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GENETICS AND PATHOPHYSIOLOGY OF HUMAN OBESITY

David E. Cummings and Michael W. Schwartz
Department of Medicine, Division of Metabolism, Endocrinology and Nutrition, University of Washington, VA Puget Sound Health Care System and Harborview Medical Center, Seattle, Washington 98195; e-mail: davidec@u.washington.edu; mschwart@u.washington.edu

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■ **Abstract** Obesity has become a leading public health concern. Over 1 billion people are now overweight or obese, and the prevalence of these conditions is rising rapidly. Remarkable new insights into the mechanisms that control body weight are providing an increasingly detailed framework for a better understanding of obesity pathogenesis. Key peripheral signals, such as leptin, insulin, and ghrelin, have been linked to hypothalamic neuropeptide systems, and the anatomic and functional networks that integrate these systems have begun to be elucidated. This article highlights some of these recent findings and their implications for the future of obesity treatment.

"Banish plump Jack, and banish all the world."
William Shakespeare, King Henry IV Part 1

INTRODUCTION

Obesity has emerged as a preeminent public health problem. The National Center for Health Statistics reports that 61% of adults in the United States are overweight (body-mass index 25–29.9) and 26% are obese (body-mass index $\geq$30) (1). No longer an affliction solely of Western society, obesity has increased worldwide by $>$75% since 1980 (2). With over 1 billion people now overweight or obese (3), the World Health Organization has proclaimed this to be a global epidemic. Particularly alarming is the explosion of childhood obesity. For example, the number of obese children in France has increased fivefold during the past decade (4), and the prevalence of overweight children in the United States has more than doubled since 1976 (5). Although affected individuals often focus on the social stigma of obesity, this condition is far more than a cosmetic problem; it is strongly associated with diabetes, hypertension, dyslipidemias, coronary heart disease, pulmonary afflictions, osteoarthritis, and more (6, 7). These comorbidities conspire to increase overall mortality, which, according to numerous large studies in humans, rises

steadily as a function of increasing body weight (8, 9). It has been reasonably argued that obesity is beginning to overtake infectious diseases and undernutrition as the most significant contributor to illness worldwide (7).

Despite the compelling demand for anti-obesity therapeutics, existing nonsurgical options are surprisingly limited and ineffective (10). For most people, no more than a 5%–10% loss of body weight can be maintained through diet, exercise, and use of the few available anti-obesity medications (11). Moreover, because none of these agents acts on physiological pathways that are particularly specific to body-weight regulation, they are fraught with side effects that often prohibit their use in the very populations who need them.

Current pharmacotherapy for obesity resembles that for hypertension several decades ago—the few available medicines have limited efficacy and there are no reliable predictors of response (11). Obesity and hypertension share several other features in common. They are both polygenic disorders influenced heavily by genetics and to a lesser degree by the environment. Body weight and blood pressure are both regulated parameters that are defended by complex and highly redundant physiological systems. In hypertension and obesity, the defended parameter is regulated at an abnormally high level. Just as dramatic advances in hypertension treatment arose from insights into the mechanisms that govern blood pressure, similar advances in obesity therapy may soon spring from rapidly expanding knowledge of the molecular determinants of body weight. This review highlights salient recent insights into the genetics and pathophysiology of obesity and their implications for its treatment.

A MULTIFACTORIAL ETIOLOGY

Despite popular stereotypes portraying obesity as a problem of gluttonous behavior and poor will power, unassailable evidence now shows that genetic factors play a dominant role in determining body weight within a given environment (12). Family clustering of obesity exists, with a relative risk among siblings of 3–7 (13), and the concordance of body-mass index is much higher between monozygotic than dizygotic twins (74% versus 32%, respectively), despite equally shared environments (12, 14). The body-mass index of adopted children is linearly related to that of both of their biological parents, even when there is no direct contact with them, and is unrelated to that of either adoptive parent, even though these individuals provide the daily menu (15). These and other data suggest an estimated heritability for obesity of 50% to 90%, with a relatively minor role for cultural transmission (12).

The paramount role of genetic factors in body-weight regulation seems difficult to reconcile with the burgeoning of human obesity in recent years. Clearly, adiposity is not an entirely predetermined genetic parameter. Evidence indicates that obesity is an oligogenic disease, whose expression can be modulated by numerous polygenic modifier genes interacting with each other and with environmental factors such as food choices, physical activity, and smoking (3). In support of

this conclusion is the observation that among rodents, the effect of genetic background on response to high-calorie diets is as great as or greater than the effect of different genetic backgrounds on adiposity with a fixed diet (12). Small bodyweight differences among inbred strains are magnified by high-fat diets, indicating gene $\times$ environment interactions. A few genes are so important that mutations in them cause morbid obesity in almost any environment (see below). The majority, however, can be thought of as susceptibility genes, each exerting relatively small effects and acting in combination to influence the expression of obesity phenotypes in permissive environments.

Why would the human genome contain such a plethora of gene polymorphisms that favor accumulation and defense of an excessive level of adiposity? The explanation forwarded by the "thrifty genotype" hypothesis is that genes were subjected to evolutionary pressures over millions of years that favored alleles promoting weight gain, because the environment was characterized by unreliable access to food until very recently (16). Individuals genetically inclined toward gluttonous eating in times of plenty and/or efficient storage of ingested calories would be more likely to survive famines and thus propagate their "thrifty" genes. It is not surprising that cultures throughout history have revered corpulent human icons as symbols of good health. Unfortunately, with the rapid globalization of Western society, we now increasingly live in environments for which our thrifty genome is maladaptive. These environments are characterized by easy access to highly palatable, highly caloric food, sedentary vocations, and leisure-time activities dominated by television and computers (17). In these environments, our thrifty genome increasingly expresses obese phenotypes that are no longer adaptive.

THE LIPOSTATIC MODEL OF BODY-WEIGHT REGULATION

Body weight is regulated within a narrow, individualized range, the level of which is determined by a combination of genetic and environmental factors. Among the most compelling data demonstrating this regulation is the observation that people in Western cultures typically gain 0.5–1.0 pound per year during most of their adult lives (18). The imbalance between ingested and expended calories required to achieve this amount of weight gain is 10–20 kcal/day—the energy content of one Ritz® cracker—which is $<1\%$ of daily energy requirements. Thus, despite substantial day-to-day energy imbalances characteristic of most humans, cumulative energy intake and expenditure are precisely matched over long periods of time (to within 0.17% per decade) (19). The biological process responsible for this regulation is known as energy homeostasis. Because of this process, perturbations of body adiposity away from the defended level engage adaptive responses in energy intake (appetite) and energy expenditure (thermogenesis), which operate in reciprocal directions to restore the defended level of adiposity (19–21). For example, attempts to lose weight by caloric restriction are compromised by both an increase in hunger and a decrease in metabolic rate, the magnitude of which rise in

proportion to the amount of weight lost. Because of these adaptive responses, recidivism after dietary weight loss is nearly universal (22).

Implicit in this homeostatic system of body-weight regulation is a mechanism whereby the status of body-fat stores is communicated to the brain, which is the arbiter of adaptive responses to changes in body-fat content. In his "lipostatic model," Kennedy (23) hypothesized 50 years ago that this communication was achieved by factors that circulate in proportion to body-fat stores and act in the brain to reduce food intake. Coleman (24) provided experimental evidence for the existence of such humoral adiposity signals in an elegant series of parabiosis experiments conducted more than 30 years ago, although the identity of these signals was unknown at that time.

An afferent adiposity signal involved in body-weight regulation should fulfill several key criteria (25). It should circulate and enter the brain in proportion to body-fat content. Peripheral or central administration of the agent should decrease food intake and body weight (without causing systemic illness), whereas a deficiency of the signal should render the opposite effects. Finally, a signal transduction system mediating these actions should exist in brain neurons involved in energy homeostasis. Two molecules have been clearly shown to meet these criteria: leptin and insulin.

Woods & Porte (26) first proposed a role for insulin in energy homeostasis in 1979. Although all the necessary criteria to establish insulin as an adiposity signal have since been demonstrated (27), the concept that insulin's central actions physiologically promote weight loss has been difficult to prove because its peripheral actions have the opposite effect. However, the importance of insulin in body-weight regulation was recently confirmed by two sets of observations in rodents. First, hyperphagia and increased fat accumulation result from either neuron-specific deletion of the insulin receptor (28) or perihypothalamic injection of insulin receptor antisense oligonucleotides (which inhibit insulin receptor synthesis) (29). Second, insulin mimetics that access the brain more readily than does native insulin have been shown to reduce body weight and protect against diet-induced obesity (30). These findings have potentially important clinical implications, since they identify centrally active insulin analogues as candidates for anti-obesity therapy.

The discovery of leptin by Friedman and colleagues in 1994 was a watershed event in body-weight research (31). This adipocyte hormone unequivocally satisfies the above criteria as a critical adiposity signal (32). Like insulin, leptin circulates in proportion to body-fat content (33), crosses the blood-brain barrier (34), interacts with receptors on neurons known to influence energy balance, and exerts long-acting effects to reduce adiposity by decreasing appetite and increasing thermogenesis (27). Leptin is the dominant hormone in a classical endocrine negative-feedback loop that dynamically regulates body weight (Figure 1), and available evidence indicates that it is more important than insulin in the central regulation of energy homeostasis (27). Changes in body adiposity are reflected by changes in circulating leptin levels, and the brain responds with

reciprocal modulations of energy intake and expenditure to restore the defended level of body fat. Rodents (32) and humans with inactivating mutations in the gene encoding leptin (35) or its receptor (36) suffer uncontrollable hyperphagia and massive obesity, proving an indispensable role for leptin signaling in the maintenance of normal body weight. Such individuals also have reproductive dysfunction, interestingly similar to that observed in mice lacking neuronal insulin receptors. This and other findings suggest possible cross talk between signaling events downstream of central leptin and insulin receptors. The hypothesis that such signaling convergence occurs at the level of an enzyme known as phosphatidylinositol-3-OH kinase (PI-3 kinase) is under active investigation (37).

With the discovery of leptin came the exciting hope that obesity might be a condition of leptin deficiency that could be reversed by leptin replacement. Unfortunately, it quickly became clear that the vast majority of human obesity is characterized by leptin levels that are appropriately high for the degree of adiposity (33) yet fail to reduce appetite as equivalent levels would in lean individuals. Common obesity thus appears to be a condition of functional leptin resistance, and consequently, efforts to treat it with leptin administration have been disappointing thus far (38). Because inactivating leptin receptor (LepR) mutations are exceedingly rare (36), great attention is now focused on identifying the molecular events that lie downstream of the LepR in key hypothalamic target neurons.

CENTRAL TARGETS OF ADIPOSITY SIGNALS

The central effector pathways that regulate body weight in response to afferent information from peripheral adiposity signals such as leptin and insulin comprise a complex web of neuropeptides that can be segregated into two broad categories (27). Catabolic neuropeptides are stimulated by leptin and insulin, and promote weight loss by decreasing food intake and increasing energy expenditure. Anabolic neuropeptides are suppressed by leptin and insulin, and promote weight gain by increasing food intake and decreasing energy expenditure. Within these categories, peptides involved in energy homeostasis can be further sorted into two categories: those expressed in neurons that are regulated directly by leptin and insulin (first-order neurons), and those expressed in neurons primarily regulated by synaptic input downstream of first-order neurons (second-order neurons or higher).

First-Order Neurons

The prototypic first-order neuronal targets of leptin and insulin action are catabolic proopiomelanocortin (POMC) and anabolic neuropeptide-Y/Agouti-related protein (NPY/AgRP) neurons. These reside in the hypothalamic arcuate nucleus (ARC) (27), a brain area endowed with high concentrations of receptors for leptin and insulin (Figure 2) (39). These neurons exert opposing effects on energy balance and are reciprocally regulated by changes in energy

stores, as communicated via fluctuations in adiposity signals. First-order neurons express signaling isoforms of the leptin and insulin receptor and respond directly to changes in levels of these hormones. Thus, adaptive responses to perturbations in body adiposity are hypothesized to involve reciprocal changes in the activity of arcuate POMC and NPY/AgRP neurons.

Catabolic POMC neurons are concentrated in the dorsolateral ARC (27). They are activated by leptin (32) and insulin (30) and are suppressed in states of negative energy balance or genetically defective leptin signaling. POMC is cleaved—probably by prohormone convertase 1 (PC1) (40)—into melanocortins including αMSH, which exerts catabolic actions via melanocortin-4 receptors (Mc4r) and, to a lesser extent, via Mc3r (41). These melanocortin receptors are found in brain areas that regulate food intake and autonomic activity. Thus, central administration of melanocortin agonists in experimental animals decreases food intake and increases energy expenditure, leading to weight loss, whereas antagonists do the opposite (42). The importance of melanocortins as mediators of leptin action is demonstrated by the observation that low doses of melanocortin receptor antagonists strongly attenuate the ability of exogenous leptin to decrease food intake (43). Similarly, anorexia induced by involuntary overfeeding (e.g., gastric infusion of an oversupply of nutrients) is reversed by low-dose central melanocortin blockade (44). Mutations throughout the leptin-melanocortin signaling pathway produce profound obesity in rodents and humans (see below), proving that this pathway is critical to maintaining normal body weight. Arcuate POMC neurons coexpress cocaine- and amphetamine-regulated transcript (CART), an anorexic neuropeptide that is regulated similarly to POMC by alterations in energy stores (45).

Anabolic NPY/AgRP neurons are concentrated in the ventromedial ARC, adjacent to POMC neurons (27, 46). They are suppressed by leptin and insulin and are activated by states of negative energy balance as well as by other forms of leptin or insulin deficiency. Central administration of NPY increases food intake and decreases energy expenditure in rodents and other mammals, and chronic infusion promotes weight gain. Among the five known NPY receptors, the Y1 and Y5 isoforms are most strongly implicated as mediators of these anabolic actions. A critical role for NPY in body-weight regulation is challenged by the findings that neither hypophagic nor lean phenotypes are manifest in murine knockouts of the genes encoding NPY, Y1, or Y5 (47–49). However, acute administrations of NPY antisense oligonucleotides, NPY-blocking antibodies, or Y-receptor antagonists do inhibit food intake (46). These apparently contradictory observations may be explained by developmental adaptations that could occur in genetic forms of defective NPY signaling. One theory proposes that NPY is most important for stimulating food intake when energy stores are severely threatened, as indicated by decreased inhibitory input from adiposity signals such as leptin and insulin. This interpretation fits with evidence that NPY is required for full expression of the obese phenotype in leptin-deficient *ob/ob* mice (50), as well as for the hyperphagia associated with uncontrolled insulin-deficient diabetes (51), a condition characterized by low circulating levels of both insulin and leptin (52).

First-order targets of leptin and insulin action in the ARC are elegantly interconnected (Figure 2). NPY neurons coexpress AgRP (53), which exerts anabolic actions by competitively antagonizing melanocortin signaling at Mc3r and Mc4r (54), an action potentiated by the receptor adapter molecule syndecan-3 (55). In addition, γ-aminobutyric acid–containing projections from NPY/AgRP neurons directly suppress firing of POMC neurons, possibly augmented by inhibitory input from NPY acting through Y1 receptors (56). Thus, arcuate NPY/AgRP neurons are uniquely capable of simultaneously activating a key anabolic signaling pathway (via NPY receptors) and inactivating a critical catabolic signaling pathway (via melanocortin receptors). The hypothesis that NPY/AgRP neurons are auto-inhibited by NPY acting on Y2 receptors (56) provides a potential explanation for the seemingly paradoxical obese phenotype of Y2-deficient mice (57). Similarly, POMC neurons may be auto-inhibited by melanocortins acting on Mc3r (56).

Because NPY and AgRP are coregulated by alterations in energy stores (communicated by fluctuations in adiposity signals) and both exert anabolic effects, they are partially redundant. However, their anabolic actions can be differentiated not only by the receptors upon which they act, but also on the basis of their orexigenic kinetics. Following a single injection of NPY into brain ventricles, food intake increases robustly, but for only a few hours, whereas AgRP triggers modest increases of food intake for a much longer period (up to a week following a single central injection) (58). In addition, AgRP is upregulated far more dramatically than is NPY by fasting or genetic leptin deficiency, while both are equally induced in the setting of diabetic hyperphagia (46). Thus, NPY and AgRP may play distinct roles in the feeding responses to different kinds of physiological stresses.

Second-Order Neurons and Efferent Pathways in Energy Homeostasis

A neuroanatomic framework has been delineated that supports a model in which first-order neurons in the ARC integrate information about the status of body-fat stores, then relay this information to brain regions that control appetite and energy expenditure (59).

Arcuate NPY/AgRP and POMC neurons project to the lateral hypothalamic area (LHA) and adjacent perifornical area, where they appear to make monosynaptic connections with neurons that express anabolic neuropeptides, including melanin-concentrating hormone (MCH) and orexins A and B (59). The LHA has long been deemed a "hunger center" because electrical stimulation of this area causes hyperphagia and obesity, whereas lesions yield the opposite results (60). Current literature suggests that such outcomes involve stimulation or ablation, respectively, of MCH neurons. This contention is supported by the observations that MCH-deficient mice are hypophagic and lean (61), whereas transgenic overexpression or intracerebroventricular injection of MCH near the LHA increases food intake and body weight (62, 63). Neurons in the LHA project diffusely throughout the neuraxis, making monosynaptic connections with several regions of the cerebral

cortex that could contribute to the perception of hunger and triggering of eating (59). MCH may also decrease energy expenditure by suppressing the thyroid axis, and consistent with this, MCH knockout mice are hypermetabolic (61).

Arcuate NPY/AgRP and POMC neurons also project densely to the hypothalamic paraventricular nucleus (PVN) (27, 59). This area communicates with the cerebral cortex and appears to participate, along with the LHA, in the transduction of leptin signaling into modulation of hunger. In contrast to the anabolic LHA, the PVN sends output that is predominantly catabolic, and the region has long been identified as a "satiety center" because lesions here produce hyperphagic obesity (60). Catabolic output from the PVN is relayed in part from hypophysiotropic neurons expressing thyrotropin-releasing hormone (TRH), corticotropin-releasing hormone (CRH), and oxytocin. These second-order neurons transduce input from the ARC and other sources into changes of appetite as well as energy expenditure and neuroendocrine function. TRH not only increases thermogenesis by stimulating the thyroid axis, but also decreases food intake. Monosynaptic connections have been demonstrated between first-order arcuate POMC neurons and PVN TRH neurons, and the ability of leptin to increase thyroid hormone levels requires an intact ARC (59). Leptin is also reported to stimulate PVN production of CRH, which in turn decreases food intake, while increasing energy expenditure via the sympathetic nervous system.

In addition to regulating energy expenditure via the thyroid axis, leptin may also do so via pathways that involve direct and indirect connections between ARC neurons and sympathetic preganglionic neurons of the spinal cord (59). For example, a subset of POMC neurons in the ARC, as well as CRH and oxytocin neurons in the PVN, project to sympathetic motor output areas. These send efferent projections to brown adipose tissue, stimulating thermogenesis via β-adrenergic receptors.

Finally, arcuate NPY/AgRP and POMC neurons communicate with brainstem areas involved in food-intake control (such as the nucleus of the solitary tract), both directly via monosynaptic connections and indirectly through the PVN and LHA. An extensive literature implicates the nucleus of the solitary tract as a principal target of short-acting, food-stimulated satiety signals that contribute to the termination of individual meals. These signals include mechanical gastric stretch, as well as enteric neurocrine peptides such as cholecystokinin, glucagon, glucagon-like peptide 1, amylin, and bombesin-related peptides (64, 65).

To regulate overall food intake, leptin and insulin must ultimately affect the size and/or frequency of individual meals. Considerable evidence indicates that leptin may accomplish this via connections from the hypothalamus to the brainstem that act as gain setters, modulating sensitivity to meal-related satiety signals. Similar gain setting of the response to satiety signals may result from leptin acting directly in the brainstem (66, 67). Brainstem centers such as the nucleus of the solitary tract, dorsal motor nucleus of the vagus, and area postrema express the substrates for responding to adiposity signals. These include LepR, insulin receptors, NPY, POMC, and melanocortin receptors. Furthermore, administration of leptin or melanocortins into or near the brainstem exerts many of the same effects

as do hypothalamic injections. Thus, the brainstem may also be an integrative center involved in long-term energy homeostasis (66).

The model of energy homeostatic neural circuitry presented here is undoubtedly a simplification of a much more complex system. For example, many neurons in the PVN, LHA, and perifornical area project back to the ARC, indicating bidirectional communication between centers of first- and second-order neurons. Moreover, leptin receptors are expressed in the PVN and LHA, which suggests that regions we have portrayed as second-order sites may also receive direct afferent input from adiposity signals. However, leptin receptor density is far greater in the ARC than in these other areas, and the model we present continues to be supported by a growing literature (27).

GHRELIN: THE FIRST KNOWN OREXIGENIC HORMONE

Ghrelin, the recently discovered endogenous ligand for the growth hormone secretagogue receptor (68), is also the only known appetite-stimulating hormone (69–71). This acylated, 28–amino-acid peptide is secreted primarily by the stomach, circulates in blood, and activates NPY/AgRP neurons in the ARC (72). Peripheral or central ghrelin injections powerfully increase short-term food intake in rodents and may decrease energy expenditure and fat catabolism (69–71, 73). Ghrelin has been shown to be orexigenic when administered at approximately physiological doses in rodents (74) and humans (75), suggesting that normal fluctuations of endogenous circulating ghrelin can affect appetite.

Ghrelin is implicated in both the short- and long-term regulation of appetite and body weight. Circulating levels sharply increase before and fall after every meal in humans (76). This and other observations in rodents are consistent with a role for ghrelin in the initiation of individual meals. However, repeated or continuous ghrelin administration not only affects meal patterning but also increases body weight in rodents (69, 70, 73). Furthermore, circulating ghrelin levels increase in several models of negative energy balance, including low-calorie diets (77), chronic exercise (K.E. Foster, D.E. Cummings, unpublished), cancer anorexia (78), cardiac cachexia (79), and anorexia nervosa (80). These findings suggest that ghrelin may participate in the adaptive response to weight loss and thus in long-term body-weight regulation. However, weight loss achieved with a low-fat diet does not elicit a compensatory rise in circulating ghrelin (D.S. Weigle, D.E. Cummings, J.Q. Purnell, unpublished), and vertical-banded gastric bypass surgery is associated with profoundly suppressed ghrelin levels (77). Thus, the weight-reducing efficacy of these methods can potentially be explained in part by their effects on circulating ghrelin.

In weight-stable people, ghrelin levels correlate negatively with body-mass index over a wide range (81, 82), consistent with a compensatory rather than causal role for ghrelin in common obesity. However, humans with Prader-Willi syndrome, the most common form of syndromic obesity, have markedly elevated plasma

ghrelin levels (82). These are comparable to or higher than levels reported to stimulate appetite and food intake during peripheral ghrelin infusion (74, 75). Hyperghrelinemia may thus contribute to the severe hyperphagia and obesity associated with Prader-Willi syndrome. It is conceivable that the growth hormone deficiency and/or hypogonadotropic hypogonadism of Prader-Willi syndrome could also arise from ghrelin-mediated dysregulation of NPY neurons in the ARC.

GENETICS OF HUMAN OBESITY

Rodent models of obesity have played a key role in elucidating pathways that govern body weight. Knowledge of these pathways, combined with modern quantitative genetic techniques, is allowing researchers to begin to unravel the genetic basis of human obesity.

Monogenic Obesity and the Importance of Leptin-Melanocortin Signaling

Mutations in six human genes have been identified, which, acting alone, cause morbid obesity that is largely independent of environmental factors or disease modifier genes (12, 83). Though rare, these mutations provide valuable insights, identifying genes that are indispensable for normal body-weight regulation. Inactivating, recessive mutations in the genes for leptin, LepR, POMC, and PC1 all give rise to voracious hyperphagia and profound, childhood-onset obesity in homozygous individuals (Figure 3). Affected individuals also show pituitary endocrine dysfunction, such as hypogonadism, hypothyroidism, or hypocortisolism.

Only 12 people in 6 pedigrees have been described with any of these mutations (83). In contrast, dozens of different obesity-associated mutations in the human Mc4r gene have been reported (83). This is by far the most common form of monogenic human obesity, accounting for up to 4% of common morbid obesity (84). Unlike the recessively transmitted monogenic obesity conditions just described, those associated with Mc4r mutations are usually autosomal dominant with variable penetrance, arising from haploinsufficiency in Mc4r signaling rather than from dominant negative mechanisms (85–87). The phenotype of Mc4r deficiency resembles common obesity and is not associated with pituitary dysfunction. Human obesity also appears to arise from disruption of the transcription factor SIM1 (88). The targets of SIM1 are unknown, but the gene is essential for formation of the PVN, a principal site of Mc4r expression (59) and a second-order leptin target.

It is particularly noteworthy that all six known forms of human monogenic obesity involve proteins in the leptin-melanocortin signaling pathway (leptin, LepR, POMC, PC-1, Mc4r, and SIM1; see Figure 3) (83, 89). Similarly, at least five of the six naturally occurring single-gene models of murine obesity (*ob*, *db*, *fat*, A^y, and *mg*) result from mutations in this same pathway, as do all three monogenic obese rat strains (83). Transgenic disruptions of central melanocortin signaling

also yield obesity phenotypes, either through gain-of-function mutations in AgRP or loss-of-function mutations in POMC, Mc4r, or Mc3r (12). It is clear from these observations that tonic central melanocortin signaling limits food intake and body weight. The similarity of phenotypes in rodents and humans with homologous mutations involved in leptin-melanocortin signaling demonstrates the strong conservation of this pathway across species. These observations powerfully attest to the primacy of leptin-melanocortin signaling in human body-weight regulation and identify Mc4r as a superb target for pharmacological agonists to treat obesity. In addition to being logical choices for common obesity, such agents might even override haploinsufficiency in melanocortin signaling to combat this relatively common form of monogenic obesity. Indeed, a modest reduction of body weight and adiposity was recently reported in normal-weight humans receiving a melanocortin agonist intranasally for six weeks (90).

Obesity-Related Mendelian Disorders and Candidate Genes for Polygenic Obesity

Numerous pleiotropic syndromes with Mendelian inheritance include obesity in their phenotypes. Chromosomal locations for most of these have been mapped (25 to date) (83), but causative genes are generally not yet identified. Some notable examples of such syndromes include Prader-Willi, Bardet-Biedl, and Beradinelli-Seip congenital lipodystrophy.

As of October 2001, 58 putative susceptibility genes for common human polygenic obesity had been identified, based on their known roles in energy homeostasis in animals combined with sequence variations associated with obesity phenotypes in humans (83). In addition, 59 chromosomal regions were identified as likely to encode obesity-susceptibility genes, based on genome-wide scans and other linkage studies searching for polymorphic markers that cosegregate with obesity phenotypes in large collections of nuclear families (83, 89). Research is under way to pinpoint these genes. Particularly consistent findings among different studies are reported for the short arm of chromosome 2 at band 21, within which the POMC gene is located. Finally, 165 quantitative trait loci pertaining to obesity have been reported from animal cross-breeding experiments (83). Modern quantitative genetics will undoubtedly facilitate continued refinement of the complex map of human polygenic obesity (91).

IS ADIPOCYTE DEPLETION AN OPTION FOR OBESITY TREATMENT?

The lipostatic model of energy homeostasis predicts that peripheral anti-obesity approaches designed to increase thermogenesis or impair adipose tissue development will be compromised by adaptive hyperphagia, resulting from decreased negative feedback by adiposity signals (Figure 1). This prediction is supported by the observation that adipose mass that is surgically removed by lipectomy is

ultimately restored, albeit in new locations. Adaptive CNS responses to weight loss may help explain the pharmaceutical industry's failure thus far (despite years of effort) to develop β3-adrenergic receptor (β3-AR) agonists that stimulate thermogenesis enough to cause substantial weight loss. However, transgenic mice with extreme overexpression of uncoupling protein–3, a thermogenic target of the β3-AR (92), are lean despite compensatory hyperphagia (93). These findings suggest that extraordinary increases of energy expenditure may be required to override CNS responses to fat loss.

It is reasonable to anticipate that ongoing fundamental discoveries in adipocyte biology will eventually lead to drugs that can arrest fat cell development, eliminating adipose tissue entirely. Attempts to ablate adipose tissue should be approached with considerable caution, however, based on sobering lessons learned from rodents and humans with genetic deficiencies in adipocyte development. Recently engineered models of lipoatrophic, or "fatless," mice demonstrate that having too little adipose tissue, like having too much, causes untoward metabolic consequences. Separate research groups generated adipose-tissue–deficient transgenic mice by expressing either a dominant negative (94) or dominant positive (95) transcription factor selectively in adipocytes, thus impairing adipogenesis. The former approach eliminated white adipose tissue completely, the latter approach did so partially, and brown adipose tissue was thermogenically inactive in both cases. Leptin levels were reduced by 90%–95%, and consequently mice were markedly hyperphagic. Even though the mutants were lean, they developed somatomegaly, generalized organomegaly, and hepatic steatosis (fatty liver). Remarkably, both strains showed severe, insulin-resistant diabetes, with high circulating levels of glucose, insulin, and triglycerides. They had reduced fecundity and died prematurely. The mechanism of insulin resistance was explored in one model and found to involve impaired insulin activation of insulin-receptor-substrate–associated PI-3 kinase in muscle and liver, presumably because of excessive triglyceride accumulation that was detected in those tissues (96). Hepatic steatosis, along with the entire phenotype, was dose-dependently reversed by surgical implantation of adipose tissue from donor mice, proving that the absence of fat caused the diabetes (97).

One might speculate that diabetes in fatless mice arises because leptin-deficient hyperphagia causes nutrient overload, and in the absence of adipose tissue, triglycerides are shunted into muscle and liver, impairing insulin action. However, nutrient excess is not required for the diabetes, which persists even with severe caloric restriction (98, 99). Thus, investigators hypothesized that the absence of one or more adipose-derived factors caused insulin resistance by altering the partitioning of fat so as to favor deposition in muscle and liver. A likely candidate for such a factor was leptin, which can mobilize triglycerides from nonadipose tissues (98), apparently by activating AMP kinase (100). Moreover, both leptin and melanocortin signaling in the hypothalamus improve insulin sensitivity in peripheral tissues (101). The finding that physiological leptin replacement reversed the diabetic phenotype in the model of partial adipose ablation suggests a key role for leptin deficiency

in its pathogenesis (98). In the strain with complete adipose ablation, long-term leptin administration improved, but did not cure, the diabetes, suggesting that the absence of adipose-derived factors besides leptin contributes to insulin resistance (102). This contention is supported by the observation that lipoatrophic mice and humans are more prone to diabetes than are leptin-deficient individuals in both species (102). In one study, insulin resistance in fatless mice was completely reversed by physiological replacement of both leptin and the adipocyte-derived, insulin-sensitizing hormone adiponectin, but was only partially ameliorated by either agent alone (103).

Together, these experiments suggest that both leptin and adiponectin are required to maintain normal insulin sensitivity, and therefore, excessive elimination of adipose tissue, the source of these hormones, is paradoxically diabetogenic. These principles probably apply to lipoatrophic humans, in whom insulin-resistant diabetes is a prominent feature. Consistent with mouse experiments, leptin replacement in lipoatrophic people partially reversed the diabetic phenotype (104). The important conclusion from this line of investigation is that diabetes can result from either a paucity or plethora of fat tissue. Thus, peripheral anti-obesity approaches that target adipogenesis alone may prove problematic. More therapeutic benefit may lie in preventing positive energy balance and excessive nutrient flux than in simply limiting the size of adipose depots.

IMPLICATIONS FOR THE FUTURE OF OBESITY TREATMENT

Because body weight is regulated primarily by the brain, centrally acting agents are likely to be necessary to combat obesity. The menu of CNS targets for new anti-obesity drugs is ever increasing, thanks to the ongoing elucidation of molecules involved in the communication between peripheral adiposity signals and central effector pathways that govern energy homeostasis.

Given that leptin resistance and insulin resistance typically accompany obesity, a logical goal is to develop methods to increase CNS sensitivity to these adiposity signals. Enhancing transport of leptin and/or insulin across the blood-brain barrier is one potential approach. An example of progress in this arena is the recent report of weight loss in rodents administered insulin mimetics that partition into the brain more effectively than does native insulin (30). Although therapy with leptin itself has been disappointing thus far (38), it may yet prove useful in selected individuals with relative leptin deficiency (105). An alternative approach is to enhance the intracellular signaling events triggered by activation of leptin and/or insulin receptors in the brain. An ideal drug would affect both leptin and insulin, and the possibility that CNS signaling by these two hormones converges at the level of PI-3 kinase offers a potential target for this strategy. Leptin also signals through the Jak-Stat system, and signaling via both intracellular pathways appears to be terminated by dephosphorylation of key signaling molecules by the protein-tyrosine

phosphatase PTP-1B (106, 107). Thus, blocking PTP-1B should increase sensitivity to both leptin and insulin, and the phenotype of PTP-1B–deficient mice is consistent with this expectation (108, 109).

A formidable challenge to approaches targeting either PI-3 kinase or PTP-1B is to achieve tissue selectivity, since these are pleiotropic signal-transduction molecules. One potential solution is to manipulate second-order (or higher) neuronal targets of leptin and insulin, which may function more specifically in energy homeostasis and may also lie downstream of obesity-related leptin resistance. Theoretically, any agonist of a catabolic neuropeptide or antagonist of an anabolic neuropeptide could be considered in obesity therapy. Based on genetic and other evidence, Mc4r agonists and MCH antagonists are particularly promising exemplars of this type of strategy. The hypothesis that a ghrelin antagonist might facilitate weight loss is another area of active, recent research. The chances of success in this endeavor are diminished by the observation that baseline circulating ghrelin levels in common obesity are low, but the high levels found in people with Prader-Willi syndrome identify these individuals as potentially ideal candidates for anti-ghrelin therapy (82). Moreover, weight reduction increases ghrelin levels in obese individuals (77), a response that may predispose to the recovery of lost weight. Pharmacological blockade of this rise in ghrelin might thus improve the success of weight loss achieved by conventional methods.

The control of body weight is an extremely complex, polygenic process, and weight loss is robustly resisted by redundant systems that have evolved during millions of years of periodic famine. Thus, it is extremely unlikely that any one approach will prove to be a magic bullet for all obesity. Nevertheless, there is cause for considerable optimism that multiple classes of new anti-obesity medications may soon be developed. It is possible that customized cocktails of these agents will enable obesity to be managed much as we now manage other polygenic disorders such as hypertension.

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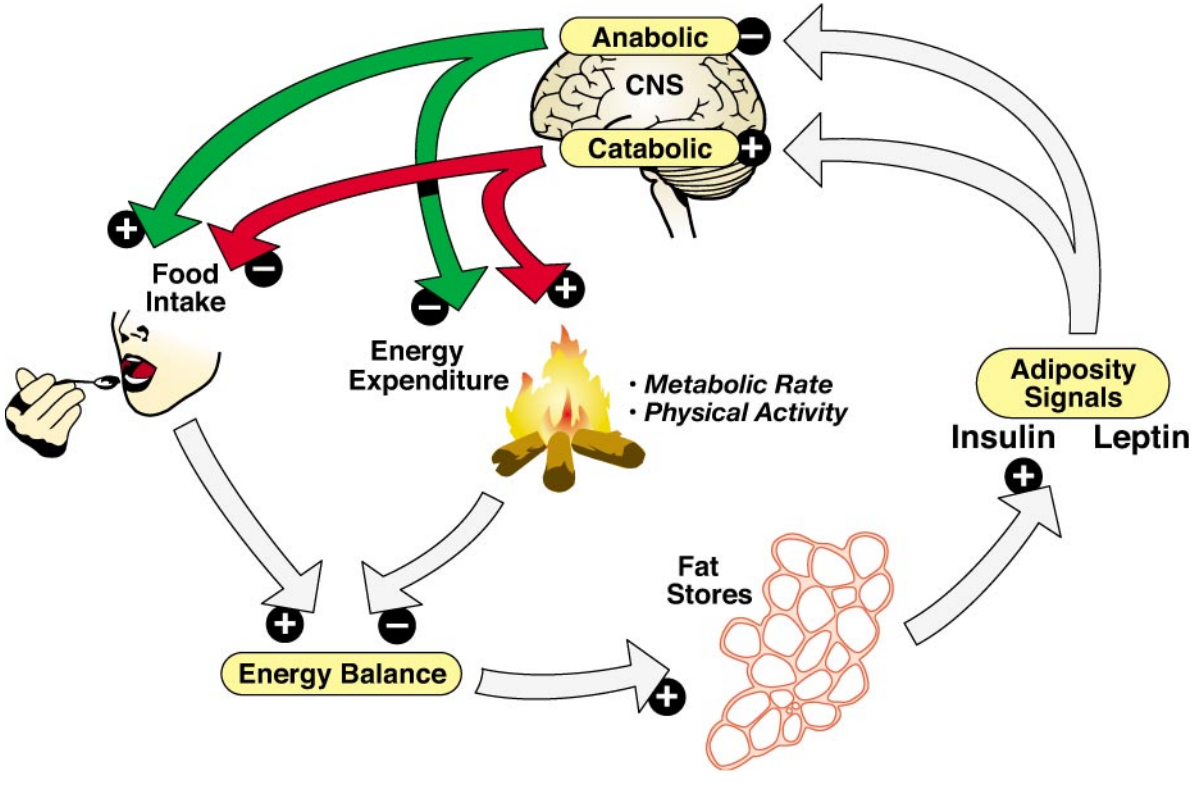

Figure 1 Model to explain compensatory adjustments of energy intake and expenditure in response to changes in body-fat content. Leptin and insulin are adiposity signals that are secreted in proportion to body-fat content and act in the hypothalamus to stimulate catabolic effector pathways while inhibiting anabolic pathways. These pathways exert opposing effects on energy balance (the difference between calories consumed and expended), which in turn determines the amount of body fat. (Reprinted with permission from Reference 27.)

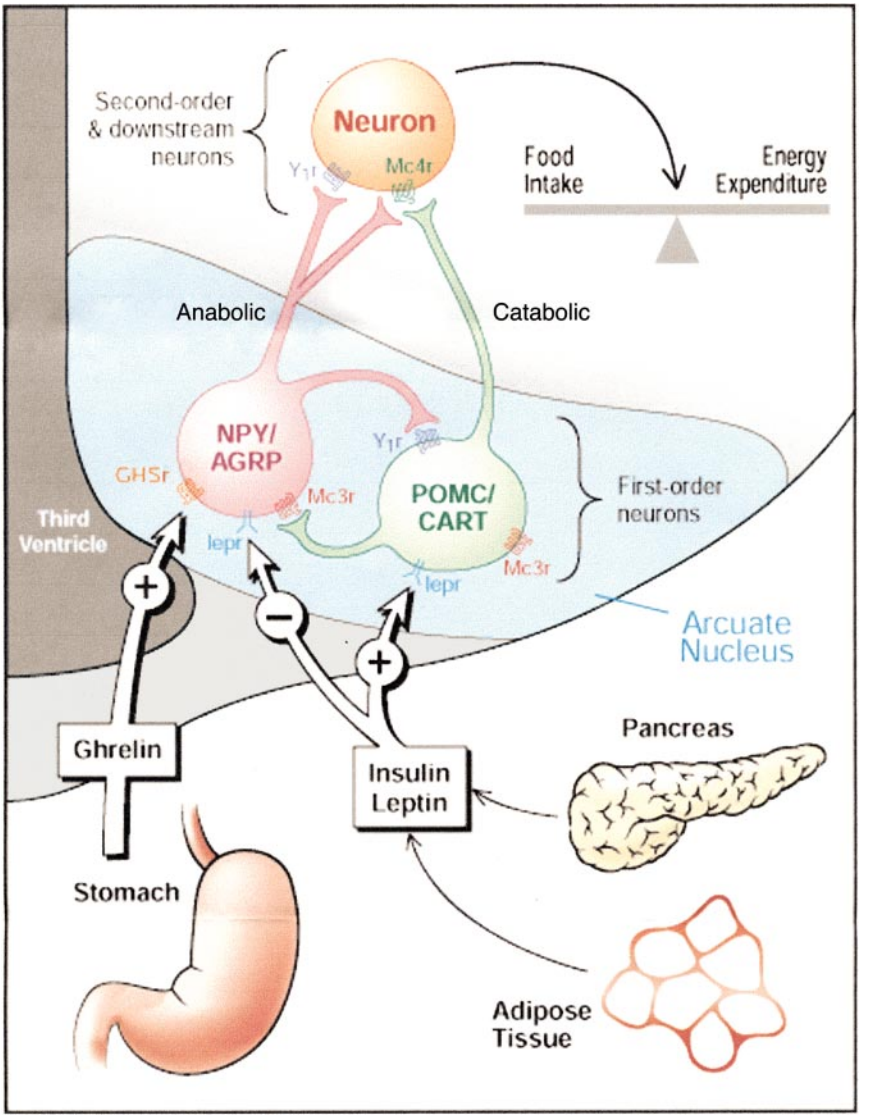

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Figure 2 (See figure on previous page) Control of energy homeostasis by neurons in the hypothalamic arcuate nucleus (ARC). The ARC houses two sets of neurons—NPY/AgRP and POMC/CART neurons—which are regulated by circulating hormones. As described in the text, NPY (neuropeptide Y) and AgRP (Agouti-related protein) stimulate food intake and decrease energy expenditure. In contrast, α-melanocyte–stimulating hormone (a cleavage product of proopiomelanocortin) and CART (cocaine- and amphetamine-regulated transcript) inhibit food intake and increase energy expenditure. Leptin and insulin circulate in proportion to body adipose stores; they inhibit NPY/AgRP neurons and stimulate adjacent POMC/CART neurons. Reduced leptin and insulin levels are therefore predicted to activate NPY/AgRP neurons while inhibiting POMC/CART neurons. Ghrelin is a circulating peptide secreted primarily from the stomach that can activate NPY/AgRP neurons, thereby stimulating food intake; this provides a potential molecular mechanism for integrating long-term energy balance signals with short-term meal pattern signals. (Reprinted with permission from Reference 39a.)

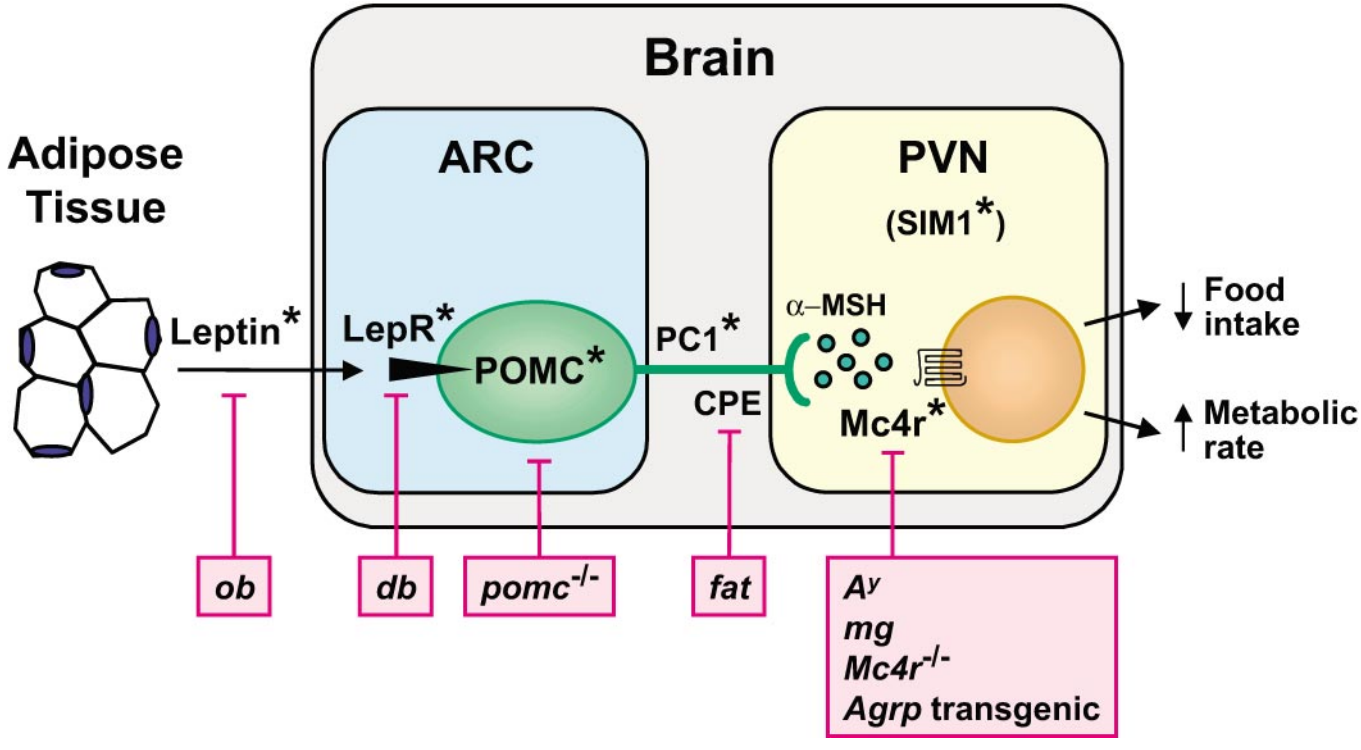

Figure 3 Mutations in the leptin-melanocortin signaling pathway that cause monogenic obesity (as described in the text). Asterisks indicate genes that are mutated in the six known human monogenic obesity syndromes. Spontaneous and transgenic forms of murine monogenic obesity are shown in pink boxes. ARC, hypothalamic arcuate nucleus; POMC, proopiomelanocortin; PC1, prohormone convertase 1; CPE, carboxypeptidase E; PVN, paraventricular nucleus; Mc4r, melanocortin-4 receptors.

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