Regulation of Food Intake, Energy Balance, and Body Fat Mass: Implications for the Pathogenesis and Treatment of Obesity

Stephan J. Guyenet and Michael W. Schwartz

Diabetes and Obesity Center of Excellence and Division of Metabolism, Endocrinology, and Nutrition, Department of Medicine, University of Washington School of Medicine, Seattle, Washington 98195

Context: Obesity has emerged as one of the leading medical challenges of the 21st century. The resistance of this disorder to effective, long-term treatment can be traced to the fact that body fat stores are subject to homeostatic regulation in obese individuals, just as in lean individuals. Because the growing obesity epidemic is linked to a substantial increase in daily energy intake, a key priority is to delineate how mechanisms governing food intake and body fat content are altered in an obesogenic environment.

Evidence Acquisition: We considered all relevant published research and cited references that represented the highest quality evidence available. Where space permitted, primary references were cited.

Evidence Synthesis: The increase of energy intake that has fueled the U.S. obesity epidemic is linked to greater availability of highly rewarding/palatable and energy-dense food. Obesity occurs in genetically susceptible individuals and involves the biological defense of an elevated body fat mass, which may result in part from interactions between brain reward and homeostatic circuits. Inflammatory signaling, accumulation of lipid metabolites, or other mechanisms that impair hypothalamic neurons may also contribute to the development of obesity and offer a plausible mechanism to explain the biological defense of elevated body fat mass.

Conclusions: Despite steady research progress, mechanisms underlying the resistance to fat loss once obesity is established remain incompletely understood. Breakthroughs in this area may be required for the development of effective new obesity prevention and treatment strategies. (J Clin Endocrinol Metab 97: 745–755, 2012)

Over the course of industrialization, affluent populations have experienced an “epidemiological transition” characterized by an increased prevalence of certain disorders that are uncommon both in nonindustrial populations and in wild animals (1). Among these, obesity is perhaps the most conspicuous. Affecting approximately one third of adults in the United States (with an additional one third falling into the overweight category) (2), obesity has become a leading cause of morbidity, mortality, and reduced quality of life (3), a problem aggravated by the limited efficacy of nonsurgical treatments. Although the obesity epidemic can be traced to an increase in per capita energy intake over the past 40 yr (Fig. 1) (4, 5), which in turn is linked to changes in our collective diet, little is known about the physiological mechanisms underlying this trend. Particularly vexing is the question of why this disorder, once established, is so refractory to treatment. Here, we review the mechanisms controlling food intake in the context of energy homeostasis (the biological process that matches energy intake to energy expenditure over long time intervals), with a focus on obesity pathogenesis and the dramatic recent increase in obesity prevalence.

Abbreviations: AgRP, Agouti-related peptide; ARC, arcuate nucleus; BMI, body mass index; CCK, cholecystokinin; DIO, diet-induced obesity; GLP-1, glucagon-like peptide-1; GWAS, genome-wide association studies; HFD, high-fat diet; LHA, lateral hypothalamic area; NPY, neuropeptide Y; NTS, nucleus of the solitary tract; POMC, proopiomelanocortin; PYY, peptide YY; RYGB, Roux-en-Y gastric bypass.
Short-Term, Meal-Related Determinants of Food Intake

Because humans, like most mammals, consume food in discrete bouts (or meals), total daily energy intake is a function of the size, frequency, and composition of meals. The perception of hunger and the decision to initiate a meal involve complex and poorly understood interactions between genetic, social, learned, environmental, circadian, and humoral cues (6, 7). As such, this process is quite variable and, although several endogenous peptides have been identified with the ability to stimulate feeding (6, 7), a unifying, physiological explanation for the experience of hunger and the decision to commence eating is still awaited.

A popular notion in the lay literature merits comment. Nearly 60 yr ago, Jean Mayer and his contemporaries hypothesized that because hypoglycemia potently stimulates appetite, hunger is normally triggered by sensing of declining plasma glucose levels or rates of glucose utilization by hypothalamic “feeding centers” (8). Decades of subsequent research have demonstrated that to the contrary, meal onset is not causally related to preprandial blood glucose (or insulin) levels within the normal physiological range (9). Yet the notion that low glucose (or elevated insulin) levels drive feeding behavior and promote fat gain remains widely popular, due largely to the marketing of commercial diet plans based on the glycemic index or reduced carbohydrate content. Among various scientific rationales that have been advanced for such diets is that excessive insulin secretion induced by rapidly digested carbohydrate foods causes a subsequent, transient fall of plasma glucose levels; this, in turn, triggers excess feeding and ultimately causes obesity. Another idea proposes that increased fasting and/or postprandial insulin levels induced by carbohydrate foods acts directly on adipocytes to increase fat storage, promoting fat gain over time. Although clinical trials have established that reduced carbohydrate diets can safely induce modest long-term weight loss (10), the mechanisms typically advanced to explain this benefit have little in the way of experimental support and are not informative with respect to the control of food intake. Moreover, reduced carbohydrate diets do not necessarily outperform diets with a higher carbohydrate content (e.g., the “Mediterranean” diet) when outcomes are measured after 1 yr or more (10).

Once feeding commences, the amount consumed is determined by factors involved in satiety perception (Fig. 2). The term “satiation” refers to the perception of fullness that leads to meal termination, whereas “satiety” describes the reduced interest in food after a meal. These responses ensure that feeding is terminated before gastric capacity is reached and that an appropriate interval passes to allow the disposition of ingested nutrients before the next meal begins (11). Unlike hunger perception, these processes are relatively well understood, involving combined effects of gastric distention and the release of peptide signals from enteroendocrine cells lining the gastrointestinal tract (12).
Gastric distension is sensed by mechanoreceptor neurons in the stomach and relayed to the hindbrain via vagal afferent and spinal sensory nerves (13). The majority of satiation-inducing gut peptides also mediate their effects via vagal afferent fibers, although some enter the brain from the circulation and exert their effects directly (12). Examples of satiation/satiety peptides released from intestinal enteroendocrine cells include cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), oxyntomodulin, peptide YY (PYY3–36), apolipoprotein A-IV, and enterostatin (12). Additional satiety-inducing peptides released from the endocrine pancreas include pancreatic polypeptide, glucagon, and amylin (14–18). CCK is a prototypic satiation peptide that is secreted by the duodenal and jejunal mucosa primarily in response to fat and protein ingestion, and it decreases food intake rapidly but transiently via the activation of vagal afferents (12, 19, 20). Meal size is increased by interventions that disrupt CCK signaling, establishing a physiological role for this peptide in satiation (21). GLP-1 and amylin are the only other satiation peptides shown to meet this criterion thus far (18, 22).

Ghrelin is an acylated peptide secreted from the gastric mucosa that, unlike satiety peptides, stimulates feeding and is implicated in meal initiation (6). Consistent with this concept, circulating ghrelin peaks just before meal onset and declines rapidly during and immediately after the meal (6, 12). However, because mice lacking a ghrelin signal do not exhibit altered meal patterns (23), the contribution of ghrelin to meal initiation relative to other factors remains uncertain.

Afferent signals involved in satiety are processed initially in the hindbrain. The nucleus of the solitary tract (NTS) plays a particularly important role in the processing of satiety-related input from vagal sensory fibers, and the adjacent area postrema, being located outside the blood-brain barrier, can sense input from circulating peptides directly (12). Evidence that hindbrain circuitry is itself sufficient to regulate meal size stems from experiments in “decerebrate” rats, in which the hindbrain and forebrain are surgically disconnected (24, 25). Although these animals are incapable of spontaneously initiating meals and rely on liquid food delivered directly into the mouth, they nonetheless terminate meals normally in response to gastric distention or satiation peptides such as CCK (24, 25). Because decerebrate rats fail to adjust meal size to compensate for changes in energy balance (26), however, communication between forebrain and hindbrain circuits appears necessary for adaptive changes of meal size to occur in response to changing energy needs. The neurocircuitry involved in this integration includes hypothalamic neurons that sense humoral input involved in energy homeostasis (e.g., leptin) and project to the hindbrain, where they modulate the sensitivity of NTS neurons to satiety signals in a manner that compensates for changes of body fat mass (27).

**Long-Term Regulation of Food Intake and Energy Balance**

The hormone leptin is secreted by adipocytes in proportion to body fat mass and plays a key role in energy homeostasis by informing the brain of changes in both energy balance and the amount of fuel stored as fat (Fig. 2) (28–30). Leptin acts in the brain as a negative feedback regulator of adiposity, constraining fat mass by limiting energy intake and supporting energy expenditure (28). Decreased leptin signaling promotes increased food intake, positive energy balance, and fat accumulation (28–30). Although plasma leptin levels reliably reflect body fat mass under weight-stable conditions, they can also change in response to short-term alterations of energy balance, well before significant changes of fat mass have occurred (31).

Leptin’s effects on energy balance are mediated via leptin receptors in hypothalamic areas such as the arcuate nucleus (ARC), paraventricular nucleus, ventromedial hypothalamic nucleus, and lateral hypothalamic area (LHA) (28). Many extrahypothalamic regions are also leptin-sensitive, including the NTS and midbrain regions central to reward and motivation (32). The ARC is a major site for sensing and integrating peripheral energy balance signals, including hormones (leptin, insulin, and ghrelin) and nutrients (fatty acids, amino acids, and glucose) (28). These effects are mediated by at least two distinct leptin-sensitive neuron subpopulations in the ARC. Neurons that express proopiомelanocortin (POMC) synthesize and release melanocortin peptides such as α-MSH that are potently anorexigenic (inhibit food intake) and are stimulated by leptin and insulin (28). Melanocortin signaling appears to play a key physiological role to defend against excess fat gain, particularly during exposure to energy-dense, highly palatable foods (33, 34).

Located adjacent to POMC cells are orexigenic neurons that express neuropeptide Y (NPY) and agouti-related peptide (AgRP; an endogenous antagonist of the melanocortin-4 receptor). These cells are regulated in a manner reciprocal to POMC cells (28), and they play a key role to enable/stimulate feeding behavior (35). NPY/AgRP neurons are also GABAergic, and γ-aminobutyric acid is implicated as an important regulator of feeding released by these neurons (36, 37). NPY/AgRP neurons synapse onto and inhibit POMC neurons, and both cell types regulate energy balance via projections to brain regions that influ-
ence motivation/reward, energy expenditure, hunger, and ingestive behaviors (28).

The adaptive response to fat loss induced by calorie-restricted diets illustrates how coordinate regulation of ARC neurons participates in energy homeostasis. Negative energy balance and loss of body fat lower plasma levels of adiposity negative feedback signals (e.g. leptin and insulin) while also raising ghrelin levels. In response, NPY/AgRP neurons are activated, whereas POMC cells are inhibited, a combination that potently promotes hyperphagia (increased food intake), positive energy balance, and the recovery of lost fat (28). These responses to fat loss appear to be operative in obese as well as lean individuals (Fig. 3).

**Food Reward and Palatability**

In the United States, fast food has increased from 2 to 18% of total food spending over the last 50 yr, whereas soft drink consumption has increased 3.5-fold (38). These trends can be traced to increased food availability, systematic efforts to increase the reward value of food, and aggressive marketing that in combination have undoubtedly helped drive the obesity epidemic over the past four decades (4, 5).

Reward can be defined as the process whereby certain behaviors are reinforced in response to specific environmental stimuli. Animals and humans rapidly learn to associate olfactory, gustatory, and environmental cues with food properties that, in turn, reinforce behaviors related to the acquisition and consumption of rewarding food (39). Relevant food properties include caloric density and texture as well as the content of fat, starch, simple sugars, salt and free glutamate; under certain conditions, these factors can influence food intake and body fatness (39–47). In addition, a variety of other cues can be associated with these factors and become rewarding over time, resulting in acquired preferences (40, 41, 47). Palatability is defined as the pleasure or hedonic value associated with food, and it has been consistently shown to influence meal size in humans (48).

The “cafeteria diet” model of rodent obesity illustrates the importance of food reward and palatability in appetite regulation and obesity pathogenesis (49). In this model, rodents are provided with an assortment of human commercial “junk foods” in addition to standard unpurified chow. The animals overconsume palatable foods at the expense of less palatable yet more nutritious chow, and susceptible rat strains develop obesity rapidly (50). The impressive behavioral impact of food reward is illustrated by the observation that rats will voluntarily endure foot shocks or extreme cold to obtain a cafeteria diet, even when standard chow is freely available in unlimited amounts (51, 52).

Central nervous system (CNS) circuits involved in food reward are integrated with those governing energy homeostasis to allow food-seeking behaviors to be adjusted according to energy needs. Although the mechanisms underlying this integration are not fully understood, hormones including leptin, ghrelin, PYY, CCK, and insulin are implicated (32). The LHA is an important example of an area that participates in both reward processing (53, 54) and energy homeostasis (55), and hence may integrate inputs pertinent to food reward with those involved in body fat mass regulation.

Numerous brain regions coordinately evaluate and reinforce the rewarding value of food (56–58), including corticolimbic, hypothalamic, and midbrain circuits involved in reward processing (e.g. dopaminergic neurons of the ventral tegmental area and substantia nigra) the insula, amygdala, striatum, nucleus accumbens, orbitofrontal cortex, and the LHA (58). Signaling by dopamine and opioid peptides is particularly important in the reward and hedonic valuation of food, respectively (32, 58). Specifi-
cally, dopamine signaling is thought to contribute to the “wanting” of food (e.g. motivational aspects), whereas opioids are implicated in the “liking” of food (e.g. hedonic value or palatability) (59). Consistent with this view, opioid receptor agonists strongly increase the intake of palatable food over standard chow in rodents, whereas opioid antagonists decrease both the intake and the hedonic value of palatable food (60, 61). Although the µ-opioid receptor antagonist naltrexone was recently shown in clinical trials to lower body weight in obese subjects when combined with the norepinephrine–dopamine reuptake inhibitor bupropion (62), efforts to obtain Food and Drug Administration (FDA) approval for this combination have thus far proven unsuccessful. The mechanism of action may involve enhanced melanocortin signaling, consistent with a role for opioid and dopamine signaling to influence energy homeostasis circuits (62).

The endocannabinoid system includes the ligands anandamide and 2-arachidonylglycerol that can act on either of two cannabinoid receptor subtypes (CB1 and CB2). This system earned its name after confirmation that marijuana exerts its psychoactive effects primarily through CB1 receptor activation (63). Endocannabinoids are small lipophilic molecules ubiquitously present in brain reward areas (64) and, whereas CB1 agonism selectively increases the consumption of palatable food (65) and is used to enhance appetite in the setting of cancer and other chronic disease states, antagonists of these receptors cause weight loss in overweight humans and selectively suppress the consumption of highly palatable foods in rodents (66, 67). The mechanism of fat loss is complex but includes reduced food intake and enhanced leptin sensitivity and is primarily mediated by CB1 receptors in the CNS (68–70). Despite unquestioned weight loss efficacy, the FDA has yet to approve CB1 antagonists for human obesity treatment, citing psychiatric side effects including an increased risk of suicide (66).

These findings collectively suggest that obesity can arise when animals or humans are confronted with foods whose palatability/reward value greatly exceeds that to which they are genetically adapted, and hence that interventions that inhibit food reward can prevent fat gain and promote fat loss. In considering these hypotheses, it is important to bear in mind that obesity in both humans and animal models involves the biological defense of an elevated level of body fat mass (Fig. 3). A key issue, therefore, is to understand how a change in the reward value of a diet impacts the energy homeostasis system.

**Obesity and Energy Homeostasis**

Because survival in a natural environment can be threatened by either too little or too much body fat, the energy homeostasis system is presumed to have evolved to maintain the level of adiposity appropriate for each species’ ecological niche. There is general agreement that this system responds robustly to reduced fat mass by increasing both hunger and energy efficiency via a mechanism involving a low leptin signal, and that these responses are quite effective in returning fat mass to its original, preintervention level (Fig. 3A) (71, 72).

A more controversial question is the extent to which this homeostatic system defends against excess fat gain, a notion seemingly at odds with the steady increase of obesity prevalence in affluent nations (57, 73, 74). Yet numerous studies suggest that both overweight and lean individuals mount responses that resist excess fat gain and are able to lose most or all of the excess fat acquired during periods of experimental overfeeding via a mechanism involving post-overfeeding hypophagia (Fig. 3A) (75–79). This inherent resistance to fat gain in humans closely parallels what is observed in rodents that are either overfed by intragastric feeding or are exposed to refined highly palatable food and subsequently returned to an ad libitum, low-palatability chow [although the degree of fat loss can vary (80–82)]. Combined with evidence that these adaptive responses require intact leptin signaling (83), a physiological role for leptin to protect against pathological fat gain is implied.

Obesity can therefore be viewed as a state in which the defended level of body fat is increased, analogous to increased blood pressure in essential hypertension (Fig. 3B). Yet obesity development is also clearly linked to reward/hedonic drives (57, 58), raising the possibility that reward/hedonic circuits can impact homeostatic systems in a manner that favors the defense of an elevated body fat mass (Fig. 2). This concept is strengthened by the extensive and reciprocal neuroanatomical connections involved in the regulation of food intake and energy homeostasis that are shared by these two systems (84, 85).

Furthermore, interventions that alter CNS dopamine signaling can potently affect food intake and body fat mass, although both the direction and magnitude of these effects depend on the brain areas and dopamine receptor subtypes involved (86–91). As one example, variation at the dopamine D2 receptor gene locus can influence responses to palatable foods in ways that predict subsequent fat gain (91, 92), and D2 receptor availability in the striatum is reduced in obesity. These observations led to the notion that obesity arises from a “reward deficit,” in which affected individuals overeat to compensate for a diminished perception of food reward (58, 93). However, this hypothesis is inconsistent with reports of increased food reward sensitivity in obese individuals (94), and it predicts that low-reward food should cause compensatory
stantial fat loss, postprandial levels of PYY3–36 and GLP-1 produced levels of body fat mass. After RYGB but before submucosal exposure of the ileum may favor the defense of a reduced level for fat loss after RYGB (102). Thus, contact with luminal nutrients may diminish food reward (56), so removing it from neural signals arising from gastric distention also increase due to a surgically induced reduction of stomach volume, and this may enhance the inhibitory effect of gut peptides on appetite and food intake. In addition, the duodenum, bypassed in RYGB, participates in nutrient sensing involved in reward processing (56), so removing it from contact with luminal nutrients may diminish food reward valuation. Indeed, several studies have reported alterations in reward functions after RYGB, consistent with a role for altered reward processes in the fat loss observed (101). Although the extent to which food reward is influenced by gastrointestinal or pancreatic peptides remains unclear, studies using pharmacological doses of CCK are consistent with such a possibility (104). These findings support the hypothesis that after RYGB, alterations in reward processing, in conjunction with a more anorexigenic gut peptide profile and increased gastric distension, collectively support the defense of a reduced fat mass.

Genetic Factors

Although rare, single-gene mutations can cause obesity, and much of what is known about energy homeostasis was discovered through the study of these monogenic obesity syndromes. To date, all known nondysmorphic monogenic obesity syndromes in humans arise from loss-of-function mutations in genes involved in the leptin signaling pathway (105).

Although heritable factors (reflecting a combination of genetics and epigenetics) are estimated to explain 45 to 75% of body mass index (BMI) variability in human populations (106), monogenic disorders account for only a small fraction (<5%) of human obesity. Thus, obesity susceptibility may be a polygenic trait. Consistent with this notion, genome-wide association studies (GWAS) have identified more than 40 common polymorphisms that associate with BMI variability in humans (107, 108). Their estimated collective contribution to BMI variability, however, remains quite small (<2%) (109), presumably because GWAS methodology does not detect gene-gene or gene-environment interactions. Nevertheless, GWAS, like monogenic obesity syndromes, implicate altered hypothalamic function in the pathogenesis of common obesity (107, 110).

In addition to genetic variability, developmental and epigenetic factors are implicated in obesity risk. In animal models, both in utero undernutrition and maternal overnutrition increase subsequent obesity risk in offspring, and children born to obese mothers are at an elevated risk of obesity relative to those born to lean mothers (111). Prepregnancy fat loss due to bariatric surgery attenuates subsequent obesity risk in offspring (112), suggesting that independent of genetic predisposition, developmental factors contribute meaningfully to the transgenerational transmission of obesity risk.

Growing evidence suggests that interacting genetic (113) and possibly developmental factors play an important role to determine obesity susceptibility when human populations are confronted with an obesogenic environment (Fig. 2). Relevant environmental factors include not only the types of foods available, but factors that affect food choice, such as education level, income, and related socioeconomic variables (114). From this perspective,
dramatic, recent increases of obesity prevalence in Western societies can be viewed as resulting in large part from ever-increasing exposure of a genetically susceptible population to highly palatable, energy-dense foods.

**Leptin Resistance: Cause or Effect of Obesity?**

Obesity is characterized by increases of both fat mass and circulating leptin levels (72, 115, 116), suggesting a state of leptin resistance in which elevated leptin levels are required to overcome a defect in the leptin signaling cascade. Unlike in states of insulin resistance, in which a healthy pancreas can simply secrete more insulin as needed, increased body fat mass is required to maintain hyperleptinemia. Leptin resistance, therefore, offers a plausible mechanism to explain the defense of an elevated homeostatic “set point” for body fat mass. In support of this hypothesis, fat loss induced by caloric restriction elicits compensatory responses in obese individuals that promote the recovery of lost fat (including increased hunger and metabolic efficiency) (72, 115, 116), which can be suppressed by restoring plasma leptin concentrations to pre-fat loss levels (72).

The hypothesis that leptin resistance contributes to obesity pathogenesis is supported by evidence that rodents fed a purified, high-fat diet (HFD) acquire a striking loss of leptin sensitivity in ARC neurons (117, 118). Because targeted deletion of leptin receptors from any of several hypothalamic neuronal subpopulations is sufficient to cause obesity in mice (119, 120), the acquisition of hypothalamic leptin resistance is a plausible explanation for the defense of elevated body fatness in animal models of diet-induced obesity (DIO). Genetic interventions that prevent hypothalamic leptin resistance also protect against DIO (121–125), suggesting that the latter is required for the former to occur. Moreover, leptin resistance is detectable in ARC neurons even after relatively short periods of HFD feeding, before substantial fat gain (118). At the cellular level, inflammatory signaling has emerged as a potentially important mediator of leptin resistance (Fig. 2) (126). An induction of proinflammatory cytokines and other markers of inflammation is clearly evident in the hypothalamus of rodents with DIO (122, 126) and, just as inflammation in peripheral tissues contributes to obesity-induced insulin resistance, cellular inflammatory signaling also potently inhibits leptin signal transduction in neurons (122, 125).

Among several cellular mechanisms implicated in obesity-associated hypothalamic inflammation are activation of JNK (126) and IKK-NF-κB (122) signal transduction pathways, possibly as a consequence of endoplasmic reticulum stress, an upstream activator of these signaling pathways. Suppressor of cytokine signaling 3 and protein tyrosine phosphatase 1B are molecules downstream of NF-κB activation that inhibit leptin (and insulin) signaling and are induced in the hypothalamus of animals with DIO (127, 128). A deficiency of either of these genes confers resistance to DIO in mice (121, 123, 124), supporting a link between inflammatory signaling, CNS leptin and insulin resistance, and the development of obesity in this model. Another potential mediator of neuronal resistance to leptin (and insulin) is protein kinase C-θ, a serine-threonine kinase that is induced in the hypothalamus by intracellular accumulation of fatty acid metabolites (129, 130), analogous to its role as a mediator of free fatty acid-induced insulin resistance in skeletal muscle (131).

Very recent work reveals evidence of neuron injury occurring rapidly in the ARC of rats and mice placed on a HFD, accompanied by microglial and astroglial responses that may (at least initially) be neuroprotective in nature (132). The onset of hypothalamic injury during HFD feeding in rats and mice occurred before obesity onset, and an increased gliosis signal was detected in the hypothalamus of obese humans using magnetic resonance imaging, suggesting that a similar process may operate in humans. Although the implications of this work await further study, acquired injury of neurons in a brain area central to energy homeostasis offers a plausible mechanism for both hypothalamic inflammation and the defense of an elevated level of body fat in obese individuals (Fig. 2) (132).

Although these and related observations offer important insight into the pathogenesis of DIO, many pieces of the puzzle are still missing. Among these are cohesive explanations for the mechanisms underlying hypothalamic inflammatory signaling and injury during HFD feeding and translational studies that address the hypothesis mechanistically in humans.

**Conclusion**

Although substantial progress has begun to identify neurohumoral mechanisms underlying obesity, nonsurgical obesity treatment has improved little over the years. If obesity involves the biological defense of an elevated level of body fat, as current evidence suggests, advice to simply “eat less, move more” cannot be expected to remedy the problem. This is because interventions that reduce body fat stores without a corresponding decrease in the defended level of fat mass elicit compensatory responses that promote the recovery of lost fat and are difficult to consciously override. Because these responses constitute perhaps the single largest obstacle to effective obesity treat-
ment, breakthroughs in understanding the biological defense of elevated body fat mass may be required to enable the development of effective new obesity prevention and treatment strategies.

Acknowledgments

Address all correspondence and requests for reprints to: Michael W. Schwartz, M.D., Diabetes and Obesity Center of Excellence, University of Washington at South Lake Union, 815 Mercer Street, N334, Box 358055, Seattle, Washington 98109. E-mail: mscwartz@u.washington.edu.

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