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What's in a Name? In Search of Leptin's Physiologic Role*

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THE IDENTIFICATION of the ob gene (1) and the discovery that its encoded protein, leptin, is an adipocyte-derived hormone that is essential for normal regulation of body weight (2–4) have permanently altered the field of metabolic physiology. Over a 3-yr period, more than 800 papers on leptin have been published, creating a substantial and rapidly changing body of knowledge. As often occurs, however, the initial conception of the physiological role of a newly discovered protein requires revision in the light of emerging information. In this paper, I will review the relevant literature and will propose a modified view of leptin's physiological role. This perspective, although respectful of the profound impact that leptin's discovery has had upon our understanding of obesity and on the field of obesity research, will attempt to deemphasize the physiological status of leptin as an anti-obesity hormone, stressing instead its roles as a signal of energy deficiency and as an integrator of neuroendocrine function. Although this field is expanding rapidly, and many of these ideas are clearly works in progress, it is hoped that this perspective will be of value to workers in the field.

Initial conception of the physiological role of the ob gene product leptin

The identification of the ob gene through positional cloning (1) and the discovery that its encoded product is a circulating hormone that is deficient in the *ob/ob* mouse (2–4) set the stage for leptin to be considered an "adipostatic hormone." That is, the physiological role of leptin was seen as rising with increasing adiposity, to generate a signal that limits further weight gain. This view, repeated throughout the leptin literature, has much to recommend it. First, it resonates well with the fact that total leptin deficiency, although very rare, causes severe obesity in both rodents (1) and man (5); and in the rodent (so far), obesity as a result of mutation in the leptin gene is reversed by replacement with recombinant leptin. Indeed, the view that leptin's function is to resist obesity and promote leanness led to the choice of the name "leptin" (2), from the Greek root leptos, meaning thin. Second, this view of leptin concords well with the postulation, based on substantial indirect evidence, of an adipostatic system for weight control (reviewed in ref. 6). An adipostatic mechanism was proposed to explain the relative stability of weight over time in many animals and their capacity to respond to involuntary overfeeding with adaptations, including reduced appetite and increased thermogenesis, which restore body weight and composition to previous levels. According to this view, rising levels of leptin signal the brain (and possibly other sites) that excess energy is being stored (in the form of fat), and this signal brings about adaptations that resist obesity. When this signal is deficient, the brain perceives energy stores to be insufficient, and the physiological response is to increase appetite and decrease energy expenditure, both of which push energy balance towards energy storage and weight gain.

This initial view, that leptin functions primarily as an anti-obesity hormone, requires revision stimulated both by new data and by theoretical considerations. The new data includes the demonstration that leptin has numerous biological effects distinct from those expected of an adipostatic, anti-obesity hormone, and the fact that resistance to leptin's anti-obesity action is observed in both experimental animals (7–9) and in man (10, 11). On a theoretical level, it seems likely that a potent anti-obesity adipostatic system would be subject to negative genetic selection during the course of evolution.

Leptin action and the "thrifty genotype": an evolutionary perspective

Through evolution, as in much of the world today, it is almost certain that chronically inadequate and/or intermittant energy availability confronted terrestrial organisms for major periods of their lives. The view of early man as a hunter-gatherer, for example, suggests periods of inadequate food intake punctuated by the bounty of the kill. In such an environment, we can hypothesize that strong evolutionary pressure would select for traits promoting two adaptive responses. The first would promote efficient storage of energy when food was available. This would enhance survival by increasing energy stores during periods of insufficient food.

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Such traits have previously been referred to as constituting a thrifty genotype (12). A related but distinct trait that would also confer survival advantage would produce physiological adaptations during periods of insufficient energy intake. These changes would promote survival by reducing energy expenditure, by ensuring substrate fluxes to tissues such as brain that require energy at constant rates and by increasing food seeking behavior.

The concept of a thrifty genotype was first introduced by Neel in 1963 (12), 32 years before the discovery of leptin. In his original conception, he proposed that a "quick insulin trigger" would promote increased energy storage when food was available, favoring survival during the hunter-gatherer period. He further hypothesized that this pattern of insulin secretion would engender insulin resistance, which would then promote diabetes when food supplies were abundant and continuously available. It is this aspect of the thrifty genotype concept that has received the greatest attention. Although several aspects of this scheme have not proven correct, the proposal that genetically determined capacities that are favorable during hunter gatherer existence may be detrimental under conditions of abundance was profound. In 1991, Wendorf and Goldfine (13) proposed a revision of the thrifty genotype hypothesis, wherein they proposed the key phenotypic manifestation to be insulin resistant glucose uptake in skeletal muscle. They hypothesized that the advantage of insulin resistance in muscle would be to limit hypoglycemia during periods of starvation (by limiting muscle glucose use), but that this same phenotype would promote hyperglycemia and energy storage in fat during periods of nutritional abundance. This paper extended the concept of the thrifty genotype to starvation as well as feeding and is attractive on two accounts. First, insulin resistance of muscle glucose uptake and storage as glycogen is a risk factor for type II diabetes (14), and second, transgenic mice with muscle-selective insulin resistance are susceptible to obesity when placed on a high fat diet (15).

It is now necessary to update the thrifty genotype concept, relating it to the emerging biology of leptin. It is clear that a thrifty genotype (and phenotype) that promotes energy storage in response to feeding opposes the function of a molecule such as leptin that limits energy storage as fat. Stated another way, an effective role for leptin as an adipostatic hormone would subvert this aspect of the thrifty genotype and would be predicted to reduce survival when food is scarce. It is likely, therefore, that a role for leptin as a potent anti-obesity signal would be selected against under these environmental conditions. In response to this analysis, it might be suggested that a thrifty genotype would result when leptin was ineffective or partially disabled. This fits with the observation that heterozygous ob/+ mice survive starvation longer than do wildtype +/+ mice (16, 17) Although true, it is unlikely that leptin evolved for the purpose of being disabled or ineffective. Therefore we must consider the question: for what physiological purpose did leptin actually evolve?

Leptin levels in the blood fall when energy intake is limited and energy stores in fat are declining (18, 19). Might leptin have evolved to signal the shift between sufficient and insufficient energy stores? If falling leptin signaled the brain to initiate responses that would reduce the risk of starvation and death, this would surely be an important physiological role. Starvation evokes a number of responses, including reduction in fertility, suppression of metabolic rate and thyroid hormone levels, and activation of the hypothalamic-pituitary-adrenal axis (reviewed in ref. 20), each of which has survival value. Because falling leptin is experimentally linked to each of these adaptations (21), at least in rodents, this action of leptin is likely to be a key component of its physiology. The same cellular mechanism (whatever it is) that causes leptin to fall with insufficient energy intake/stores might raise leptin levels with overfeeding and obesity. However, a survival advantage might accrue to those individuals who had a limited response to this part of the leptin dose response curve, thereby manifesting the thrifty genotype (Fig. 1).

Two important points emerge from this paradigm. First, this view is not inconsistent with the fact that severe obesity results from mutations that disable leptin or its receptor. With continuous leptin deficiency, the brain "perceives" starvation and promotes hyperphagia and efficient metabolism despite adequate energy stores that progress to obesity. Indeed, any defects that create such a starvation signal in the midst of plenty, such as defects in producing leptin, delivering leptin to its site of action, or responding to the leptin signal, would be expected to promote obesity. This important fact does not imply, however, that the physiological function of leptin is to prevent obesity from overfeeding. Second, it is clear that a genotype/phenotype that is adaptive when food intake is intermittant (*e.g.* a limited physiological response to rising leptin that enhances capacity for energy storage) may be maladaptive in the midst of continuous caloric abundance by promoting obesity and its complications. This underlines an important principle of genetics: that a particular geno-

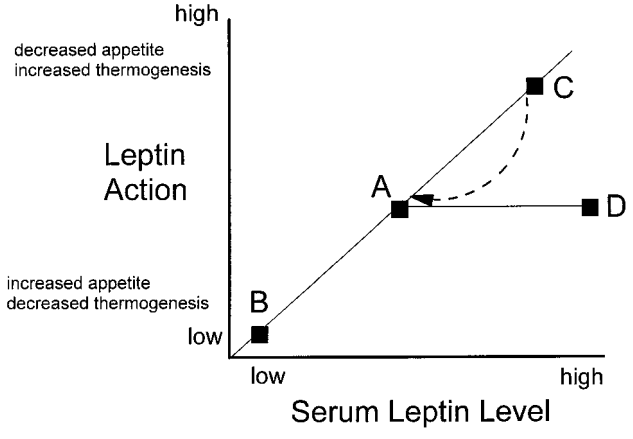

FIG. 1. A theoretical relationship between serum leptin levels and leptin action. During starvation, as leptin levels fall, withdrawal of leptin action results in increased appetite and decreased thermogenesis, as well as other changes not noted here. As feeding continues, two patterns can be seen. In one, (D) leptin rises with increased feeding and fat stores, but leptin action fails to rise further because of a limitation at some step in leptin transport, action at the target cell, or at a later step in the pathways regulating appetite. This apppears as "leptin resistance", and is also a feature of the "thrifty genotype". In another (C), leptin action to reduce appetite and increase thermogenesis continues to rise as levels rise. As indicated by the *arrow*, this will tend to prevent obesity from developing and may be viewed as the "lean genotype".

type/phenotype cannot always be viewed, per se, as adaptive or maladaptive, without information about the environmental conditions to which the affected individual is exposed.

To summarize this evolutionary perspective: the ability of falling leptin during starvation to promote increased energy intake, to decrease energy expenditure, and to promote partitioning of energy towards fat suggests that leptin plays a role in defending the thrifty phenotype by falling with starvation. Although transition from this low leptin starved state to a fed state with restored leptin is likely to be important to physiological health, a continuous rise in leptin action as energy storage proceeds would subvert the thrifty phenotype by limiting the capacity for energy storage. Thus I hypothesize that, in an environment with periods of starvation punctuated by feeding, evolution would favor a leptin dose response curve that functioned briskly as a switch between some level of sufficient energy storage and another level perceived as insufficient (*e.g.* between the fed and fasted states) but that failed to limit further energy storage as levels rose with increased energy stores. The latter state would most likely be described as "leptin resistance" (Fig. 1).

It is important to stress that this analysis does not disregard the experimental evidence supporting a capacity of animals to respond to overfeeding by increasing thermogenesis (*i.e.* inefficient metabolism) and by decreasing spontaneous food intake (22). Indeed, increased leptin action is perfectly suited for bringing these adaptations about, because leptin can diminish food intake (2–4) and increase heat production by activating thermogenesis in brown adipose tissue (23), and possibly other sites, through induction of the newly identified mitochondrial uncoupling proteins UCP-2 (24, 25) and UCP-3 (26–28). We can reformulate the question as follows: leptin has the capacity to serve as a signal that prevents obesity when animals are subjected to abundant food supplies, but whether or not this capacity is realized depends upon the shape of the leptin biological dose response curve. Whether or not the leptin dose response curve displays increased activity at high leptin levels may have been determined by the conditions that confronted the species over evolutionary time scales. If the adverse consequences of obesity were more deleterious than the inability to maximize energy stores, evolution would select for the capacity to respond briskly to leptin and, thus, for avoidance of leptin resistance. Variations between strains of animals or individual members of a species in regard to this parameter would have major implications for their susceptibility to obesity. Likewise, variations in the steepness of the curve describing the relationship between leptin secretion/levels and adipocyte size/fat stores would influence the body fat mass that is obtained.

Leptin as a starvation signal: the neuroendocrine connection

Because starvation is a recurrent threat to survival, numerous physiological systems have developed to defend against it. Among the most important responses to starvation are behavioral changes, including increased food-seeking behavior and hunger; metabolic changes, including those that promote provision of energy to tissues through a switch from carbohydrate to fat-based metabolism (29); and reduction in metabolic rate, which along with initial size of the energy storage pool, is expected to play a key role in determining the total duration of survival. Does a single signal entrain and orchestrate these complex responses? Insulin, the most critical hormone of metabolic homeostasis, falls with fasting and rises with feeding and has diverse actions across this entire dose response range. The fall of insulin with starvation is critical to the metabolic switch from carbohydrate to fat-based metabolism, through actions on numerous biochemical processes in organs including fat, muscle, and liver (29). Great effort has gone into studies aiming to determine whether insulin has additional actions to influence appetite, energy expenditure, and neuroendocrine status in response to over- or undernutrition. Because insulin can apparently be transported across the blood brain barrier (30) and, when injected centrally, can reduce appetite and expression of hypothalamic neuropeptide Y (31), a role for insulin in the central regulation of energy balance has been proposed. Taken as a whole, however, these observations about insulin, although provocative and logical, have left most investigators believing that one or more additional signals linking the periphery and central control sites has yet to be discovered.

Leptin is clearly such a molecule. First, it was shown that leptin levels fall fairly rapidly (*i.e.* within hours) with energy deprivation in rodents (18, 19), and they do so (initially) out of proportion to the loss of fat stores. This suggests that, in addition to being a readout of energy stores, the leptin level is a sensor of energy balance or the relationship of energy intake to expenditure at a point in time. Next, a classic replacement strategy was employed to show that starvation-induced changes in neuroendocrine status were blunted or prevented entirely when a starved animal was replete with leptin. Thus, the activation of the hypothalamic-pituitary-adrenal (HPA) axis, and suppression of the thyroid and reproductive axes, were blunted or prevented by leptin repletion during starvation in rodents, establishing that these effects are signaled, at least in part, by the fall in leptin (21).

What are the consequences of these leptin-entrained endocrine responses? The most critical product of the HPA axis is the glucocorticoid hormone, corticosterone in the rodent and cortisol in man. At least two of many beneficial functions of increased glucocorticoid secretion in starvation can be cited. First, glucocortocoids gained their name from their ability to promote the shift to hepatic gluconeogenesis that is needed to supply the brain with glucose when exogenous sources of nutrition are limited. They accomplish this by numerous mechanisms including the stimulation of proteolysis in muscle (to provide substrate) and the activation of enzymes of gluconeogenesis in the liver. Second, as starvation is a time of stress that is more likely associated with physical challenge and struggle, the actions of glucocorticoids that relate to the stress response would be advantageous. The fall in leptin is the first defined mechanism to explain the activation of the HPA axis in response to starvation.

All other things being equal, starvation is expected to produce death more rapidly when the metabolic rate is higher. Because thyroid hormone is a dominant regulator of

basal metabolic rate, a fall in thyroid hormone during starvation is likely to be advantageous, so long as other potentially adverse consequences of hypothyroidism do not occur. The metabolic rate falls during food restriction, as do levels of T3 in humans (33) and T4 and T3 in rodents (21), but the contribution of decreased thyroid hormone levels in producing the hypometabolism of starvation has not been established. Starvation can lower metabolic rate by lowering levels of thyroid hormone, but mechanisms may also exist apart from the effects of decreasing levels of T3 and T4. These include changes in lean body mass, reduction in brown adipose tissue activity (34), and possibly changes in the expression or function of new uncoupling proteins. It is noteworthy that changes in each of these parameters (*e.g.* lean body mass, brown adipose tissue activity, and UCP-3 expression) have been reported to respond to changing leptin levels. Thus, leptin is capable of regulating metabolic rate in starvation by several mechanisms, including changes in the thyroid axis (35–37). Interractions between these mechanisms may also exist. Thus, thyroid hormone increases the expression of UCP-3 in skeletal muscle of the rat (28), and it is possible that some or all of the action of leptin to induce UCP-3 is secondary to the leptin effects to induce thyroid hormone levels.

Chronic nutritional deficiency, leading to stunted linear growth, results in large measure from insufficient nutrition for synthesis of tissues that underlie growth. There is also a regulatory aspect to this outcome. That is, there may be a disadvantage to increasing size (and thereby metabolic needs) when calories are chronically scarce. This may account for the suppression of the growth hormone axis during starvation. Starvation causes suppression of both GH and IGF-I in rodents, and this suppression may be prevented by leptin repletion (38). In humans, GH is increased during starvation, but IGF-I is suppressed (39), and the role of leptin in this has not yet been studied.

An important connection between nutrition and reproduction has long been noted. The development of live and healthy progeny requires a large allotment of calories, and it would compromise both mother and the fetus if the process began with insufficient calories stored in fat. This is the likely teleological explanation for the ability of caloric deprivation both to prevent full sexual maturation and to limit reproductive competence in sexually mature females. It is less clear what benefit derives from the reproductive axis being diminished in starved males, but this is also well described to occur (36).

How does leptin influence these diverse endocrine effects of starvation? Leptin most likely exerts its most important effects through the central nervous system, specifically within the hypothalamus. It is not yet established through what neural circuitry these effects are brought about. An initial theory viewed hypothalamic NPY as a key target (40). NPY containing cells in the arcuate nucleus have leptin receptors (41), and leptin suppresses NPY expression at this site (40, 42). Administration of NPY can activate the HPA axis (43) and can also exert a variety of effects upon the hypothalamic-pituitary-gonadal axis (44). However, the effects of starvation to activate the HPA axis, suppress reproduction, and activate the thyroid axis all occur normally in mice with knockout of the NPY gene (45, 46), indicating that other, as yet unidentified hypothalamic factors must be involved. Regarding the thyroid axis, we have observed that starvation causes suppression of TRH expression in the paraventricular nucleus of the hypothalamus in the rat, despite falling levels of T4, which should increase TRH, and that leptin treatment during starvation prevents this suppression (37). Whether this effect is a direct action of leptin on TRH neurons or is mediated by an indirect projection from leptin responsive neurons is presently unknown. It should be noted that leptin has also been described to have direct actions upon peripheral target organs such as the pituitary (47), adrenals (48), and gonads (49), and the possible role of these actions will await further study.

Leptin and the metabolic response to starvation

Although a role for falling leptin in the endocrine response to starvation seems clear, it is not yet established to what degree leptin plays a role in the metabolic adaptation to starvation, a situation where falling insulin is the dominant hormonal change. Falling insulin is thought to be the major factor bringing about increased lipolysis, decreased uptake of glucose in muscle and fat, and increased hepatic glucose production, which characterize starvation. The falling insulin level may also play a direct and important role in the fall in leptin production by the adipocyte during starvation, as insulin has been observed to stimulate leptin gene expression *in vitro* (50–52), and leptin levels rise *in vivo* during a prolonged euglycemic insulin clamp (53). However, it is not yet clear to what degree falling leptin might contribute, along with falling insulin, to the metabolic adaptations to starvation. Repletion of leptin alone in the starving mouse failed to prevent the rise in ketones or the fall in glucose levels (36), suggesting that insulin is the primary hormone in this adaptation, but such studies need to be extended to evaluate the possibility of more subtle metabolic effects of falling leptin that could be important. Given the observation that leptin is capable of exerting potent metabolic effects on peripheral target tissues (54, 55), at least some of which may be direct rather than through the brain (56), further studies on the metabolic physiology of leptin are warranted.

Interpretation of studies on the metabolic physiology of leptin will require integration of biochemical observations with the physiological context in which they occur. For example, during fasting, when lipolysis is activated, both insulin and leptin levels fall, as discussed above. The fall in insulin is clearly linked to this process. Because addition of leptin is described as activating lipolysis in adipose tissue directly (56), it is unclear what role this might play in the physiology of starvation. Does the fall of leptin during starvation act as a brake on lipolysis to counter the action of falling insulin? Studies aimed at addressing questions such as this are required if the role of leptin in metabolic adaptation to the fed and fasted states is to be understood.

Endocrine actions of leptin independent of starvation or feeding per se

The effects of leptin on endocrine function as its levels fall during starvation fit easily within the paradigm of leptin as a molecule that signals the switch between sufficiency and insufficiency of energy stores. These findings have led, however, to discovery of additional actions of leptin on endocrine function that are further removed from the energy sufficiency paradigm. The first example relates to the adrenal axis. There is a diurnal rhythm of leptin levels that is entrained by eating. In rodents, leptin levels rise during the dark cycle when rodents do most of their eating (36); in man, levels rise throughout the day and peak in the early morning (57). Individual meals are not associated with an increased leptin level in man (58). These diurnal patterns of leptin are the inverse of the typical patterns of the HPA axis in both rodents (21) and man (58). Correlations do not prove causal connections, and much is known about the central mechanisms for regulation of circadian rhythms, including the critical input from the suprachiasmatic nucleus. However, it is reasonable to consider whether leptin may be one of several influences over the pattern of the diurnal rhythm of the HPA axis. An anatomic substrate for a possible pathway by which leptin responsive neurons might influence the output of the suprachiasmatic nucleus has recently been described (58a). The possible interaction between leptin and the HPA axis extends further. It appears that leptin has a pulsatile pattern apart from the diurnal rhythm (59). Given that leptin is secreted by widely dispersed adipose cells that are unlikely to have any coordination, this finding was quite surprising. This pulsatility is seen only when frequent samples are taken, and whether the pattern results from pulsatility at the level of secretion or clearance is not known. Interestingly, this pattern is inversely correlated with the pulsatile pattern of ACTH and cortisol (59). Because acute leptin injection *in vivo* can suppress the rise in the HPA axis induced by stress (60) in rodents, and because leptin has been seen to acutely suppress hypoglycemia-induced secretion of CRH from hypothalamic slices (60), it is reasonable to hypothesize that leptin may have a role in the normal negative feedback function of the HPA axis. Such a relationship would explain the fact that states of severe leptin deficiency or resistance are associated with activation of the HPA axis. It has also been suggested that leptin may inhibit the HPA axis by a direct action on the adrenal gland to inhibit cortisol (48). Thus, the inverse relationship between leptin and glucocorticoids may derive from action at two sites in the HPA axis (48).

On the other hand, leptin has been reported to increase expression of CRH messenger RNA (mRNA) in the paraventricular nucleus of the hypothalamus (PVN) (42), and this pathway has been hypothesized to represent a mechanism for the central actions of leptin (61), given that CRH administered centrally reduces food intake (62) and increases sympathetic output to brown adipose tissue (63, 64), two actions of leptin. These disparate observations can be reconciled, however. The PVN is a complex nucleus, and CRH neurons in the PVN have distinct anatomic and functional identities (65). One population projects to the median eminence, where released CRH gains access to the pituitary gland to regulate secretion of ACTH and, thereby, adrenal glucorticoids. We believe that in this population of cells, leptin is likely to be inhibitory. A second population of CRH neurons in the PVN projects to other sites, including the autonomic preganglionic centers in the brainstem. It is likely, although as yet unproven, that leptin activates these neurons. Such a model may account for the existing data in this area.

Regarding the thyroid axis, it is of interest that a diurnal rhythm of TSH has been seen (66, 67), with levels peaking in the early morning hours, when leptin levels are at their highest. Given the observation on the action of leptin to stimulate TRH gene expression in the hypothalamus during starvation (37), it is possible that leptin may be involved in this process.

The effect of leptin on the reproductive axis may also extend beyond the paradigm of starvation and feeding. In mice, leptin administration from the time of weaning accelerates the onset of puberty (35, 68, 69). In boys, leptin levels appear to peak at or before the time of pubertal onset when studied in a longitudinal fashion through the peripubertal years (70). These findings are consistent with the possibility that leptin may be one of several signals that acts on the GnRH system, either directly or indirectly, to influence the timing of the pubertal program. The essential nature of this signal is demonstrated by the fact that *ob/ob* mice without leptin fail to undergo pubertal development, a process that is restored by administering leptin (71). Whether leptin acts as a metabolic gate by reaching a necessary level, or actually peaks to produce a signal is currently unresolved, as a study of puberty in monkeys revealed no increase in leptin levels before puberty (72). It is obvious that observations on leptin action on the endocrine system in rodents require careful study in subhuman primates and humans. Important differences between leptin action among these species may be present.

While pursuing this issue in mice, we sought to determine whether leptin levels peaked just before puberty in this species. When we measured leptin levels post-weaning, days before the physical signs of puberty, no peak was found. We then measured leptin levels from day 3 after birth to the post-weaning period and found that leptin levels underwent a marked surge between days 5 and 15, peaking sharply at day 10. This was associated with an increased expression of leptin mRNA in subcutaneous adipose tissue and was unrelated to any variation of adipose tissue as a percent of body mass during this period. These findings raise the possibility that leptin plays a developmental role in addition to the functions related to energy balance and neuroendocrine function. In this regard, it is important to note that the brains of leptin deficent *ob/ob* and leptin resistant *db/db* mice weigh substantially less than those of lean littermates, and this differences increases with age (73). The mechanistic basis for these striking differences in brain size (and probably function) brought about by leptin deficiency is unknown.

Actions of leptin on other organ systems

When considering the biological role of a molecule such as leptin, it is necessary to mention actions of leptin on other organ systems, apart from the nervous system and endo-

crine/metabolic realms. Leptin has been reported to act on hematopoeitic cells (74) and to alter renal function (75), an effect that could be indirect via the sympathetic nervous system, or direct on renal cells. The reason why leptin should have been selected to exert these actions, as wellas other unanticipated actions certain to be discovered in the ensuing years, is not yet evident.

Summary and conclusions

I have tried to review the rapidly emerging evidence that leptin is an adipocyte-derived hormone that is a powerful regulator of metabolism and neuroendocrine function. Because leptin levels parallel changes in nutritional status and energy storage across a broad range from starvation to obesity, leptin is well-positioned to signal energy insufficiency or energy excess, causing responses that could counter the adverse consequences of either starvation or obesity. I have reviewed some of the reasons why a response to starvation might be retained, whereas the response to limit obesity, despite its value in a world of nutritional excess, might have been selected against by evolution, accounting for the high prevalence of obesity in the modern world. Once the mechanism for this resistance is unlocked, new treatments for obesity are likely to emerge. I have also reviewed the evidence that leptin's regulatory effects are not limited to signalling the state of energy stores.

This perspective, it should be emphasized, in no way diminishes the importance of leptin's discovery for obesity research, which has been nothing short of profound. Rather, these ideas suggest that the importance of leptin includes, but extends substantially beyond, the physiology of obesity avoidance. Indeed, the physiological significance of leptin is just beginning to unfold.

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