The Role of Leptin in the Control of Body Weight

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Physiologic responses to high and low leptin concentrations are strikingly asymmetrical. High concentrations often produce minimal effects, whereas low concentrations provoke strong counterregulatory responses. A model and rationale for the physiology is presented.

Key Words: leptin concentrations, counterregulatory responses, energy balance, weight, obesity

Introduction

The critical role of leptin in the control of body weight is indicated by the extreme early-onset obesity that occurs in rodents and humans with loss-of-function mutations in the genes for leptin or its receptor. In addition, a great deal is now known about the molecular physiology of the hypothalamic and brain stem neuronal pathways that mediate the coordinate effects of leptin on energy intake and expenditure. What is not yet clear, however, is exactly what role leptin plays in the normal physiology of energy homeostasis and body composition. The powerful effects of leptin deficiency on fertility may provide important clues to this question.

Determinants of Circulating Leptin Concentrations

In ad libitum–fed animals, leptin is synthesized in and released from brown (BAT) and white (WAT) adipose tissues in proportion to rates of leptin mRNA synthesis per cell in those adipocytes. In neonatal animals, BAT is apparently the primary source of circulating leptin, whereas in older animals and humans, WAT is the major source.[1]

The concentration of leptin in blood is highly correlated with total fat mass, though concentrations are uniformly two- to threefold higher in post-pubertal fe-

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males than in males.[2] As puberty proceeds, leptin concentrations (adjusted for fat mass) decline in males and increase in females.[3] The suppressive effect of androgens on leptin synthesis is stronger than the stimulatory effect of estrogens. In addition to these endocrine effects, the distribution of body fat influences circulating leptin concentration, and accounts for a major portion of the sexual dimorphism in leptin concentrations.[4] Subcutaneous adipocytes produce approximately two times as much leptin per cell as intra-abdominal cells, probably owing in part to the larger volume of subcutaneous adipocytes. The strong positive correlations between adipocyte size, leptin mRNA, and protein release may be due to the effects of cell volume on glucose and/or free fatty acids flux, which in turn may modulate leptin expression via glucosamine-mediated effects on leptin gene expression.[5]

Caloric restriction decreases leptin expression/production per adipocyte within 18 to 24 hours, thus preceding any significant change in adipocyte size. These effects may be conveyed, in part, by decreased insulin and increased epinephrine concentrations in plasma. Insulin increases leptin gene expression whereas catecholamines decrease it.[6]

Circulating leptin concentrations may differ considerably among individuals with the same fat mass. Some of these differences are due to effects of insulin, glucocorticoids, and sex steroids on leptin expression.[7] If leptin acted primarily to suppress fat mass, one might predict that such differences in circulating leptin would lead to equilibration of fat mass at lower values. That this response does not occur has been attributed to resistance to leptin acting in both the central nervous system (CNS) and in peripheral tissues. The molecular mechanism of such resistance is not clear, but increased levels of hypothalamic SOCS3 (suppressor of cytokine signaling) have been proposed as a molecular mediator of acquired resistance to leptin. SOCS suppresses signaling at the leptin receptor, and in other receptors in the cytokine family, by inhibiting JAK2 activity (hence STAT activation).[8] For reasons discussed later, such apparent resistance to leptin may, in some instances, actually reflect a threshold effect on leptin action.

Leptin's Primary Physiologic Role

Given the evolutionary premium on efficiency in the storage and use of molecules that provide energy to

sustain cellular homeostasis and provide locomotion, and the particular environmental circumstances likely to have characterized hominid/human evolution, it seems probable that a greater emphasis has been placed on solutions to energy conservation and protection of somatic fuel stores than on the ability to dispose of transient excess calories by constitutive or facultative metabolic inefficiencies. The existence of proteins capable of shunting the proton gradient of mitochondria directly to heat, e.g., uncoupling protein 1 (*Ucp1*), probably reflects physiologic requirements for body temperature maintenance in small mammals rather than a general need to waste the chemical enthalpy of food or stored calories in the service of suppression of body fat. From this perspective, it is more relevant to emphasize leptin's role in energy conservation and preservation of fat storage than the converse. Leptin appears in evolution with the vertebrates, and may have been co-opted by mammals as a means of assuring that sexual maturation and pregnancy would not occur in the absence of sufficient fuel stores for fetal growth and suckling. Leptin is not sine qua non in this regard, however, because *ob/ob* mice segregating on Balb/cJ are obese and fertile,[9] and one of the human females homozygous for an inactivating leptin receptor (LEPR) mutation has gone into puberty spontaneously at 20 years of age (K. Clement, personal communication, 2001).

Absolute (genetic) or relative (hypocaloric intake) leptin deficiency results in lowering of metabolic rate and physical activity, increased hunger and food intake (increased meal size), suppression of the gonadal and thyroid endocrine axes, activation of the adrenal axis, and reduction in immune function (TH1 cell activity).[10] Small replacement doses of leptin will reverse some or all of these phenotypes in animals.[6,11] Doses of exogenous leptin sufficient to approximately double circulating leptin concentrations (per unit of fat mass) have minimal effects that are reciprocal to those described for leptin deficiency. Increasing leptin doses to produce approximate tenfold increases in blood levels causes hypophagia, increased metabolic rate, and rapid loss of body fat in otherwise normal mice and rats. However, once virtually all body fat is gone, normal food intake and energy balance resume, suggesting that leptin action may depend on other fat-derived molecules.[12] Consistent with this inference is the observation that in parabiosis experiments, +/+ parabionts of *db/db* (leptin over-secreting) animals do not recover energy balance,[13] but rather die of starvation, and that the anorexiant effects of conditioned adipocyte media are not dependent solely upon their leptin content.[14] Responses in monkeys and humans to high doses of leptin are much more variable.[15] The universal and potent responses to low(er) concentrations of leptin, minimal responses to moderate elevations, and

variable responses to extreme (pharmacologic) elevations, suggest that leptin's primary physiologic roles may reside at the low end of the concentration spectrum where leptin provides a continuous monitor of both the mass of adipose tissue and the magnitude and direction of flux of calories through that tissue.

The process of weight loss on a hypocaloric diet, and the maintenance of a reduced body weight by either a formerly obese or a never-obese individual, are accompanied by physiologic adjustments/states that closely resemble those of a leptin-deficient animal (or human): lower energy expenditure, hunger, suppression of gonadal axis and thyroid metabolism, and diminished sympathetic nervous activity.[16] This antihedonic state is probably responsible for the discomfort of dieting, and the more vexing clinical problem of maintaining a reduced body weight. Studies of children and adults suggest that in some individuals a hypometabolic state may precede initial weight gain to obesity, and that the weight gain itself may be a means of normalizing metabolic status.[17] The weight-maintenance energy requirements (normalized to body composition and size) of the obese and non-obese are equal at usual body weights.[16]

The striking ability of low-dose (replacement) leptin to normalize energy expenditure and the thyroid axis in weight-stable obese and never-obese humans (maintained at a body weight 10% below usual) is consistent with the idea that the metabolic/behavioral adjustments of the reduced-obese state reflect the physiologic consequences of relative leptin deficiency.[18]

Chemical Anatomy of Energy Homeostasis

Neuroanatomic/physiologic studies indicate that neurons/fiber tracts in the ventral/dorsal medial hypothalamus participate in the suppression of food intake/weight gain and increase energy expenditure, whereas lateral hypothalamic neurons promote energy intake and reduce energy expenditure. Ablative lesions of these regions of the hypothalamus lead, respectively, to maintenance of new levels of body fat above or below those present before the lesions were made.[19] In the 1950s, "the adipostatic hypothesis" provided a model of how adipose tissue might generate signals to the hypothalamus regarding its mass.[20,21] In the 1970s, the parabiosis experiments of Coleman and others provided physiologic support for the model, and suggested that the mouse *ob* and *db* mutations might be in respective ligand and receptor for such a system.[13] Positional cloning and molecular selection experiments led to the isolation of these genes (leptin, leptin receptor), and to confirmation of important elements of the adipostatic hypothesis.[10] Many genes encoding molecular components of this complex regulatory pathway have now been identified (e.g., neuropeptide Y [NPY], pro-opiomelanocortin

[POMC], melanocortin 4 receptor [MC4R], Agouti-related peptide [AgRP], melanin-concentrating hormone [MCH], prohormone convertase 1 [PC1], cocaine-amphetamine–related transcript [CART], OREXIN). The chemical anatomy and expression patterns of neurons synthesizing these orexiant and anorexiant peptides are consistent with the physiology implied by the earlier hypothalamic ablation/stimulation experiments.[10]

Genetics of Obesity

Twin and adoption studies indicate a 30 to 80% genetic contribution (in a specific environment) to obesity risk variance.[22] Some of the genes now known to participate in energy homeostasis have been implicated by direct analysis of sequence variations and/or by statistical arguments based on association or linkage. However, these latter studies, as well as similar studies in mouse, rat, and other species, also implicate genetic regions that do not contain known genes in the control of energy homeostasis.[23] Thus, there are clearly many additional genes for this class of molecules remaining to be identified.

How can our current understanding of the molecular neuroanatomy of energy homeostasis be made congruent with the clinical phenomenology of weight reduction and the compelling evidence regarding the genetic contribution to susceptibility to obesity?

Regulation of Body Weight

The control of food intake is achieved by effects on meal frequency and meal size, with meal size playing the predominant role under most physiologic circumstances. All of the rodent mutations resulting in hyperphagic obesity have their primary effect on meal size.[24] Preabsorptive signals emanating from the gastrointestinal tract (e.g., cholecystokinin [CCK], glucagon-like peptide [GLP]) reach the brain stem via vagal afferents and interact with forebrain-mediated signals (e.g., leptin, insulin, estrogen, cognitive) integrating longer-term signals of metabolic status to make decisions regarding meal termination. In this way, shorter-term feedback signals from the gut and liver are biased by input from higher centers in the CNS. Thus, these are integrated, not parallel, physiologic processes.[25]

Body mass and composition are ultimately determined by the long-term balance between energy intake and expenditure, and the effects of processes that affect the distribution of stored calories among protein, carbohydrate, and fat (partitioning). Genes with primary effects on energy intake (*Htr2c*), partitioning (*myogenin*), and expenditure (*Ucp1*) have been identified.[10] Based upon the phenotypes of naturally occurring and induced mutations in humans and animals, food intake is the most quantitatively important of these three subphenotypes with regard to determination of body weight. For example, in pair-feeding experiments, leptin has been shown to affect all three phenotypes determining body weight and composition, with the order of quantitative effect = intake > partition > expenditure.[26] With regard to food intake, the effect of leptin deficiency is primarily on meal size.[24]

As noted earlier, given the likely evolutionary premium on conservation of somatic energy stores, the regulation of body fat would be expected to be asymmetrical in the sense that decreases in body fat would be responded to more aggressively than increases in body fat. The genes encoding components of these pathways are numerous; their respective roles in the determination and defense of body energy stores in animals or humans remain largely unknown. It is likely that the multiple genes are involved in any individual, and that the responsible genes (and their proportionate roles) vary by age and ethnicity. However, based upon the arguments presented above, one would expect the most potent influences to be exerted by genes with primary effects on energy intake (e.g., leptin and molecular response components such as NPY, alpha melanocyte-stimulating hormone [αMSH], and MC4R).

Threshold Model for Leptin Feedback

One model (Figure 1) for such a system might include a hypothalamic threshold for leptin signaling that would, in turn, reflect the aggregate effects of DNA coding and regulatory sequence variants in the genes that encode components of the leptin-signaling cascade. The aggregate effect of such variants, some of which might enhance function, and most of which would impair it, would determine the concentration of peripheral leptin required to generate a sufficient signal through a partially impaired molecular pathway. In instances where, for example, *MC4R* was under-expressed or reduced in signaling capacity, the generation of more αMSH (POMC) might rectify the problem. In addition, or in situations where increased signaling intensity through the affected suppressive (e.g., MC4R) pathway was not sufficient, higher ambient leptin would reduce expression/release of orexigenic peptides such as NPY or AgRP. In (presumably) less frequent instances of activating/hyperfunctioning allelic variants of orexigenic peptides (NPY, AgRP, MCH), higher leptin concentrations could suppress expression of the orexigenic peptides and increase expression of anorexigenic peptides (αMSH, CART, corticotrophin-releasing factor [CRF]). Once sufficient leptin (fat mass) was achieved, equilibrium of body composition would be reached. The amount of body fat required to reach such equilibrium would be determined by the details of numbers and types of allelic variants present in any individual.

This model is supported by the effects of heterozygosity for *Lep* and *Lepr* mutations to increase body fat in rodents, and by the additive effects on body fat of being
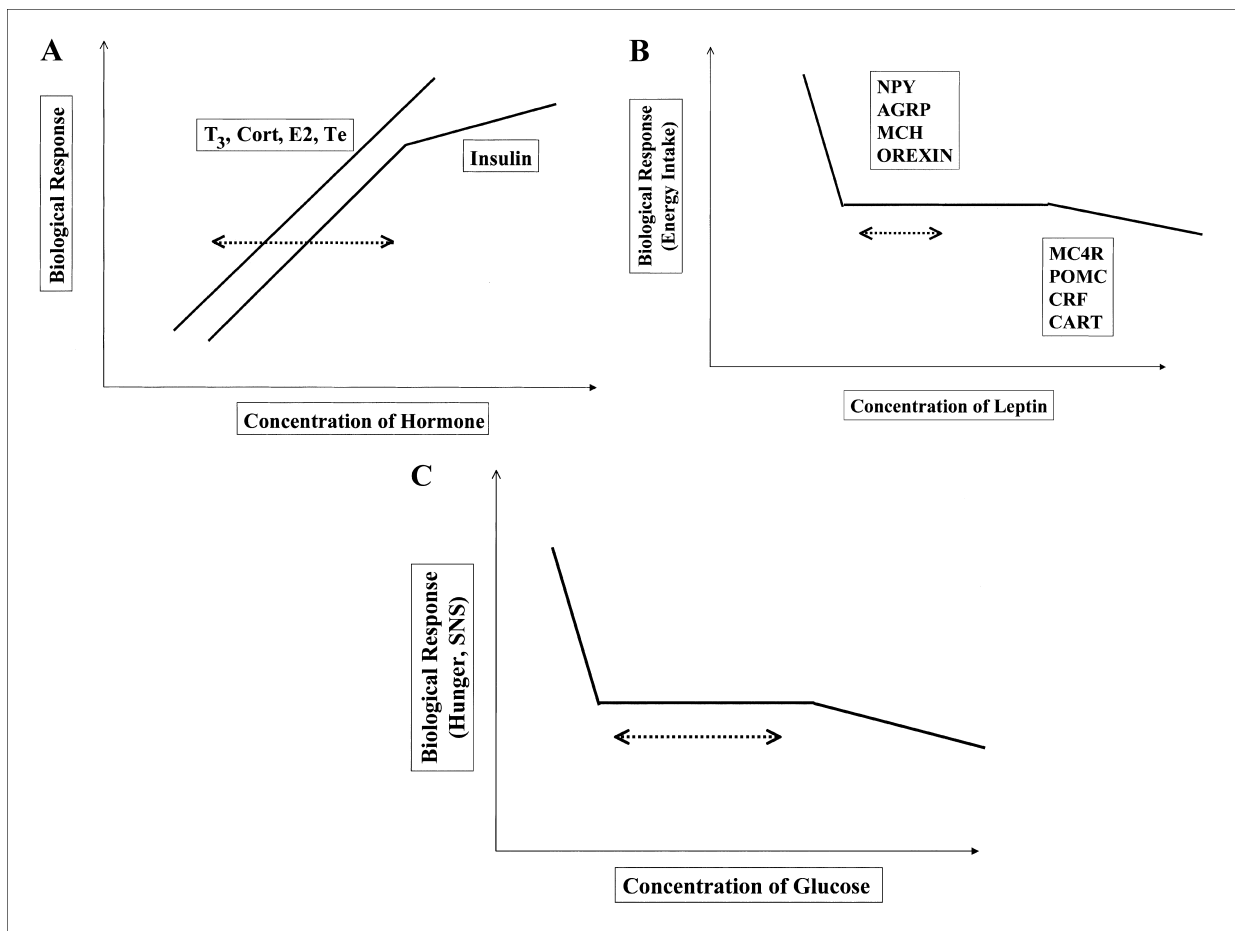
Figure 1. A. Schematized dose-response relationships for gonadal and adrenal steroids in comparison with the peptide hormone insulin. Horizontal dotted line is physiologic range of hormone concentration. T_3 = triiodothyronine; CORT = cortisol; E_2 = estradiol; TE = testosterone. In general, biologic response is proportionate to hormone concentration. At high concentrations, the response to insulin is decreased by molecular mechanism not yet fully understood. B. Leptin threshold model. The major biologic response(s) are evoked by decline in ambient leptin below a lower threshold. When this occurs, owing to insufficient fat mass or reduced production of leptin by adipocytes (negative energy balance), a full-blown hypothalamic neuronal response occurs. The resulting increased expression of NPY, AgRP, MCH, and Orexin results in behavioral and metabolic changes that increase energy intake and reduce energy expenditure. When leptin concentration is moderately increased above physiologic levels, no significant response occurs. At very high levels (e.g., 10 times by virtue of exogenous administration) there is a more proportionate (to ambient hormone concentration) reduction in energy intake mediated by increased actuvity of anorexigenic peptides/pathways. NPY = neuropeptide Y, AGRP = agouti-related peptide, MCH = melanocyte-concentrating hormone, MC4R = melanocortin 4 receptor, POMC = pro-opiomelanocortin, CRF = corticotrophin-relasing factor, CART = cocaine-amphetamine–related transcript. C. Physiologic precedence for the asymmetrical response model proposed in B includes the functional responses to high and low blood glucose concentrations. Hyperglycemia results in an osmotic diuresis and resultant increased thirst, but otherwise only mild short-term physiologic changes. Hypoglycemia, on the other hand, provokes a powerful, concerted series of endocrine, cardiovascular, and behavioral changes designed to restore blood glucose to a level above a life-threatening thresold. SNS = sympathetic nervous system.

heterozygous for inactivating mutations of *Lep* and *Lepr*.[27] Humans heterozygous for inactivating mutations of *LEP* are also fatter than +/+ family members.[28] Rats heterozygous for a loss of function *Lepr* mutation show increased sensitivity to the orexigenic effects of exogenous NPY (G. Smith, personal communication, 2001).

In this threshold model, higher body fat is a correction—through increased leptin production—for impaired leptin signal transmission. The aggregate effect of the constituent allelic variants is to constitute a threshold for leptin action. The presence of circulating leptin concen-

trations below this threshold is detected as an insufficiency of fat stores, in response to which compensatory increases in food intake and reduction in energy expenditure are made. The threshold for any individual is determined by genetic and, probably, developmental processes. When leptin concentrations exceed this threshold by moderate amounts (e.g., two- to threefold), the reciprocal response is not proportionate to the increase in leptin, permitting the organism to store additional caloric reserves as fat. The asymmetry of responses to low and high leptin accounts for the generally advantageous ten-

dency of animals to gain body fat in circumstances of a surfeit of available food calories. The rapid decline in leptin production by fat cells of food-restricted animals insures that the behavioral/metabolic processes designed to conserve body energy stores will be invoked before those fat stores have actually declined to any physiologically significant extent.

Conclusion

Leptin's primary physiologic role appears to be the defense of somatic fat stores in service of reproductive function. The hormone may achieve this function by a novel type of endocrine interaction with its major target organ, the hypothalamus. This interaction is characterized by a non-linear dose-response relationship (leptin vs. energy homeostasis phenotypes) that includes a step-function or threshold-like response to low ambient leptin. The physiologic definition of low leptin is contextual and includes sequence variation in genes of the molecular response cascade to leptin, aspects of neuronal development, and metabolic status.

Acknowledgments

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