ABSTRACT

The prevalence of overweight and obesity has reached epidemic proportions, affecting 64.5% of adults in the US population. Weight gain is often simply attributed to more calories taken in than energy expended. While ultimately true, the variables involved in this equation of energy balance are complicated and constitute an exquisitely balanced system that maintains body weight. Weight gain is a response to a perceived change in the energy balance equation, and the fat cell (adipocyte) is a multienocrine organ affecting this response. The "thrifty gene" hypothesis may help to explain the evolution of this system, why it exists, and how it leads to obesity in modern culture. Although many factors play a role in body weight regulation, leptin is one variable that has given us insight into the mechanism of weight maintenance: too little leptin or decreased sensitivity to leptin may account for difficulty in losing weight or regain of lost weight. Small amounts of weight gain may induce significant clinical pathology. Adipocytes are multienocrine organs, releasing many hormones implicated in the myriad diseases associated with obesity. Visceral adipocytes appear to be particularly active in this regard. Research is beginning to suggest that overweight and obesity are not the result of low willpower but an imbalance in the neuroendocrine regulation of weight.

equation of energy balance are complicated and constitute an exquisitely balanced system of weight maintenance. Weight gain is a neuroendocrine response to any change in the energy equation; the fat cell (adipocyte) is a multiendocrine organ affecting this response.

An elegant hypothesis to help explain this neuroendocrine response involves “the thrifty gene” that we may have inherited from our ancestors. According to this hypothesis, during the evolution of humans, exposure to intermittent periods of starvation, high-protein diet, and episodic need for high levels of physical activity led to genetic selection of metabolically efficient genes (ie, genes involved in cellular processes that efficiently store energy calories for use during periods of starvation). Under conditions of acute modernization, in which we are subjected to increased calories, increased dietary fat, and decreased physical activity, having thrifty genes that favor the storage of excess energy results in an epidemic of obesity, insulin resistance, and type 2 diabetes.

NEUROENDOCRINE REGULATION OF WEIGHT

Energy balance is regulated through the central nervous system via a series of short-term and long-term inputs and outputs (Figure 2). Short-term inputs include the sight and smell of food, taste, stretch receptors and chemoreceptors in the gastrointestinal tract, circulating nutrients, and gut hormones. All of these inputs feed into the brain. The long-term inputs, which also feed into the brain, include circulating nutrients, adipokines (eg, leptin, adiponectin, and tumor necrosis factor-alpha) secreted by the fat cell, and other hormones (eg, insulin, cortisol, growth hormone, and thyroxine). Short-term control of output (energy expenditure) is influenced by meal size, meal duration, the digestion and absorption of food, metabolic rate, storage of calories, and the thermogenic response to food. Long-term factors controlling output are hunger, the size of energy stores (eg, glycogen, triglycerides), other hormonal signals, and thermogenesis. Therefore, this can be considered a homeostatic system with both afferent and efferent pathways.

One of the most well-studied factors in energy balance input is the hormone leptin. Although it is only 1 part of a complex system, it appears to play an important role regulating body weight and provides insight into the mechanisms involved. Leptin is released from adipocytes in response to increased fat mass, high-calorie (ie, starchy, fatty) foods, and vagal

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**Figure 1. Prevalence of Overweight and Obesity Among U.S. Adults Aged 20 to 74 Years**

BMI = body mass index; NHANES = National Health and Nutrition Examination Survey.

*Age-adjusted by the direct method to the year 2000 US Bureau of the Census estimates using the age groups 20-34, 35-44, 45-54, 55-64, and 65-74 years.


**Figure 2. Energy Balance Equation**

GI = gastrointestinal; TNF-α = tumor necrosis factor-alpha.
Leptin acts by entering the brain through the circulatory system to reduce food intake, reduce serum glucose and insulin levels, and increase metabolic rate, ultimately leading to both fat and weight loss. However, animal studies have shown that within just a few days of eating high-calorie foods, leptin resistance develops, possibly as a direct result of cross-talk in leptinergic neurons from glucose, and partly as a result of a reduction in leptin signaling induced by high levels of insulin. In effect, consumption of fatty foods reduces the effectiveness of an important afferent signal from adipose tissue that should indicate an increase in the amount of fat stored, reduce appetite, and increase metabolic rate. In response, the body attempts to restore homeostasis by increasing food intake and reducing energy expenditure, because the information received by the brain is that the body does not have enough energy stored in adipose tissue for normal functioning. Individuals susceptible to obesity would be much more likely to gain weight.

Obese persons have higher serum levels of leptin than normal-weight persons. Steinberg recently showed a more than 2-fold increase in leptin levels in obese patients compared with lean patients, yet the rate of fatty acid metabolism was significantly higher in the lean population, suggesting peripheral resistance to leptin among obese patients. Together, this research indicates obesity may not be the result of insufficient leptin levels but an insensitivity to leptin.

Although this explanation is not the complete picture, it provides a basic understanding behind the neuroendocrinology of obesity. Obesity appears to not be due to lack of willpower, but is a neuroendocrine response to a perceived lack of energy resources in the body, induced by the eating and exercise habits of modern society.

How could obesity begin? If a normal-weight person eats too much food, homeostasis dictates that he or she should increase energy expenditure or decrease food intake to balance out energy stores. In someone who has gained excess weight through a high-calorie diet, these compensatory mechanisms may be blunted. Furthermore, when the overweight person goes on a diet, food intake is reduced and therefore adipose stores are reduced. Leptin levels drop in response to a reduction in adipose tissue. In animal studies, decreased leptin levels increase food intake and reduce energy expenditure, balancing out the reduction in food intake, making it difficult for the overweight animal to lose weight.
Leptin appears to affect food intake and energy expenditure through its effects in the arcuate nucleus on neuropeptides involved in energy balance: inhibiting neuropeptide Y and agouti-related peptide, which increase appetite, and stimulating production of alpha melanocyte stimulating hormone, and cocaine- and amphetamine-regulated transcript, which tend to reduce appetite and increase metabolism. This network also responds to cholecystokinin and other gastrointestinal hormones.4,5,13

**Clinical Trials of Anti-Obesity Targets**

In clinical trials, recombinant leptin has not been as effective at inducing weight loss as was initially hoped. In a study of 54 lean and 73 obese patients (with increased leptin levels), 4 doses of recombinant leptin (or placebo) were given subcutaneously for 24 weeks. The results showed significant weight loss with the 2 highest doses of leptin, almost completely due to fat loss (Figure 3). However, there was considerable variability in weight loss among individual subjects. It may be that higher doses of leptin are required to compensate for a decreased sensitivity to leptin, given that the obese study subjects already had elevated levels of leptin.14 However, the highest dose used in this study was 30 times the normal level of leptin, and high leptin levels are associated with thrombosis and inflammation-pathologic states associated with obesity.

Sibutramine is an appetite suppressant that acts by inhibiting noradrenaline and serotonin reuptake. Animal studies have shown that activation of serotonin receptors in the paraventricular nucleus of the hypothalamus inhibits the action of neuropeptide Y on feeding and metabolism.15 The exact relationship is not clear, however, because other studies show that the hypophagic effects of sibutramine in rats is not mediated by neuropeptide Y neurons in the arcuate nucleus.16 Nonetheless, in an animal study designed to test whether restoring leptin levels would enhance the efficacy of sibutramine by reducing the counter-regulation to weight loss, leptin was administered at low doses sufficient to restore leptin to pre-weight-loss levels. Rats were given a high-fat diet for 8 weeks, which produced weight gain. At that point, rats were given either leptin alone, sibutramine alone, leptin + sibutramine, or vehicle. The results showed no weight loss with leptin alone (Figure 4), a 6-g weight loss with sibutramine, and a 23-g weight loss with leptin.
+ sibutramine (P < .01). Therefore, it appears the weight loss achieved in this study was through the synergistic effects of sibutramine and leptin, and the results further support the concept of connected afferent and efferent systems of weight control.17

Leptin levels are reduced in humans who have lost body fat, which appears to partly explain the weight-loss plateau experienced by so many people on weight-loss programs, and could be a cause of weight regain over time.18,19 To study the impact of leptin on the plateau phenomenon, research subjects at Columbia University participated in a study to analyze the levels of leptin, body composition, aspects of energy expenditure, and circulating concentrations of leptin and thyroid hormones T3 and T4 (known to decrease with weight loss). Analyses were performed at 3 time points: 1) at normal body weight, 2) after 10% weight loss but with weight stabilized; and 3) after 10% weight loss with daily injections of leptin to restore levels to those at usual body weight. Patients were initially put on a liquid formula diet to lose 10% of their body weight. Weight loss was then maintained with a constant exercise regimen and caloric intake, and no further weight loss for 1 month. After that period, leptin (0.08 mg/kg in males, 0.14 mg/kg in females) was given twice daily for 3 weeks to restore morning levels to pre-weight-loss levels. As shown in Figure 5, the results show more weight loss and further reduction of fat mass with leptin administration. Furthermore, the non-resting energy expenditure (ie, energy expended during physical activity) and T3 levels returned to original levels. These results suggest that leptin is able to reverse the “starvation” response seen during weight loss as fat stores (and therefore leptin stores) are reduced, and supports the concept that an active resistance mechanism is at work to prevent weight loss.20

CLINICAL PATHOLOGY OF WEIGHT GAIN

One of the most significant yet underappreciated facets of weight gain is the substantial increase in pathology that results from small amounts of weight gain. Many underestimate how much weight gain it takes for a patient to suffer metabolic consequences. Willett et al have shown the risk of type 2 diabetes increases 4-fold for women within the normal range of body mass index (BMI) (ie, 21 to 25 kg/m²). In the early stages of overweight, the risk of diabetes increases 6-fold from baseline (Figure 6). For men, a 4-fold increase in the risk of diabetes is observed at moderate levels of overweight (ie, up to BMI 27 kg/m²). Also, many of the major disorders associated with obesity (cholelithiasis, hypertension, coronary heart disease) increase by several-fold just above the normal range of BMI.21

Like weight maintenance, the mechanisms of overweight pathology are complex. Adipocytes are important endocrine organs releasing hormones with far-reaching effects throughout the body. The Table shows an abbreviated list of the hormones produced by adipocytes. The outcomes of increased hormone production can include inflammation, hypertension, dyslipidemia, thrombosis, breast cancer, and type 2 diabetes.

Visceral fat is the most dangerous type of fat; it appears to be an “overflow” fat store. When fat accumulates in the abdomen, it is in the portal circulation, bathing the liver in free fatty acids and leading to insulin resistance and the metabolic syndrome—a syndrome of defined risk factors that places people at high risk for atherosclerosis, hypertension, cardiovascular disease, myocardial infarction, stroke, peripheral arterial disease, and endothelial dysfunction. The syndrome is defined by waist circumference as well as levels of cholesterol, fasting blood glucose levels, triglycerides, and blood pressure. A weight loss of 10% can reduce visceral fat stores by 25% to 50%, explaining why small amounts of weight loss improve health so dramatically—removing visceral fat improves metabolic fitness (ie,

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<td>Increased fat stores result in:</td>
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<tr>
<td>▶ Increased lipoprotein lipase</td>
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<td>▶ Increased angiotensinogen</td>
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<td>▶ Increased free fatty acids, leading to increased insulin</td>
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<td>▶ Increased plasminogen activator inhibitor-1</td>
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a measure of the risk factors associated with obesity). In the Diabetes Prevention Program, as well as other large-scale trials, an initial weight loss of 7% followed by maintenance of 4% weight loss at 4 years reduced the risk of developing type 2 diabetes by 58%.22

CONCLUSION

The causes of obesity are complex, but a growing body of evidence suggests that obesity is caused by resistance to afferent signals induced by the high-fat, high-carbohydrate, low-activity lifestyle we lead. Similarly, the ability to lose excess weight is counteracted by the body’s defense mechanism in an effort to spare energy stored as fat for times of emergency. Once excess weight is added, the body appears to be desensitized to afferent signals such as insulin and leptin, upsetting energy balance and “tricking” the body into storing more fat to compensate. A more detailed understanding of the neuroendocrine response to food and weight gain will ultimately help us to overcome the obstacle of the weight plateau. Meanwhile, it is becoming clear that overweight and obesity are not just due to a lack of willpower—they are the result of a neuroendocrine imbalance.

REFERENCES