weight on leptin therapy. Although leptin has been reported to induce modest weight loss among lean healthy individuals, the primary data were not shown in that study, and a dataset showing the results of leptin treatment in lean individuals was lacking until recently[136]. However, recent evidence has confirmed that treatment with leptin decreases food intake and adipose tissue mass in lean people (C. S. Mantzoros (Harvard Medical School), unpublished data). In future studies, it will be important to further delineate the threshold for the endogenous leptin level that is predictive of a leptin response among these individuals.

The recent finding that lean people lose weight on leptin therapy is consistent with several additional lines of evidence. As mentioned

Table 2 | Comparison of obesity and diabetes subtypes

	Diabetes	Obesity
Type	Type 1 diabetes	Type 1 obesity
Causes	Immunologic maturity-onset diabetes of the young	Leptin mutations Transcriptional defects
Plasma hormone levels	Absent or low insulin levels	Absent or low leptin levels (men, < 5 ng/ml; women, <16 ng/ml)
Therapy	Insulin replacement	Leptin replacement
Type	Type 2 diabetes	Type 2 obesity
Causes	Insulin resistance, B-cell dysfunction	Leptin resistance
Plasma hormone levels	High insulin levels	High leptin levels
Therapy	Insulin ineffective Incretins Insulin sensitizers Metformin Sulfonylureas SGLT2 inhibitors	Incretins Bariatric surgery Leptin therapy in combination with peptides Leptin sensitizers (e.g., celastrol) Dorsal raphe nucleus modulators

Type 1 and type 2 obesity. Most obese people are hyperleptinaemic and show little or no weight loss after leptin treatment. However, recent evidence has indicated that a subset of obese people have low endogenous plasma leptin levels and robustly respond to leptin treatment. Animal data also indicate that decreased leptin gene expression can lead to a hypoleptinaemic, leptin-responsive form of obesity. These data suggest that obesity can be classified similarly to diabetes. Thus, type 1 obesity is associated with low plasma leptin levels and can be considered analogous to type 1 diabetes, which results from decreased insulin expression, typically secondarily to immunologic destruction of pancreatic cells. Hormone replacement is an effective treatment in these forms of diabetes and obesity. Most cases of obesity are the result of leptin resistance, analogously to type 2 diabetes, which is typically associated with obesity leading to insulin resistance and B-cell dysfunction. Hormone replacement is typically not optimal for managing hormone-resistance syndromes, and other therapeutic approaches are, or must be, used.

above, people with lipodystrophy who are treated with leptin typically lose weight. In one study, many such patients lost significant amounts of weight, including three patients whose endogenous leptin levels were in the normal range (~3–10 ng/ml). However, even people with elevated leptin levels might respond to leptin treatment, given that two hyperleptinaemic patients with partial lipodystrophy have been found to lose weight during leptin therapy (R. Brown (NIDDK, NIH), unpublished data). As mentioned, leptin treatment has also been found to decrease weight in people with hypothalamic amenorrhea, although the starting leptin level in the individual patients was not reported[130]. Finally, leptin treatment in a small cohort of overweight or mildly obese men with hepatic steatosis selected for low endogenous plasma leptin levels (<10 ng/ml) has been found to result in decreased steatosis and significant weight loss (E. Oral (University of Michigan), unpublished data).

In agreement with the possibility that lower leptin levels might be predictive of weight loss after leptin treatment, a recent report has shown highly significant (~12%) weight loss in obese people in the lowest decile of endogenous leptin concentration (<16 ng/ml in women and <5 ng/ml in men), although the most pronounced effect may have been in individuals with even lower leptin levels[137]. Different thresholds were defined for each sex because women usually have a higher body fat content and hence higher baseline plasma leptin levels than men. Thus, although a low starting level is predictive of a response to the hormone, the precise leptin level that is predictive of significant weight loss among obese people (and presumably lean people with similar leptin levels) remains to be determined. It will thus be crucial to rigorously define the threshold leptin level that is predictive of a biologic response, as well as to determine the dose–response relationship of leptin therapy among lean and obese people with low and normal endogenous levels.

In most obese individuals, however, plasma leptin levels are significantly elevated and are highly correlated with adipose tissue mass, although each analysed cohort contains a subset of individuals with relatively low leptin levels[20,138]. Several single-nucleotide polymorphisms have been identified to be associated with low plasma leptin levels in obesity, one of which is in the human homolog of LncOb RNA[100,139]. Leptin treatment of obese patients with elevated plasma leptin levels, in contrast to patients with low hormone levels, in a patient cohort that was not selected according to starting leptin levels, did not result in a significant overall response to leptin treatment[136]. However, other data have shown a significant increase in the proportion of patients losing more than 10% or 5% of their weight under leptin versus placebo treatment, and a retrospective analysis has further suggested enrichment in responders among patients with lower starting plasma leptin levels[137].

Differing plasma leptin levels in people with type 1 versus type 2 obesity. The aggregate data suggest that a subset of obese people with low or relatively low endogenous leptin levels lose weight on leptin therapy and that the likelihood of a response diminishes at progressively higher hormone levels. The finding that lean people and some obese people with low plasma leptin respond, whereas most do not, further indicates that non-responders are leptin resistant. Although the cause of leptin resistance is known in obese people with mutations that decrease leptin or melanocortin signalling (that is, people with mutations in the leptin receptor, POMC or melanocortin 4 receptor), in most cases, the cause is unknown[102]. Leptin therapy is of limited value in this setting, but alternative therapeutic approaches remain viable, including using leptin in combination with amylin, which results in significant weight loss in humans (~13.7%)[108]. Clinical trials with celastrol, a leptin sensitizer that decreases weight in DIO mice, are also underway[109].

The finding that people with low plasma hormone levels show a greater response than those with high levels is reminiscent of diabetes (Table 2): individuals with type 1 diabetes have low plasma insulin levels and respond well to insulin treatment, whereas individuals with type 2 diabetes are insulin resistant and require high doses of insulin, often in combination with insulin-sensitizing drugs. This parallel finding suggests that obesity might be viewed in a similar manner: type 1 obesity (or metabolic disease) would be defined as obesity associated with low plasma leptin levels and leptin sensitivity, whereas type 2 obesity would be characterized by obesity in the presence of elevated plasma leptin levels and leptin resistance. Similarly to that in diabetes, the therapeutic approach to each obesity type would differ. Although the precise leptin levels that are predictive of leptin sensitivity have not been clearly defined, the aforementioned evidence suggests that obese people with leptin levels in the same range as those in lean people (<5 ng ml^{-1} for men and <16 ng ml^{-1} for women) might respond.

However, there are at least two notable differences in leptin and obesity versus insulin and diabetes. First, there are likely to be fewer obese people with low leptin levels than with diabetes and insulin deficiency (that is, type 1 diabetes). The percentage of obese people in the former category remains to be determined. Second, provided that a sufficiently high dose is administered, insulin can invariably elicit a biologic response, even in the most insulin-resistant people. However, even very high levels of exogenous leptin do not elicit a significant response in leptin-resistant animals or humans. This difference may reflect the potentially lethal consequences of complete loss of insulin action from ketoacidosis, as evidenced by the paucity of null mutations in insulin or the insulin receptor in the general population. In contrast, individuals with null mutations in leptin or its receptor exist, although the associated infertility and risk of predation has probably diminished the allele frequency in the population[102,117]. Defects in leptin signalling are strongly selected against, on the basis of the very high probability of loss intolerance (pLi) for the leptin receptor (0.99) and the medium score for leptin (0.46) in the gnomAD database, thus indicating that neither gene tolerates mutations[140]. The slightly lower score for leptin probably reflects that sequence variation has a greater effect in ligands than receptors. Nonetheless, the evolutionary forces that shaped the responses to insulin and leptin are likely to be distinct.

Evolutionary considerations

The size of the adipose tissue mass is under evolutionary selection, particularly in mammals, in which adipose tissue has evolved as a highly specialized organ for storing lipids as a source of calories during times of privation[5]. The thrifty-gene hypothesis posits that in the 'wild', where calories are sometimes limiting, the efficient deposition of calories as fat provides protection against starvation during famines. This hypothesis further posits that when calories are readily available, such as in the modern environment, this adaptation leads to diabetes and obesity.

An orthodox interpretation of this hypothesis related to the consequences of famines has recently been questioned on the basis of the suggestion that famines sufficiently severe to exert selective pressure on people with decreased adipose tissue mass are relatively infrequent[7,8]. However, a minimal level of adiposity is probably necessary to limit the potentially dangerous consequences of the food insecurity that often affects hunter–gatherer populations, which do not farm crops or store large amounts of food. Thus, a minimal level of adiposity is likely to be required to promote survival during 'lean' times[7,141,142]. Sufficient adipose tissue mass can also help to maintain core temperature in colder climates by providing insulation as well as a source of calories for thermogenesis. Adequate fat stores also prevent the infertility and immune suppression resulting from hypoleptinaemia that can develop with nutritional deprivation[86,88,90]. The deleterious effects of low leptin levels on immune function may have become increasingly important as humans began to congregate in villages and later cities, thus leading to epidemics of infectious disease[143]. In addition, adequate stores of adipose tissue have been suggested to provide a selective advantage for surviving the anorexia developing after infections[8].

The predator-release hypothesis provides an alternative to the thrifty-gene hypothesis and suggests that obesity can be maladaptive by limiting mobility and thus an animal's ability to escape danger, thus rendering affected individuals more susceptible to predators[7]. This hypothesis further suggests that the absence of predators among most modern human populations has led to an increased incidence of obesity as a result of genetic drift due to an accumulation of predisposing alleles that are no longer selected against. Additional selective pressure against obesity may also have been present as humans evolved, even after the risk of predators diminished, because the tendency of obese mothers to develop gestational diabetes increases the frequency of miscarriages and also leads to larger babies. An increased foetal size can lead to cephalopelvic disproportion, which can have catastrophic consequences for the mother and child when Caesarean sections are unavailable. However because the negative sequelae of obesity are generally present in older individuals, reproduction has generally been completed. Thus the extent to which obesity is selected against in 'modern' human populations has been controversial and has led to questions regarding whether there is a selective advantage for longevity (Box 1). Recent evidence has thus suggested that such a selective advantage does exist and thus would indicate that obesity is still under genetic selection[6].

The thrifty-gene and predator-release hypotheses are not mutually exclusive, and together they suggest that the tendency of a population toward obesity is a result of balancing selection between the relative risk of periodic food insecurity (and potentially famine) and the risk of predation in the environment in which that population evolved. These distinct evolutionary pressures may potentially explain the profound predisposition of Pacific Islanders (and other Aboriginal populations) to obesity[6]. Pacific populations were not typically vulnerable to predators but instead experienced substantial food insecurity while traveling extremely long distances to populate new islands and in the aftermath of frequent typhoons. In contrast, in environments with larger numbers of predators and the development of agriculture to provide constant supplies of nutrients, such as in Eurasia, obesity and diabetes are less prevalent[6]. Indeed, Caucasians, especially compared with many Aboriginal populations, appear to be relatively resistant to obesity.

The development of leptin resistance could thus be adaptive or maladaptive, depending on the environment in which the founding population evolved. In an environment where predation is the primary risk, maintaining leptin sensitivity over a broad dynamic range would prevent the development of obesity and promote survival, whereas leptin resistance would be maladaptive. In contrast,

Box 1 | Do evolutionary forces still affect obesity and leptin resistance in modern humans?

Whether selective pressures for obesity (and leptin resistance) are still operating in modern times remains under debate. For example, because the co-morbidities of obesity—diabetes, hypertension and heart disease—do not generally manifest until later ages, after reproduction has been completed, genetic drift rather than selection has been suggested to have led to its increasing incidence. However, a decreasing incidence of diabetes on the Pacific Island of Nauru in recent times suggests that evolutionary selection is ongoing[6,149]. Consequently, for type 2 diabetes, which is strongly associated with obesity, especially among Pacific Islanders, this condition can still have deleterious effects on the population. First, these diseases do affect individuals of reproductive age in Island populations, and severe obesity associated with type 2 diabetes is now being seen with increasing frequency among children in some populations, even in the United States[150]. Second, there is also a higher incidence of miscarriage among people with gestational diabetes, and the larger size of the foetus in diabetic and obese mothers can lead to cephalopelvic disproportion, which has catastrophic consequences for both the foetus and the mother if a Caesarean section is not performed. Finally, evidence indicates a larger kindred size when grandmothers are alive and living locally, thus suggesting that longevity beyond the reproductive years can be selected for[151]. Thus, although the selective pressures toward and against obesity and leptin resistance appear to be less intense than they were in the past, there is reason to believe that they continue.

in environments where the prevailing risk is food insecurity and starvation, the development of acquired leptin resistance and obesity, perhaps secondarily to elevated leptin levels during times of surfeit, would enable survival through intermittent periods of food insecurity or famine. In agreement with this possibility, as mentioned, hyperleptinaemia is required for the development of obesity in C57BL/6J mice fed a high-fat diet[115]. In addition, although some mouse strains, such as C57BL/6J, become obese when fed a high diet, other mouse strains, such as Akr, do not[144]. Thus, some of the alleles that predispose individuals to either obesity or obesity resistance may exert their effects by determining whether hyperleptinaemia leads to tachyphylaxis and the development of leptin resistance. The relative risk of starvation as well as predation also differs among species, and the particular evolutionary pressures experienced by each species might be able to explain the likelihood of developing obesity when calories are abundant. Mice, for example, have a higher metabolic rate than humans and can survive for only a few days without food, whereas humans and other large mammals can survive for extended periods. This difference may explain why leptin mutations in mice are associated with a more severe set of abnormalities than null mutations in humans.

Overall, the level of adiposity has a considerable effect on evolutionary fitness. The evolution of leptin and an endocrine system that sets the level of adiposity has provided a means for ensuring the optimal level of adiposity in particular environmental contexts. Mouse strains differ in their susceptibility to obesity when fed a high-fat diet, and genetic crosses between them have identified polygenes that predispose mice to either obesity or obesity resistance, although the causal genes have not been identified[144,145]. In addition to continuing genetic studies in humans, the identification of allelic variants that predispose people to obesity or obesity resistance could enable the identification of new components of the biologic system that regulates adiposity and lead to a more comprehensive understanding of the evolutionary factors that shape the level of adiposity in different populations.

Summary and outlook

Before the identification of leptin, adipose tissue was considered by many to be a balloon-like vessel for lipids that passively stored energy when food was consumed and disbursed it in times of privation. Largely because of the identification of leptin, adipose tissue is now viewed as a highly dynamic organ playing a crucial role in the systemic control of energy balance; communicating nutritional changes to central-nervous-system centres that control appetite; and linking changes in the levels of energy stores to adaptive changes in the neuroendocrine axis, immune function and the function of arguably all other physiologic systems. Numerous new insights have thus followed the cloning of the *ob* gene, including (i) the identification of a new hormone, leptin, and endocrine system regulating food intake and body weight; (ii) the delineation of a physiologic mechanism through which changes in nutritional state regulate (all) other physiologic systems; (iii) the identification of a genetic basis for obesity, with the finding that leptin mutations cause severe obesity that can be successfully treated by hormone replacement; (iv) the provision of an entry point for studies of the neural control of food intake, revealing links between the homeostatic and hedonic control of appetite; (v) the demonstration that a substantial fraction of morbid obesity is the result of Mendelian defects in the neural circuit that is modulated by leptin; (vi) the identification of several leptin-deficiency syndromes including lipodystrophy (a cause of severe insulin resistance and diabetes) and hypothalamic amenorrhea, both of which can be treated with leptin; (vii) the realization that the pathogenesis of obesity is heterogeneous (a leptin-sensitive subset of obese individuals express decreased amounts of the hormone (analogously to type 1 diabetes), and most obese people show leptin resistance (analogously to type II diabetes); moreover, combinations of leptin with short-term signals and/or leptin sensitizers show potential for treating leptin-resistant obesity); and (viii) the identification of leptin provides an alternative to the notion that obesity is a result of a lack of willpower that can be treated by merely advising people to eat less and exercise more[146,147]. Tens of thousands of papers have now been written on these topics, and still more are likely to come.

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Competing interests

Per institutional policy, J.M.F. and the other inventors receive a portion of the royalty payments for the sale of leptin.

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