Leptin As Fat Orchestrator

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SUMMARY

This work aims to unify the disparate and sometimes contradictory studies on leptin: the"hormone of plenty." In the eight years since leptin's discovery, focused studies have anatomized leptin in pathological metabolic conditions such as obesity, eating disorders, immune challenges and measured its response to simple fluctuations of temperature or exercise level. This synthetic analysis of leptin's role as the somatic energy signal and energy allocator in disparate states of stress attempts to elucidate this enigmatic and pluripotent hormone. At the same time, leptin may help us understand the endocrine etiology of some of medicine's greatest challenges.

LEPTIN AS FAT ORCHESTRATOR

Understanding of leptin expression and action is still in its infancy. Delineating leptin's structure, production, ligand binding and transportation gives clarity to any attempts to place the hormone in pathological landscapes. In constructing a thorough, selective review of contemporary leptin literature, a clearer evolutionary portrait materializes of a hormone integral to energy remittance, regulation and response. Perhaps most significantly, further avenues emerge for deeper understanding of leptin.

The challenge exists to outline a clear picture of leptin amidst the noise of endocrine, environmental, nutritional and psychological determinants of obesity and related conditions. This task requires collaboration and cross-theorizing between the fields of nutrition, metabolism, immunity and endocrinology.

The debate is not limited within the biological mechanisms of leptin alone, however. A case study of leptin is integrally involved in two especially ardent debates: the etiology of obesity as well as metabolic-immune intercommunication.

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Leptin background

The 1994 landmark paper by Rayner and Trayhurn (2001) revealed that obese ob/ob mice exhibited elevated expression of the leptin gene but no circulating leptin whatsoever. Therapeutic leptin treatment appeared to circumvent the ob gene deficiency and reestablish metabolic balance in the ob/ob mice (Morio et al. 1999). Images soon flourished in scientific and popular media of a little mouse's transformation from fat to thin after leptin injection. Leptin still continues to fascinate lay dieters and scientists alike as reports indicate the hormone may act as a negative feedback mechanism of food intake and body weight as well as a stimulant of energy expenditure (Matsuoka et al. 1997).

Studies show that leptin levels can be predicted statistically only with four independent parameters: Body Mass Index (BMI, where BMI= kg/m2, a standard measure of health risk due to obesity), percent body fat, gender and glycerol concentration in the blood. Alone, none of these parameters are exact indicators of leptin and often underestimate obesity levels (Matsuoka et al. 1997). Biological elements of leptin cause and consequence can only be understood amonst a varied individual endocrinological landscape (Morio et al. 1999).

Hormone interplay

Endocrinology studies must be careful not to isolate hormone actions and cascades. The biological reality of endocrinology is an extensive reciprocity and codependence—at once puzzling and staggering.

One of the important supporting actors in the leptin story is neuropeptide y (NPY), secreted by cells in the gut and the hypothalamus and integral to metabolism, obesity, anxiety, depression, memory, circadian rhythms and endocrine action (Inui 1999). Neurons of the hypothalamic arcuate nucleus (ARC) secrete the peptide (Inui 1999). NPY treatments inhibit satiety, induce feeding behavior and chronically induce rodent obesity. Commonly detected throughout the CNS, this neuropeptide acts on a cellular level to modulate lipoprotein lipase activity level, insulin secretion and energy expenditure (Mantovani et al. 2001). Fulfilling its homeostatic role, NPY blunts leptin and provides insulin negative feedback in conditions of energy deficit. This orexigneic action is counterbalanced by cytokine action decreasing appetite and increasing energy expenditure (Inui

1999). In the opposite milieu, positive energy balance is achieved by NPY signals increasing appetite, lipogenic enzymes and reduced brown adipose tissue outflow (Inui 1999).

In many ways, NPY appears to be leptin's main endocrine adversary. NPY decreases with leptin treatment, and vice versa, in both fed and fasted test animals (Rayner and Trayhurn 2001). Locationally, both NPY and leptin receptors reside together in arcuate neurons. Leptin-receptor binding may affect appetite mainly via inhibition of NPY synthesis and release (Mantovani et al. 2001). In another framework, NPY might then be an actuator of leptin's alarm message.

Lack of the NPY gene as a sole mutation produces mice with normal weight, starvation-response and leptin response. NPY can not, therefore, substantiate the sole force behind energy homeostasis. Neither is it essential for leptin action. The dual mutations of the ob and NPY gene in mice, however, do attenuate obesity phenotypes (Elmquist 1998, Rayner and Trayhurn 2001).

LEPTIN: SETTING THE BODY'S FAT THERMOSTAT

A useful (albeit loose) construct for leptin action is as a weight set-point mechanism, guarding a unique individual equilibrium. Leptin conceptually adjusts the "body's fat thermostat" based on environmental conditions. Such a regulatory operation would explain the remarkable constancy of individual weight despite great variation in food intake and exercise through time.

Tenacious weight stability is evident in the challenge obese individuals face in maintaining weight loss. Often, reduced energy expenditure counters weight loss efforts (Ioffe 1998). And while dieting may improve obesity and diabetes, "normal glucose tolerance may be difficult to achieve or maintain" (Muzzin et al. 1996, p. 14804). Adipose tissue size and distribution is far from arbitrary and is in fact strictly regulated (Halaas et al 1997). Obese persons do not respond to greater and greater leptin levels. The apparent blunting of the leptin response is often explained by a leptin-resistance theory of obesity.

Injections of leptin theoretically set a lower, constant body weight target by reducing food intake. Rates of energy use are unaffected. Higher leptin infusion rates achieve weight reduction faster, but do not achieve a greater quantitative loss (Halaas et al.1997). This nadir appears to be the leptin-guided set point.

To a great extent, metabolic efficiency predisposes individuals to certain weight classes (Reidy and Weber 2002). Three different mouse obesity strains: NZO, DIO, A^y show very disparate levels of leptin resistance. NZO mice respond to extremely low intracerebroventricular leptin levels while DIO and A^y do not. Subcutaneous leptin application, on the other hand, elicited a response in DIO mice (although some research is contradictory) and not in the other two obese strains (Halaas et al. 1997). A transport obstacle of some sort might explain these obesity triggers.

The details beg for explication. Also, these types of similar variations in leptin resistance and practical "set points" should be sought in humans.

Leptin effects are precluded in A^y mice by the downstream impairment of the critical receptor in the leptin cascade, Melanocortin receptor 4 (MC-4). The agouti protein is thought to competitively inhibit binding of the α melanocyte-stimulating hormone (αMSH) to MC-4. Disruption of the leptin neural pathway at this receptor was recently imputed in 5% of severe childhood obesity (Russell 2001). Neurons brandish MC-4 receptors, Ob-Rb receptors, as well as the MSH precursor, proopiomelanocortin (POMC) (Halaas et al. 1997). All of these are subject to abnormalities accused in obesity.

Fasting and leptin

The relationship between fasting and leptin merits further study. With this goal, studies have sought leptin measurements of animals in fasting states. Starvation precipitates a dramatic fall in leptin gene expression (though readily reversible) in mice and humans. The greater the initial leptin level, the steeper its decline with weight loss (Lord et al. 1998). Thus, leptin effects seem to work via relative changes rather than quantized levels. Also, leptin decreases are apparent long before any reduction of adipose tissue, and therefore can be considered independently. Lack of insulin response is discredited as an impetus for the fasting leptin drop by examining obese mice: the insulin declines in obese mice with faulty leptin (fa/fa or ob/ob) fail to retrench leptin levels (Rayner and Trayhurn 2001).

Energy expenditure

Does leptin increase energy expenditure? Marked differences in leptin-treated energy expenditure engender incongruous conclusions. Thermogenesis and oxygen depletion seem to increase with leptin treatment (Fruhbeck et al. 1998). Reduced food intake normally causes a parallel reduction in energy consumption. Leptin, in most cases, blunts this energy frugality. Ob/ob mice, however, experience an antithetical energy expenditure peak with leptin application. Leptin action is fundamentally different than either food intake or energy availability. Caloric intake increases both lean body mass and adipose tissue while leptin affects only the latter (Halaas et al. 1997).

Females and leptin

Female rats possess higher leptin levels at any body mass (Rayner and Trayhurn 2001). While human females test at the higher end of the leptin-level spectrum, leptin levels are similar for both genders when standardized by percent body fat. Boys and girls show similar leptin levels and rates of increase with age (Matsuoka 1998). Gender inequity appears only at mid-puberty (Morio et al. 1999), when it continues to rise in girls and decline in boys. An enigmatic question remains in brain differences; why is the percentage of circulating leptin emanating from the brain so much higher in females (41%) than in lean males (13%) (Wiesner

et al. 1999)? Many interesting suppositions arise aobut differences in male and female eating behaviors. Upregulated leptin mRNA in proportionally larger adipocytes of female may explain part, but not all, of the gender difference (Fruhbeck et al. 1998). The mystery of the sexes subsists.

Reproduction and Leptin

Leptin accelerates first estrus in normal mice and reverses ob/ob mice sterility (Rayner and Trayhurn 2001). Leptin's induction of luetinizing hormone (LH, a hormone active in sexual maturation) release is most potent just before puberty in normal rats. Naturally, the theory of leptin-driven puberty onset in humans is substantiated by the rise of plasma leptin with accumulating adipose tissue through childhood.   The role of leptin in obesity-driven infertility is particularly interesting since diet restrictions resulting in weight loss restore neither fertility or normal leptin levels. The power and sustainability of the leptin signal is thus reaffirmed in communicating information to the hypothalamic-pituitary-gonadal (HPG) axis. Exactly how and why leptin is necessary for fertility and estrus cycling is still the subject of study (Stoving et al. 1998).

Both obesity and emaciation obstruct ovarian function. Amenorrhoea often precedes weight loss in human anorexics and affects certain female athletes. Interestingly, amenorrhoeic athletes lack the nocturnal leptin peak found in menstruating athletes of equal weight (Stoving et al. 1998). Leptin's nocturnal peak must pose characteristic importance, as evidenced by its noticeable absence in amenorreaic athletes. By extension, then, leptin cycling critically regulates the gonadal axis.

Pregnancy Anomaly

Pregnancy poses a natural and definitively unique environment of leptin action. Like the obesity conditions discussed earlier, pregnancy imposes weight gains and corresponding leptin increases. Leptin's satiating qualities are vitiated, in fact, by the *elevated* appetite observed in high-leptin pregnancies. A leptin resistant model similar to obesity might be applicable. Post-pregnancy difficulties in weight loss suggest a stubborn quality of leptin resistance once adopted. How does a normal pregnancy regulate such leptin sensitivity? The strategic distribution of gestational fat may play a role. Placental secretion of leptin is also little understood, as is leptin action in fetal development and weight determination (Fruhbeck et al. 1998).

LEPTIN AND OBSESSIVE FOOD BEHAVIORS

Obsessive food patterns are likely to be wired as behavioral routines in the hypothalamus. "It is not the path that we choose in life that determines our happiness, it is the way we walk it" (Pickard, as quoted in Mac Evilly and Kelly 2001, p 27). Obsessive behaviors are mediated via dopaminergic midbrain system of reward and habit formation. Leptin, as well, may play a fascinating part.

Anorexia: antithetical metabolic malady

Anorexia is a nefarious and pandemic malignancy accompanying infection, inflammation, cancer and depression. Modern outbreaks of anorexia nervosa (1% of young women) and bulimia nervosa (4% of young women) are devastating and costly illnesses. The average cost of an individual anorexic's hospital stay is $12,390. Societal and environmental causes explain much of the female susceptibility (96% of victims are female), but genetic and endocrine predispositions are likely to be imputed in coming years (O'Brien and Patrick 2001).

Energy shortages normally induce greater food consumption and reduced energy expenditure. What inhibits these responses in anorexia/cachexia? [Anorexia is loss of appetite observable in disease; cachexia, a type of anorexia, involves adipose and muscle degradation and anorexia.] The scientific finger of blame lands squarely on inflammatory cytokines. Theories of cytokine-induced anorexia address the possible default in neural controls of the glucose response (Inui 1999). IL-1β, IL-8 and TNF-α induce anorexia either directly via the CNS or peripherally by activating second messengers, such as nitric oxide and prostanoids, through the vagus nerve or brain vasculature. The anorectic effect is also amplified by cytokine stimulation of CCK, a known appetite suppressor (Inui 1999). CCK might elicit anorexia via NPY feeding inhibition. Carbohydrate foods stimulate platelet-poor plasma (PPP) serotonin (5-HT) (the so-called "feel-good" hormone) levels in normal adults (Vered et al. 2001).   It appears anorexics lack this default carbohydrate PPP serotonin response to carbohydrate intake.

Endocrine and neuroendocrine genes are foremost in the focus of present study of anorexia (Kaye et al. 2000). As expected, anorexics show lower basal leptin levels than normal-weight subjects, in proportion to their reduced percentage of body fat. Moreover, diurnal leptin fluctuation is considerably blunted in anorexic subjects compared to control subjects, despite equivalent food consumption and absorption (as measured by postprandial insulin and glucose levels) (Stoving et al. 1998).

In anorexia, as opposed to starvation, leptin works against the gradient of energy balance by maintaining fat stores despite incongruent energy consumption and expenditure. The question remains: why is the counterregulatory mechanism not triggered (Inui 1999)? Shockingly, anorexics might experience a similar leptin resistance to that of obese individuals. In theory, leptin would become ineffective in conditions of anorexia. Supporting evidence is gleaned from aging experiments that report exacerbated leptin resistance due to calorie restriction (Jacobson et al. 2002).

Ill communication in signaling mechanisms may be at fault (Russell 2001). Perhaps low anorexic insulin levels are partially responsible for a leptin decrease. Effects of irregular eating patterns and nutritional status should be integrated in any workable theory (Rock 1999). Some more outlandish theories describe anorexia as an adaptation in the face of certain traumas or infections, or as a staged de-

fense against foods that might hinder the immune response (Fernandez-Real 1999).

Hypothalamic amenorrhoea is a criterion for diagnosis of anorexia (Stoving et al. 1998). Falling plasma leptin concentrations are thought to revert many victims to a pseudo-prepubertal state. Again, though, the difficulty in disjoining leptin and weight loss consequences reappears. Tangentially, reduced leptin causes parallel decreases in LHRH and gonadotrophin release, which is distinctly detrimental to hormonal reproductive function (McCann 2001). Perhaps anorexics' propensity for irreversible bone density damage (Rock 1999) is additionally demonstrative of leptin reversion.

Weight gain in anorexics invokes disparate leptin responses even with similar weight, age and BMI (1998). Variation might reflect varying stages of nutritional distress or individual patterns of leptin and weight recovery. As a suggestion for clinical eating disorder treatment, Stoving et al. propose manipulation of leptin levels to restrain accelerated rates of weight recovery (1998). Detriments are likely to be subtle and insidious and more study should attempt to delineate the full picture of anorexic recovery. Can instructive parallels be drawn from weight gain in these subjects to weight gain in obese persons? Or perhaps weight *loss* in obese persons?

STRESS AND METABOLISM

How is stress linked to metabolism? A known consequence of the fight or flight stress response is the diversion of resources from activities necessary for long-term survival (digestion, immunity, reproduction) to those necessary for immediate survival (muscles, eyesight, alertness). The main stress hormone group, glucocorticoids (GC), is mechanistically linked to fat tissue in that it elicits differentiation and proliferation, possibly on a site-by-site basis. Moderate GC treatment normalizes leptin responses, while excessive treatment induces overfeeding and obesity despite high leptin levels. Excess and resistance of leptin are mirrored and likely related to glucocorticoid excess (Bjorntorp 2001). The inverse relationship between plasma levels of cortisol and leptin in situ raise theories of mutual inhibition. Some studies present stress's potential to diminish leptin patterns (Bornstein et al. 1998, Kain et al. 1999).

Changes in consumption resultant from stress, either positive or negative, vary according to individual and circumstance. "Stress-eating" comprises several overeating responses to emotional stress. Distress is ameliorated, in theory, by centrally- released opioids after food consumption. Explicating the phenomenon, most bearers of restrained food attitudes are female and the most salient focus is fat intake. The nebulous construct of stress-eating might be a manifestation of an internal contest between leptin and neuropeptide y, with the latter's triumph driving appetite (Bjorntorp 2001).

Leptin as signal of plenty and stress responder

The combination of stressors and free radical accumulation incurs harm on the body. A new understanding of leptin as deleterious over long time periods, sows the concept of accrued damage from a contiguous or exaggerated stress response. Even psychological manifestations of depression are most likely selected as stress responses compelling an individual to "lay low" and avoid risk (Wright 1994).

The most precise characterization of leptin, however, is as orchestrator of the body's energy furnaces, seamlessly guiding crescendos and lulls in response to stresses such as excessive cold, to burns, to exercise in mellifluous unison (Reidy and Weber 2002). Independent of fat changes, leptin triggers events to maintain homeostatic energy balance in the short-term. In times of energy crisis and imbalance, leptin's signal is most clearly heeded. Studies of Siberian hamsters report attenuated leptin response in short-photo-period (wintering) animals exposed to energy deficit as compared to long-photoperiod animals. Regardless of fat content, leptin declines most precipitously in the first 24 hours of fasting. The dramatic and rapid variation in leptin levels is demonstrative of its responder role (Oritz et al. 2001). A corollary of this theory would parallel the body's dramatic response to night eating syndrome and anorexia to fasting conditions.

Leptin selection – evolutionary perspective

The potential for leptin to reduce adipose tissue in obese individuals has received romantisized attention (and will presumably continue to) as a product of an anti-obesity gene or- better still- a magic diet pill (Unger et al. 1999). It remains extremely unlikely that leptin's evolutionarily purpose is the readjustment of adiposity in overfed states. On the contrary, the "thrifty gene" theory purports a selective advantage for organsims retaining fuel reserves to safeguard against famine in conditions of alternating food availability. The potential fitness gains from food intake are recognized and encouraged by both serotenergic and appetitive mechanisms.

Responsible science demands that future research look not only at single individuals in time, but throughout a phylogeny to examine adaptive potential, causes and consequences. Famine and starvation have been eternal and inexorable constraints; obesity, as a modern epidemic, has had little time to be selected against. Temporary energy stockpilings have been selected across diverse organisms, from the penguin before molting to the desert rat in preparation for summer famine (Unger et al. 1999). High-energy phosphate bonds in fat molecules hold great metabolic potential (Nonogaki 2000).

Leptin resistance may have adapted in present-day conditions of over-abundance to prevent the dramatic leptin actions in animals possessing sufficient fat stores. Obesity conditions, in one sense, are "`mal-adaptations' of actual lifestyle to our genome" (Fernandez-Real & Ricart 1999). The biochemical reasons for low-concentration efficacy could include a limited CNS entry, increased competition

for binding, etc. The theory also enucleates lack of leptin correlations in end-stage renal disease cases (Fruhbeck et al. 1999). The kidney failure obstructs the key regulation of leptin levels by clearance.

Leptin, nutrition and immunity

As part of the stress response, leptin incites inflammation in the immune response. Leptin mimics the exaggerated responses often induced by infection and autoimmunity and may foster heightened inflammatory responses. This puissant hormone increases IFN-y and IL-2 production, while completely inhibiting regulatory IL-4 (Lord et al. 1998). Cytokines as well as naïve and memory T cells also operate within leptin's purview. The culminating effect is inflammation, which is then blocked from feedback inhibition (Drazen et al. 2001).

Impaired nutrient utilization is often couched as a corollary of immune challenge. More likely, there is cross communication. Decreased energy ingestion and uptake is at first counterintuitive in a state of immune challenge as it challenges the pathogen for energy sources as well as the host. Leptin's involvement, if further understood, would reveal much of this clandestine activity.

Abnormalities in the aeges of metabolism and immunity are mutually dependent and exacerbating, with the TNF-leptin pathway enabling this cross-communication. Effective campaigns against nutritional deficit, disease and infection cannot be waged in isolation. A central question lingers concerning whether cytokines or leptin act as the main regulator, or is mutual feedback the only means of matching energetic needs. Aging, cancer and other diseases are not caused by leptin, but perhaps by resistance to or diminution of the hormone (Mantovani et al. 2001).

The immune response is quite energetically expensive, increasing oxygen consumption and body temperature. Energy reserves are required to mount antibody response to specific pathogens. Two countering theories explain starvation-induced immunosuppression via energy unavailability or as a stress response. Evidence suggests, surprisingly, that leptin levels respond to the energy reduction of fasting, and not the stress response of the HPA system. Siberian hamsters with short photoperiods (usually incurring low fat and leptin levels) respond to leptin treatment with increased immune function (as measured by IgG concentrations) and increased food intake without any change in cortisol level. Leptin's indirect effect, then, is increasing energy fuel through increased consumption and improving immune preparedness (Drazen et al. 2001).

Obesity Intervention

The idea that so enthralled scientists and dieters alike is that leptin might mitigate appetite and promote weight reduction. In very rare instances of mutations preventing leptin production, this can be true. Large leptin doses decrease food intake in mice and rats, especially when applied intracerebroventricularly to act at the hypothalamic command center. For the most part, however, exogenous leptin does not reduce intake and fails as an easy cure-all for obesity.

Still there may be means of rational and promising obesity intervention through diet, nutrient and exercises changes. Optimizing fuel energy release as measured by thermic effect of food (TEF) may be possible by consumption of regularly timed and high-protein meals. Sibutramine and B_3-adrenergic agonists are some propositions as boosters of basal metabolic rate through sympathetic action (Pinkney et al. 2002). UCP action and TAG/FA cycle regulation may affect individual energy expenditure, and may be useful in understanding and treating obesity (Bjorntorp 2001). Vagally mediated hyperinsulinaemia may be quieted via sympathomimetic and anti-cholinergic chemicals. Octreotide successfully reduced hyperphagia in cases of childhood hypothalamic obesity (Pinkney et al. 2002).

Hypothalamic impairment would prevent most NPY, leptin, serotonin and noradrenaline actions. Possible pharmacological targets include: NPY (Inui 1999), melanocortin-4 receptor agonists, galanin antagonists, cytokine agonists and serotonin agonists. Serotonin enhancers, fenfluramine and fluoxetine, show some success in a specific type of genetic obesity (Pinkney et al. 2002). Lipase inhibitors require specific diet restraints, but may prove effective. Cortisol might harvest another target for centrally-obese persons suffering from raised cortisol levels. The approach of corrected hypercortisolaemia achieved normalization of associated maladies in Cushing's syndrome subjects (Bjorntorp 2001). Obese patients with naturally- low leptin levels appear to respond most acutely to exogenous leptin treatment. For maladies related to low body weight, anti-leptin antibodies and molecules aimed at impairing leptin have shown success in clinical weight gain (Bryson 2000).

So much of the obesity problem remains shrouded in complexity and mystery. Where is the malfunction? Scientific focus must remain on regulatory systems, and not just symptoms and comorbidities of obesity. Although a specific leptin receptor mutation causing obesity has been disproved, gradations of receptor affinity remain a possibility. Handicapped leptin function is either a causal, resultant or conditional characteristic of obesity.

Obesity may even represent a consequence of the neuroendocrine stress responses. Is cortisol responsible for leptin resistance and ensuing obesity (Bjorntorp 2001)? If not, what is the cause of the enigmatic leptin resistance? Since leptin infusion itself is unlikely to produce the dramatic weight loss initially hoped, a more pragmatic approach would be the pursuit of causes and mechanisms of leptin resistance rather than addressing purely leptin underproduction. Additional factors, like the recently discovered resistin (SCM 200), are likely to obfuscate metabolic mechanisms further. Leptin offers promise in regulating and ameliorating metabolic disorders from diabetes to wasting disorders from HIV and cancer. Hormonal understanding and treatments are only one tool against the obesity epidemic, and should be combined with an arsenal addressing mod-

ern lifestyle issues of consumption, exercise and stress. Leptin is not a panacea.

Future implications: Leptin has gained weight

By all accounts, the leptin story is incomplete. Extensions of the quests undertaken by the Human Genome Project will elucidate the precise polymorphisms of hormone production, receptors and action related to obesity. Work is currently underway to sequence the critical 5' promoter of the glucocorticoid receptor gene, for example (Bjorntorp 2001). Quantitative Trait Loci (QTLs) will enable the pinpointing of correlations and functional significances affecting complex traits. Moving past simple mapping and identification of candidate genes is critical to explore pleitropic actions of genes, epistasis and environmental interplay (Phillips et al. 2002). Proteomics promises the revelation of additional leptin regulators running the gamut from marginal to essential (Russell 2001).

Leptin, as the signal of plenty, pronounces the good news of fuel abundance to many aeges, including the reproductive system (and thus enabling normal reproductive development and female cycling) and the immune system (and boosting the immune response). In affecting food intake and storage, leptin assures energetic intake balances with expenditure. The pluripotent hormone is more than a steadying adipostat, however, but also a dramatic responder to stresses of all kinds. Leptin functions simultaneously as tonic regulator and emergency responder. In times of metabolic and immune stress, leptin reallocates resources to the most critical activities.

Leptin takes center stage in the current struggles to elucidate and starve the American obesity epidemic. Amid wild speculation and outlandish assertions, is the core truth that leptin plays a critical role in weight regulation. Complexities of metabolism and genetics have just gained weight.

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