

Is the Energy Homeostasis System Inherently Biased Toward Weight Gain?

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We describe a model of energy homeostasis to better understand neuronal pathways that control energy balance and their regulation by hormonal signals such as insulin and leptin. Catabolic neuronal pathways are those that both reduce food intake and increase energy expenditure (e.g., melanocortin neurons in the hypothalamic arcuate nucleus) and are stimulated by input from insulin and leptin. We propose that in the basal state, catabolic effectors are activated in response to physiological concentrations of leptin and insulin, and that this activation is essential to prevent excessive weight gain. In contrast, anabolic pathways (e.g., neurons containing neuropeptide Y) are those that stimulate food intake and decrease energy expenditure and are strongly inhibited by these same basal concentrations of insulin and leptin. In the basal state, therefore, catabolic effector pathways are activated while anabolic effector pathways are largely inhibited. The response to weight loss includes both activation of anabolic and inhibition of catabolic pathways and is, thus, inherently more vigorous than the response to weight gain (stimulation of already-activated catabolic pathways and inhibition of already-suppressed anabolic pathways). Teleological, molecular, physiological, and clinical aspects of this hypothesis are presented, along with a discussion of currently available supporting evidence. *Diabetes* 52:232–238, 2003

Recent years have seen remarkable progress in understanding the genetic and molecular basis of body weight regulation. Key peripheral signals, such as leptin, have been linked to hypothalamic neuropeptide systems, and the anatomic and functional networks that integrate these systems have begun to be elucidated (1). In individuals of normal weight, day-to-day fluctuations in energy stores are detected and countered over periods of weeks to months by

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α -MSH, α -melanocyte stimulating hormone; AgRP, agouti-related protein; ARC, arcuate nucleus; BBB, blood-brain barrier; CART, cocaine-amphetamine-regulated transcript; LHA, lateral hypothalamic area; MCH, melanin concentrating hormone; Mc4r, melanocortin-4 receptor; NPY, neuropeptide Y; PI 3-kinase, phosphatidylinositol 3-kinase; POMC, prepro-opiomelanocortin.

coordinated adjustments of food intake and energy expenditure, yielding remarkable stability in the amount of body fuel stored as fat. When body fat stores are threatened, as during food deprivation or restriction, robust responses are activated that promote recovery of depleted fuel stores. Indeed, such responses pose a major obstacle to the successful long-term treatment of obesity (2).

The ease with which many individuals gain weight, by comparison, seems inconsistent with the concept of a robust regulatory system that controls body weight. Even among individuals of normal weight, the process of aging is often accompanied by substantial increases of body fat over time (3). To account for the high and growing prevalence of obesity worldwide (4), systems controlling energy homeostasis have been suggested to defend against weight loss more effectively than against weight gain (5,6).

From an evolutionary perspective, it seems likely that the ability to survive and reproduce in environments with limited access to food provided a strong selection bias in favor of regulatory systems that vigorously defend against deficits of body fat. The need to protect against weight gain, by comparison, may have been a less pressing evolutionary concern, as an overabundant food supply was presumably an uncommon threat to survival (5,7,8). As satisfying as these teleological considerations may seem, however, they shed no immediate light on underlying mechanisms and provide little direction for the steadily increasing proportion of the world's population that is overweight. Here, we draw upon recent literature to propose a model of the neurohumoral control of energy homeostasis that is inherently more tolerant of weight gain than loss and describe its potential applications to strategies for understanding the molecular pathogenesis of obesity.

Pathways involved in energy homeostasis. Homeostatic responses to changes of body fat stores involve both sides of the energy balance equation and typically persist until the recovery of body fat content is complete. During periods of energy deficit, for example, hunger is increased while metabolic rate declines, a combination that promotes rapid and efficient recovery of lost weight when access to food has been restored. Such adaptive feeding and metabolic responses involve brain pathways that sense changes in body fuel stores and exert powerful, opposing effects on energy balance (the net difference between energy intake and expenditure). Pathways that stimulate food intake and promote weight gain are referred to here as anabolic-effector pathways, whereas those that promote anorexia and depletion of body fat are

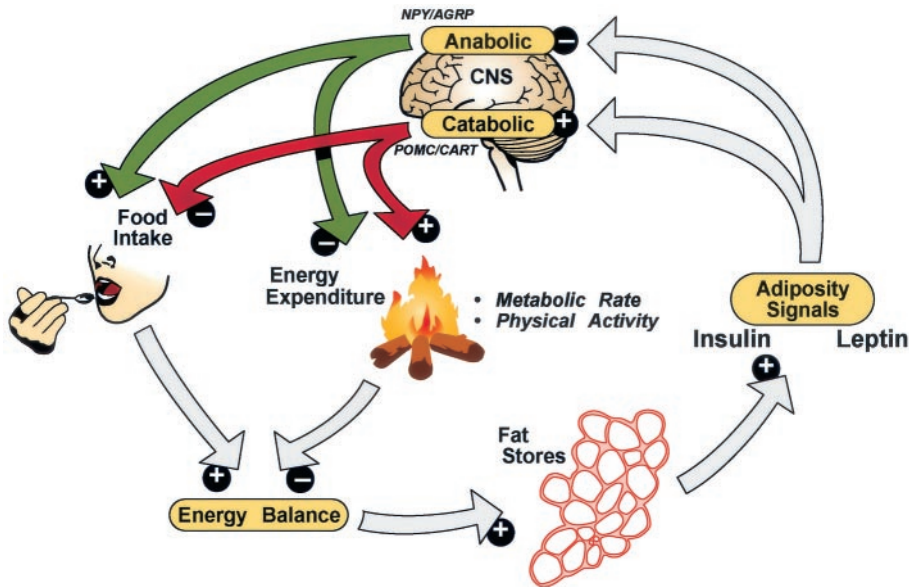


FIG. 1. Negative feedback model for regulation of body fat content. Leptin and insulin are signals that circulate in proportion to body adiposity and act in the hypothalamus to stimulate catabolic- (e.g., POMC/CART) and inhibit anabolic- (e.g., NPY/AgRP) effector pathways. These pathways have opposing effects on both energy intake and energy expenditure and, consequently, on the amount of body fuel stored as fat. Weight loss induced by caloric restriction lowers insulin and leptin levels, which in turn activates anabolic and inhibits catabolic effectors, and thereby promotes the recovery of lost weight. Modified from Schwartz et al. (9).

referred to as catabolic-effector pathways (9). Both pathways also regulate energy expenditure in ways that complement their effects on energy intake and enhance the overall response to a change in body fat content. Activation of anabolic pathways, for example, increases food intake and decreases energy expenditure, whereas the reverse is true for catabolic pathways (9).

Anabolic and catabolic pathways are generally regulated in a reciprocal manner, such that increases in the activity of one are often accompanied by decreases in the other (9). In response to fasting, for example, catabolic pathways are inhibited, while anabolic pathways are activated, thus allowing the organism to powerfully and synergistically alter both sides of the energy balance equation. Like other control systems in which there are concurrent, opposing forces bearing on a regulated parameter, such as regulation of body temperature (10), plasma osmolality (11), and blood glucose (12), this arrangement enables rapid and forceful responses that promote homeostasis.

How do these anabolic and catabolic pathways sense changes in energy balance? Current evidence supports a key role for leptin and insulin, hormones that circulate at concentrations proportionate to body fat mass and enter the brain, where they bind to and activate their respective receptors on the plasma membrane of target neurons. Low concentrations of leptin and insulin increase energy intake and reduce energy expenditure (13–15). Hence, the reciprocal nature of the neuronal response to an energy deficit (activation of anabolic pathways and inhibition of catabolic pathways) may be accounted for, at least in part, by reduced levels of these two hormones (Fig. 1).

An important anabolic pathway includes a subset of neurons in the hypothalamic arcuate nucleus (ARC) that coexpress neuropeptide Y (NPY) and agouti-related protein (AgRP) (16,17). Both peptides stimulate food intake and each acts on a distinct receptor system (NPY is an agonist of NPY receptors, while AgRP is an inverse agonist of neuronal melanocortin receptors, Mc3r and Mc4r). A major catabolic pathway is comprised of an adjacent subset of ARC neurons that synthesize α -melanocyte stimulating hormone (α -MSH), a melanocortin peptide derived

from the precursor, prepro-opiomelanocortin (POMC). Many ARC POMC neurons coexpress cocaine-amphetamine-regulated transcript (CART) (1), a peptide which, like α -MSH, potentially reduces food intake. Both NPY/AgRP and POMC/CART neurons project to neighboring hypothalamic areas that control feeding and autonomic function, including the paraventricular nucleus and lateral hypothalamic area. Neurons located in these “downstream” areas process input from the ARC and appear to play a key role to transduce this input into feeding and metabolic responses (1). Some ARC neurons also project directly to the spinal cord, where they innervate preganglionic neurons that control sympathetic nervous system outflow (1). Whereas ARC NPY/AgRP neurons are inhibited by leptin and insulin, POMC/CART neurons are stimulated by these hormones (14,18–20). These relationships support the hypothesis that neuronal circuits with opposing effects on energy balance are regulated in a reciprocal manner by negative feedback from adiposity-related signals (Fig. 1).

A cornerstone of this model is the proposition that neuronal systems involved in energy homeostasis are functionally “hard-wired” to generate a state of positive energy balance and weight gain unless input to the ARC from adiposity signals is sufficient to constrain anabolic and activate catabolic pathways. The implications of this proposition for adaptive responses mounted to resist weight gain during overfeeding are substantial and provide the central focus of this perspective.

A bias toward weight gain. Our hypothesis begins with the proposal that tonic output from catabolic pathways (e.g., POMC/CART neurons) is required to avert excessive food intake and weight gain. That is, we propose that catabolic pathways are activated in the basal state (defined as the steady state in which energy balance and body fat mass remains constant in a constant environment) by input from “normal” ambient concentrations of leptin and insulin (i.e., as expected for normal amounts of body fat). Other, as yet unidentified signals may participate as well. The tonic “on” status of these catabolic pathways in normal free-living animals constrains food intake while keeping the organism’s metabolic processes “revved up”

TABLE 1

Relative activity proposed for anabolic (NPY and AGRP) and catabolic (POMC and CART) arcuate nucleus neuropeptide systems in the basal state (at neutral energy balance) and in response to decreases or increases of adiposity

↓ Adiposity (↓ leptin and insulin)	Basal	↑ Adiposity (↑ leptin and insulin)
↑ ↑ NPY	↓ NPY	↓ ↓ NPY
↑ ↑ AGRP	↓ AGRP	↓ ↓ AGRP
↓ POMC	↑ POMC	↑ ↑ POMC
↓ CART	↑ CART	↑ ↑ CART

Note that food intake in the basal state is constrained by tonic activity of catabolic signaling pathways, with anabolic pathways being relatively inactive.

against the hard-wired tendency to conserve energy stores (eat more and expend less) when necessary. Hence, the effect of weight loss to reduce the level of adiposity-related hormones will rapidly and forcefully promote positive energy balance and weight gain via a mechanism that involves, at least in part, a decrease of catabolic pathway activity from its basal level.

By comparison, these same basal concentrations of insulin and leptin are proposed to strongly inhibit anabolic pathways (e.g., NPY/AgRP neurons). Thus, we suggest that in the basal state, catabolic pathways are activated, while anabolic pathways are relatively inactive. Consequently, the adaptive response to weight loss in normal individuals (full activation of anabolic, combined with inhibition of catabolic, pathways) should be inherently more vigorous than the response to weight gain (stimulation of already-activated catabolic pathways, inhibition of already-suppressed anabolic pathways) (Table 1, Fig. 2). While the energy homeostasis system can therefore respond to a change of adiposity in either direction, this analysis provides a mechanistic and testable explanation for its apparent bias toward energy storage as opposed to depletion.

Model predictions. Several predictions, or inferences, follow logically from this model, and each is discussed below in the context of current literature.

1) If catabolic (e.g., POMC/CART) signaling predominates over anabolic (e.g., NPY/AgRP) signaling in normal weight maintenance, destruction of the

ARC should cause weight gain. Chemical or electrolytic destruction of the ARC leads to obesity (21); the outcome is similar when knife cuts are used to sever outgoing projections from the ARC to adjacent hypothalamic areas (22). Catabolic output from the ARC therefore appears to predominate over anabolic output under usual conditions. Combined with evidence that ARC lesions attenuate the ability of leptin to reduce food intake (23), transduction of the leptin signal into altered feeding behavior appears to depend on intact catabolic responses generated by ARC neurons.

2) Responses to weight loss are bi-directional (e.g., activation of anabolic pathways and inhibition of catabolic pathways), whereas responses to overfeeding are unidirectional (e.g., comprised primarily of further activation of catabolic pathways with little change in activity of anabolic pathways). Conditions associated with weight loss, such as fasting and uncontrolled insulin-deficient diabetes, increase the expression of NPY and AgRP mRNA in the ARC (15) (Table 1), while decreasing POMC (9) and CART (24) gene expression in this brain area. By comparison, only the catabolic-effector pathways have been clearly found to respond to overfeeding. When rats are overfed by infusion of liquid nutrients directly into the stomach, for example, the development of anorexia as they gain weight is accompanied by marked increases of ARC POMC gene expression (25), whereas NPY mRNA levels are little affected (26). Therefore, signaling by at least one anabolic pathway (ARC NPY neurons) appears to be at the low end of its dynamic range in animals fed ad libitum, since it does not become inhibited further by weight gain, and yet is strongly activated by energy depletion. This unidirectional response contrasts with that of ARC POMC (catabolic) neurons, which show bi-directional regulation, as they are not only upregulated by overfeeding but are also downregulated during energy restriction.

3) Signaling by catabolic pathways, but not anabolic pathways, is required for maintenance of normal body weight. A crucial role for neuronal melanocortin signaling in energy homeostasis is supported by an abundance of literature documenting that its disruption by genetic interventions (e.g., mutations affecting POMC

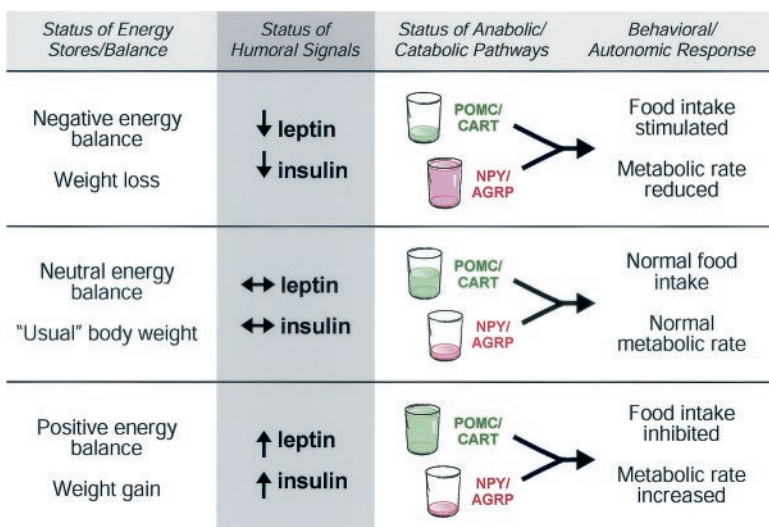


FIG. 2. Model for relationship between levels of adiposity signals (insulin and leptin) and activity of anabolic and catabolic effector pathways. When input from adiposity signals falls below normal levels, as during negative energy balance, responses that promote positive energy balance (e.g., ↑ food intake; ↓ energy expenditure) are potentially activated by the combined effects of increased anabolic and decreased catabolic effector activity. Because anabolic pathways are suppressed by normal levels of adiposity signals, their further inhibition contributes little to the response to an increase of adiposity signaling. The response to positive energy balance is consequently less robust, since it is mediated largely by increased catabolic pathway activity.

or melanocortin-4 receptors [Mc4rs] [27,28]) cause hyperphagia and obesity. In contrast, mice lacking NPY maintain normal body weight and do not suffer from anorexia or weight loss (29). Findings from genetic models therefore suggest that, unlike the requirement for catabolic signaling, normal energy homeostasis does not require tonic anabolic pathway activity. Consistent with this prediction, AgRP-deficient mice, like NPY knockout mice, also maintain normal body weight, as do mice lacking both NPY and AgRP (30). Further evidence that catabolic, but not anabolic, pathways play a critical role in weight maintenance is provided by pharmacological studies in genetically normal animals. Thus, central administration of Mc4r antagonists (31–33) potently increases food intake and body weight, while NPY receptor antagonists are not consistently effective in producing weight loss (34). Future studies (e.g., selective destruction of NPY/AgRP neurons in adult animals) are needed to more critically evaluate the role of anabolic pathways in normal weight maintenance.

4) Signaling by anabolic pathways is required for intact responses to negative energy balance. At odds with this model prediction, both NPY-deficient (29) and AgRP-deficient (30) mice exhibit intact hyperphagia in response to fasting (34). Indeed, such findings can be interpreted as evidence that these molecules play no role in energy homeostasis. The converse point, however, can also be argued. Thus, the finding that mice lacking NPY or AgRP (or both) maintain near-normal energy homeostasis may be interpreted to indicate that—by virtue of presumed evolutionary selective pressure—anabolic pathways are more plastic and redundant than catabolic pathways. Accordingly, mutations affecting the leptin-melanocortin signaling cascade can be anticipated to have an energy homeostasis phenotype, while those affecting NPY or AgRP cannot. These opposing interpretations highlight the limitations inherent in gene deletion studies with negative outcomes and emphasize the need for additional studies.

Because of concerns that deprivation-induced feeding may activate redundant mechanisms in addition to NPY/AgRP neurons, we investigated the role of NPY in a different model of energy depletion. Uncontrolled, insulin-deficient diabetes, induced by streptozotocin, causes negative energy balance despite pronounced hyperphagia. Weight loss in this condition is a consequence of insulin deficiency, as insulin is required for control of blood glucose and maintenance of body fat. In the absence of insulin, body fat is mobilized despite marked increases in food consumption, with excess calories (glucose and ketones) being lost in the urine. As expected, depleted body fat mass in this model is accompanied by lowering of plasma leptin, activation of NPY/AgRP neurons, and inhibition of POMC neurons (35). These responses collectively increase food intake. Interestingly, this hyperphagic response is markedly attenuated in NPY-deficient mice (36). These findings imply an obligate role for NPY in diabetic hyperphagia, but not in the response to fasting.

5) Signaling by catabolic pathways, but not anabolic pathways, is required for intact responses to exogenous leptin. This prediction is supported by the observation that pharmacological blockade (37,38) or genetic interruption of melanocortin receptors (39) attenu-

ates the anorexic and weight-reducing effects of leptin, in agreement with the hypothesis that melanocortin signaling is required for normal energy homeostasis. By comparison, leptin-induced anorexia is not attenuated (and in fact is augmented) in mice with genetic deficiency of NPY (29,40). The latter finding has been interpreted as evidence that NPY neurons exert effects on food intake opposite to those of leptin. Removal of NPY, therefore, increases leptin's efficacy as an anorexic agent.

6) Signaling by anabolic pathways is required for intact responses to decreased input from leptin. To investigate the role of NPY in the phenotype that results from absent leptin signaling, Hollopeter et al. (41) crossed *Npy*^{-/-} with *ob/ob* mice to generate leptin-deficient animals that also lack NPY. The marked reductions in hyperphagia and obesity exhibited by these animals relative to *ob/ob* littermates with intact NPY production confirm a crucial role for NPY in the molecular physiology of positive energy balance and obesity resulting from leptin deficiency. That these double mutants remain obese compared with wild-type controls, however, confirms that leptin deficiency does not cause obesity solely via increased NPY signaling. This outcome is consistent with our model, since reduced catabolic signaling persists in *ob/ob* mice, even in the absence of NPY.

7) Anabolic pathways are more sensitive (i.e., have a left-shifted dose-effect curve) than catabolic pathways to regulation by adiposity signals. The precise cellular mechanisms by which ARC neurons are regulated by insulin and leptin remains an important unanswered question. The hypothesis that basal concentrations of these hormones exert near-maximal inhibitory effects on NPY/AgRP neurons while only partially activating adjacent POMC/CART neurons (Fig. 2) is untested. One possible mechanism that can be invoked to explain the proposed differential sensitivity of these two neuronal subsets to input from insulin and leptin relates to the anatomical relationship between NPY/AgRP and POMC/CART neurons within the ARC. Being located in the medial aspect of this brain area, NPY/AgRP neurons are situated more closely than POMC/CART neurons to the median eminence, which lacks a blood-brain barrier (BBB) (42). In light of evidence that the medial ARC may also lack a BBB (43), it is possible that NPY/AgRP neurons are exposed to higher ambient concentrations of insulin and leptin than POMC/CART neurons. Studies that address this hypothesis may help to shed light on the hormonal regulation of ARC neurons.

Alternatively, anabolic and catabolic neurons could potentially respond to input from insulin and leptin via distinct intracellular signaling mechanisms. While leptin activates both the phosphatidylinositol 3-kinase (PI 3-kinase) (44) and the janus kinase–signal transduction and activator of transcription (JAK-STAT) pathway (45) in hypothalamic extracts, for example, neither the relative importance of these responses nor the specific cells in which they occur is known. Both the magnitude and the direction of cellular responses to receptor activation could depend on which of these intracellular pathways predominates in specific neuronal subsets and the downstream molecules with which they interact to affect neuronal function.

Downstream of the ARC: melanin concentrating hormone. Melanin concentrating hormone (MCH) is an orexiogenic neuropeptide that is synthesized in the lateral hypothalamic area (LHA) and plays a key role in energy homeostasis. Since congenital MCH deficiency causes a lean hypophagic phenotype (46), tonic input from MCH neurons appears to be required for normal control of food intake, even under basal conditions at usual body weight. This possibility seems at odds with our proposal that anabolic signaling pathways are quiescent at usual body weight. Moreover, bi-directional regulation of MCH neurons in response to upward or downward changes in body weight have been reported (47), conflicting with yet another tenet of our model.

To explain these inconsistencies, we propose that MCH neurons are not primary anabolic effectors, as defined here, but rather are integral downstream transducers of signals generated by neurons that respond to changes of body fat content. This hypothesis is supported by the rich supply of fibers from both NPY/AgRP and POMC/CART neurons in the ARC to the MCH neurons in the LHA (48). Moreover, MCH expression is inhibited by α -MSH and is increased by melanocortin receptor blockade (49). Thus, reduced MCH signaling may, at least in part, constrain food intake in response to tonic melanocortin signaling. These findings collectively suggest that MCH neurons play a crucial role in processing input from pathways originating in the ARC. If melanocortins promote weight loss, at least in part, by inhibiting MCH neurons, deletion of MCH might be expected to mimic the effect on energy homeostasis of increased melanocortin signaling. This outcome differs from that induced by loss of NPY, for example, and is further supported by potent antiobesity effects of a recently described MCH receptor antagonist (50).

Meal-to-meal control of food intake. If catabolic tone predominates in the day-to-day maintenance of body weight, what process accounts for meal initiation? Does this require a transient interruption of catabolic tone, or perhaps a transient activation of anabolic pathways? Although the answer is unclear, recent data suggest that both may occur. A key point for this discussion is evidence that NPY/AgRP neurons exert tonic inhibitory control over POMC/CART neurons, an effect mediated at least in part via γ -aminobutyric acid release (51). Transient activation of NPY/AgRP neurons, therefore, not only increases anabolic signaling, but also inhibits catabolic signaling by both antagonizing melanocortin receptors (via AgRP release) and inhibiting catabolic (POMC/CART) neuronal output.

Ghrelin is an acylated peptide secreted from the stomach and upper intestine that stimulates food intake (52,53) via a mechanism that involves activation of NPY/AgRP neurons. The hypothesis that ghrelin participates in meal initiation is supported by evidence that plasma-ghrelin levels peak just before meal onset and fall precipitously thereafter (54). To the extent that ghrelin participates in the perception of hunger and the decision to eat, these data suggest that transient activation of anabolic signaling (which, in turn, transiently disrupts catabolic tone) may play a key role. Thus, it is possible that input from adiposity signals induces tonic catabolic output that con-

strains energy intake; transient spikes of ghrelin or other meal-inducing stimuli may increase anabolic signaling while simultaneously inhibiting catabolic output, thus favoring the onset of feeding.

Many factors that participate in meal initiation, however, are not hard-wired into the physiology of energy homeostasis. Learned behaviors, sensory cues, emotional inputs, palatability of available food, as well as social or societal variables all influence the decision to eat, and none of these are tied directly to neuroendocrine circuits involved in energy homeostasis. Indeed, it has been argued that meal initiation is a process driven more by learned and other 'nonbiological' parameters than by defined hormonal stimuli, and that long-term regulation of energy intake occurs predominantly via control of meal termination (which is also sensitive to input from insulin and leptin) rather than meal onset (rev. in 55,56).

DISCUSSION

The model proposed here is not intended to explain how obesity occurs. Rather, the intent is to better understand the apparent bias of the energy homeostasis system in favor of weight gain. This information is important for the development of an interpretive and experimental framework that encompasses genetic and environmental factors related to obesity. Clarifying the regulation of neuronal pathways by adiposity signals and their contribution to adaptive responses to weight loss and weight gain is critical if we are to understand how mammalian systems evolved to defend against the threat of starvation. This evolutionary process may have involved selection of allelic variants of the genes discussed, as well as others that predispose to weight gain.

From a clinical perspective, there is a compelling need to understand how weight gain occurs so readily in the context of a homeostatic system that regulates body fat. Such understanding will assist in the selection of appropriate drug targets and will facilitate therapeutic decision-making in a future where multiple drug options for obesity treatment are likely to exist. For example, inhibition of anabolic activity is unlikely to cause weight loss by itself if anabolic pathways are already hypoactive under ad libitum feeding conditions, but it may help to maintain weight loss induced by other interventions (since weight loss should activate anabolic effectors that had previously been quiescent). Conversely, the weight-reducing efficacy of drugs that activate catabolic effector pathways (e.g., agonists of melanocortin receptors) are likely to be potentiated by concomitant inhibition of anabolic pathways that will otherwise be activated as body fat is lost. Drug combinations that both activate catabolic and inhibit anabolic pathways, or alternatively, act downstream of these neuronal systems, may ultimately be required for optimal pharmacotherapy of obesity.

The means by which our bodies strive to defend fat stores in the face of large variation in day-to-day energy intake and expenditure is an area of fundamental biomedical importance. The ability to improve the lives of individuals with disorders of this process will require a detailed understanding of how this system works. While the rapid pace at which new signaling molecules are being discovered continues to generate intense research inter-

est, valid physiological models with which to interpret experimental and clinical phenomena are essential for the development of more effective therapeutic strategies.

REFERENCES

1. Elmquist JK, Elias CF, Saper CB: From lesions to leptin: hypothalamic control of food intake and body weight (Review). *Neuron* 22:221–232, 1999
2. Pasman WJ, Saris WH, Westertep-Plantenga MS: Predictors of weight maintenance. *Obes Res* 7:43–50, 1999
3. Rossner S: Obesity through the ages of man. *Int J Obes Relat Metab Disord* 25 (Suppl. 4):S29–S33, 2001
4. Kopelman PG: Obesity as a medical problem. *Nature* 404:635–643, 2000
5. Ahima RS, Prabakaran D, Mantzoros C, Qu D, Lowell B, Flier-Maratos E, Flier JS: Role of leptin in the neuroendocrine response to fasting. *Nature* 382:250–252, 1996
6. Ahima RS, Kelly J, Elmquist JK, Flier JS: Distinct physiologic and neuronal responses to decreased leptin and mild hyperleptinemia. *Endocrinology* 140:4923–4931, 1999
7. Coleman DL: Obesity genes: beneficial effects in heterozygous mice. *Science* 203:663–665, 1979
8. Bjorntorp P: Thrifty genes and human obesity. Are we chasing ghosts? *Lancet* 358:1006–1008, 2001
9. Schwartz MW, Woods SC, Porte DJ, Seeley RJ, Baskin DG: Central nervous system control of food intake. *Nature* 404:661–671, 2000
10. Gordon CJ: *Temperature Regulation in Laboratory Rodents*. New York, Cambridge University Press, 1993
11. Stricker EM, Sved AF: Thirst. *Nutrition* 16:821–826, 2000
12. Newsholme EA, Dimitriadis G: Some thoughts on the importance of insulin in the regulation of the blood glucose level. *Experientia* 52:421–425, 1996
13. Woods SC, Seeley RJ, Porte DJ, Schwartz MW: Signals that regulate food intake and energy homeostasis. *Science* 280:1378–1383, 1998
14. Benoit SC, Air EL, Coolen LM, Strauss R, Jackman A, Clegg DJ, Seeley RJ, Woods SC: The catabolic action of insulin in the brain is mediated by melanocortins. *J Neurosci* 22:9048–9052, 2002
15. Mizuno TM, Makimura H, Silverstein J, Roberts JL, Lopingco T, Mobbs CV: Fasting regulates hypothalamic neuropeptide Y, agouti-related peptide, and proopiomelanocortin in diabetic mice independent of changes in leptin or insulin. *Endocrinology* 140:4551–4557, 1999
16. Broberger C, Johansen J, Johansson C, Schalling M, Hokfelt T: The neuropeptide Y/agouti gene-related protein (AGRP) brain circuitry in normal, anorectic, and monosodium glutamate-treated mice. *Proc Natl Acad Sci U S A* 95:15043–15048, 1998
17. Hahn TM, Breininger JF, Baskin DG, Schwartz MW: Coexpression of Agrp and NPY in fasting-activated hypothalamic neurons. *Nat Neurosci* 1:271–272, 1998
18. Schwartz MW, Seeley RJ, Weigle DS, Burn P, Campfield LA, Baskin DG: Leptin increases hypothalamic proopiomelanocortin (POMC) mRNA expression in the rostral arcuate nucleus. *Diabetes* 46:2119–2123, 1997
19. Thornton JE, Cheung CC, Clifton DK, Steiner RA: Regulation of hypothalamic proopiomelanocortin mRNA by leptin in ob/ob mice. *Endocrinology* 138:5063–5067, 1997
20. Mizuno T, Kleopoulos S, Bergen H, Roberts J, Priest C, Mobbs C: Hypothalamic pro-opiomelanocortin mRNA is reduced by fasting and in ob/ob and db/db mice, but is stimulated by leptin. *Diabetes* 47:294–297, 1998
21. Bergen HT, Mizuno TM, Taylor J, Mobbs CV: Hyperphagia and weight gain after gold-thioglucose: relation to hypothalamic neuropeptide Y and proopiomelanocortin. *Endocrinology* 139:4483–4488, 1998
22. Bell ME, Bhatnagar S, Akana SF, Choi S, Dallman MF: Disruption of arcuate/paraventricular nucleus connections changes body energy balance and response to acute stress. *J Neurosci* 20:6707–6713, 2000
23. Tang-Christensen M, Holst JJ, Hartmann B, Vrang N: The arcuate nucleus is pivotal in mediating the anorectic effects of centrally administered leptin. *Neuroreport* 10:1183–1187, 1999
24. Kristensen P, Judge ME, Thim L, Ribel U, Christjansen KN, Wulff BS, Clausen JT, Jensen PB, Madsen OD, Vrang N, Larsen PJ, Hastrup S: Hypothalamic CART is a new anorectic peptide regulated by leptin. *Nature* 393:72–76, 1998
25. Hagan M, Rushing P, Schwartz M, Yagaloff K, Burn P, Woods S, Seeley R: Role of the CNS melanocortin system in the response to overfeeding. *J Neurosci* 19:2362–2367, 1999
26. Seeley RJ, Matson CA, Chavez M, Woods SC, Schwartz MW: Behavioral, endocrine and hypothalamic responses to involuntary overfeeding. *Am J Physiol* 271:R819–R823, 1996
27. Huszar D, Lynch CA, Fairchild-Huntress V, Dunmore JH, Fang Q, Berke-meier LR, Gu W, Kesterson RA, Boston BA, Cone RD, Smith FJ, Campfield LA, Burn P, Lee F: Targeted disruption of the melanocortin-4 receptor results in obesity in mice. *Cell* 88:131–141, 1997
28. Yaswen L, Diehl N, Brennan MB, Hochgeschwender U: Obesity in the mouse model of pro-opiomelanocortin deficiency responds to peripheral melanocortin. *Nat Med* 5:1066–1070, 1999
29. Erickson JC, Clegg KE, Palmiter RD: Sensitivity to leptin and susceptibility to seizures of mice lacking neuropeptide Y. *Nature* 381:415–418, 1996
30. Qian S, Chen H, Weingarth D, Trumbauer ME, Novi DE, Guan X, Yu H, Shen Z, Feng Y, Frazier E, Chen A, Camacho RE, Shearman LP, Gopal-Truter S, MacNeil DJ, Van der Ploeg LH, Marsh DJ: Neither agouti-related protein nor neuropeptide Y is critically required for the regulation of energy homeostasis in mice. *Mol Cell Biol* 22:5027–5035, 2002
31. Fan W, Boston B, Kesterson R, Hruby V, Cone R: Role of melanocortinergic neurons in feeding and the agouti obesity syndrome. *Nature* 385:165–168, 1997
32. Hagan MM, Rushing PA, Pritchard LM, Schwartz MW, Strack AM, Van der Ploeg HT, Woods SC, Seeley RJ: Long-term orexigenic effects of AgRP- (83–132) involve mechanisms other than melanocortin receptor blockade. *Am J Physiol Regul Integr Comp Physiol* 279:R47–R52, 2000
33. Kim MS, Rossi M, Abusnana S, Sunter D, Morgan DG, Small CJ, Edwards CM, Heath MM, Stanley SA, Seal LJ, Bhatti JR, Smith DM, Ghatei MA, Bloom SR: Hypothalamic localization of the feeding effect of agouti-related peptide and α -melanocyte-stimulating hormone. *Diabetes* 49:177–182, 2000
34. Zimanyi IA, Fathi Z, Poindexter GS: Central control of feeding behavior by neuropeptide Y. *Curr Pharm Des* 4:349–366, 1998
35. Havel PJ, Hahn TM, Sindelar DK, Baskin DG, Dallman MF, Weigle DS, Schwartz MW: Effects of streptozotocin-induced diabetes and insulin treatment on the hypothalamic melanocortin system and muscle uncoupling protein 3 expression in rats. *Diabetes* 49:244–252, 2000
36. Sindelar DK, Mystkowski P, Marsh DJ, Palmiter RD, Schwartz MW: Attenuation of diabetic hyperphagia in neuropeptide Y-deficient mice. *Diabetes* 51:778–783, 2002
37. Seeley R, Yagaloff K, Fisher S, Burn P, Thiele T, van DG, Baskin D, Schwartz M: Melanocortin receptors in leptin effects. *Nature* 390:349, 1997
38. Satoh N, Ogawa Y, Katsuura G, Numata Y, Masuzaki H, Yoshimasa Y, Nakao K: Satiety effect and sympathetic activation of leptin are mediated by hypothalamic melanocortin system. *Neurosci Lett* 249:107–110, 1998
39. Halaas JL, Boozer C, Blair-West J, Fidahusein N, Denton DA, Friedman JM: Physiological response to long-term peripheral and central leptin infusion in lean and obese mice. *Proc Natl Acad Sci U S A* 94:8878–8883, 1997
40. Hollopeter G, Erickson J, Seeley R, Marsh D, Palmiter R: Response of neuropeptide Y-deficient mice to feeding effectors. *Regul Pept* 75–76:383–389, 1998
41. Erickson JC, Hollopeter G, Palmiter RD: Attenuation of the obesity syndrome of ob/ob mice by the loss of neuropeptide Y. *Science* 274:1704–1707, 1996
42. Ganong WF: Circumventricular organs: definition and role in the regulation of endocrine and autonomic function. *Clin Exp Pharmacol Physiol* 27:422–427, 2000
43. Peruzzo B, Pastor FE, Blazquez JL, Schobitz K, Pelaez B, Amat P, Rodriguez EM: A second look at the barriers of the medial basal hypothalamus. *Exp Brain Res* 132:10–26, 2000
44. Spanswick D, Smith MA, Mirshamsi S, Routh VH, Ashford ML: Insulin activates ATP-sensitive K⁺ channels in hypothalamic neurons of lean, but not obese rats. *Nat Neurosci* 3:757–758, 2000
45. McCowen KC, Chow JC, Smith RJ: Leptin signaling in the hypothalamus of normal rats in vivo. *Endocrinology* 139:4442–4447, 1998
46. Shimada M, Tritos NA, Lowell BB, Flier JS, Maratos-Flier E: Mice lacking melanin-concentrating hormone are hypophagic and lean. *Nature* 396:670–674, 1998
47. Tritos NA, Maratos-Flier E: Two important systems in energy homeostasis: melanocortins and melanin-concentrating hormone. *Neuropeptides* 33: 339–349, 1999
48. Elias CF, Saper CB, Maratos-Flier E, Tritos NA, Lee C, Kelly J, Tatro JB, Hoffman GE, Ollmann MM, Barsh GS, Sakurai T, Yanagisawa M, Elmquist JK: Chemically defined projections linking the mediobasal hypothalamus and the lateral hypothalamic area. *J Comp Neurol* 402:442–459, 1998
49. Hanada R, Nakazato M, Matsukura S, Murakami N, Yoshimatsu H, Sakata T: Differential regulation of melanin-concentrating hormone and orexin genes in the agouti-related protein/melanocortin-4 receptor system. *Biochem Biophys Res Commun* 268:88–91, 2000
50. Borowsky B, Durkin MM, Ogozalek K, Marzabadi MR, DeLeon J, Heurich R, Lichtblau H, Shaposhnik Z, Daniewska I, Blackburn TP, Branchek TA, Gerald C, Vaysse PJ, Froyay C: Antidepressant, anxiolytic and anorectic

- effects of a melanin-concentrating hormone-1 receptor antagonist. *Nat Med* 8:825–830, 2002
51. Cowley MA, Smart JL, Rubinstein M, Cerdan MG, Diano S, Horvath TL, Cone RD, Low MJ: Leptin activates anorexigenic POMC neurons through a neural network in the arcuate nucleus. *Nature* 411:480–484, 2001
52. Tschöp M, Smiley DL, Heiman ML: Ghrelin induces adiposity in rodents. *Nature* 407:908–913, 2000
53. Kamegai J, Tamura H, Shimizu T, Ishii S, Sugihara H, Wakabayashi I: Central effect of ghrelin, an endogenous growth hormone secretagogue, on hypothalamic peptide gene expression. *Endocrinology* 141:4797–4800, 2000
54. Cummings DE, Weigle DS, Frayo RS, Breen PA, Ma MK, Dellinger EP, Purnell JQ: Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. *N Engl J Med* 346:1623–1630, 2002
55. Woods SC: The eating paradox: how we tolerate food (Review). *Psychol Rev* 98:488–505, 1991
56. Woods SC, Strubbe JH: The psychobiology of meals. *Psychon Bull Rev* 1:141–155, 1994