

FIGURE 415e-3 Factors released by the adipocyte that can affect peripheral tissues. IL-6, interleukin 6; PAI, plasminogen activator inhibitor; RBP4, retinal binding protein 4; TNF, tumor necrosis factor.

ETIOLOGY OF OBESITY

Although the molecular pathways regulating energy balance are beginning to be illuminated, the causes of obesity remain elusive. In part, this reflects the fact that obesity is a heterogeneous group of disorders. At one level, the pathophysiology of obesity seems simple: a chronic excess of nutrient intake relative to the level of energy expenditure. However, due to the complexity of the neuroendocrine and metabolic systems that regulate energy intake, storage, and expenditure, it has been difficult to quantitate all the relevant parameters (e.g., food intake and energy expenditure) over time in human subjects.

Role of Genes Versus Environment Obesity is commonly seen in families, and the heritability of body weight is similar to that for height. Inheritance is usually not Mendelian, however, and it is difficult to distinguish the role of genes and environmental factors. Adoptees more closely resemble their biologic than adoptive parents with respect to obesity, providing strong support for genetic influences. Likewise, identical twins have very similar BMIs whether reared together or apart, and their BMIs are much more strongly correlated than those of dizygotic twins. These genetic effects appear to relate to both energy intake and expenditure. Currently, identified genetic variants, both common and rare, account for less than 5% of the variance of body weight.

Whatever the role of genes, it is clear that the environment plays a key role in obesity, as evidenced by the fact that famine prevents obesity in even the most obesity-prone individual. In addition, the recent increase in the prevalence of obesity in the United States is far too rapid to be due to changes in the gene pool. Undoubtedly, genes influence the susceptibility to obesity in response to specific diets and availability of nutrition. Cultural factors are also important—these relate to both availability and composition of the diet and to changes in the level of physical activity. In industrial societies, obesity is more common among poor women, whereas in underdeveloped countries, wealthier women are more often obese. In children, obesity correlates to some degree with time spent watching television. Although the role of diet composition in obesity continues to generate controversy, it appears that high-fat diets may, when combined with simple, rapidly absorbed carbohydrates, promote obesity. Specific genes are likely to influence the response to specific diets, but these genes are largely unidentified.

Additional environmental factors may contribute to the increasing obesity prevalence. Both epidemiologic correlations and experimental data suggest that sleep deprivation leads to increased obesity. Changes in gut microbiome with capacity to alter energy balance are receiving experimental support from animal studies, and a possible role for obesogenic viral infections continues to receive sporadic attention.

Specific Genetic Syndromes For many years, obesity in rodents has been known to be caused by a number of distinct mutations distributed through the genome. Most of these single-gene mutations cause both hyperphagia and diminished energy expenditure, suggesting a physiologic link between these two parameters of energy homeostasis. Identification of the *ob* gene mutation in genetically obese (*ob/ob*) mice represented a major breakthrough in the field. The *ob/ob* mouse

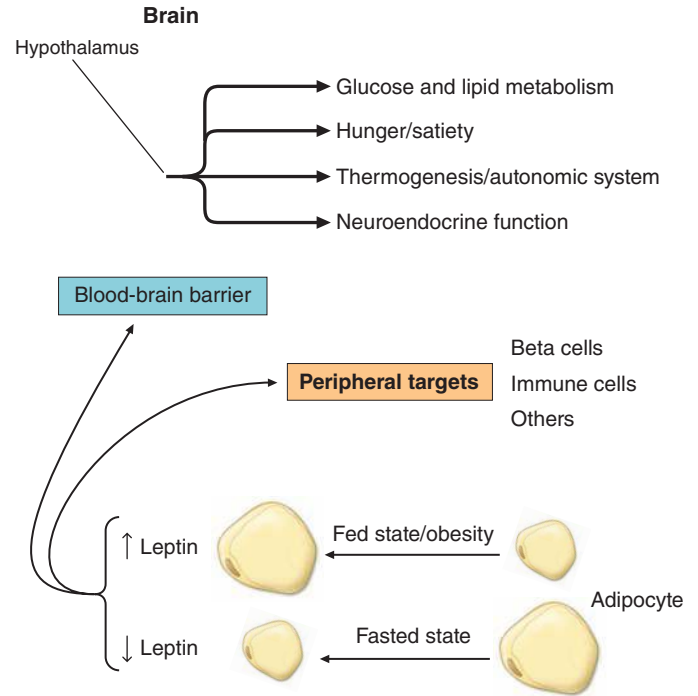


FIGURE 415e-4 The physiologic system regulated by leptin. Rising or falling leptin levels act through the hypothalamus to influence appetite, energy expenditure, and neuroendocrine function and through peripheral sites to influence systems such as the immune system.

develops severe obesity, insulin resistance, and hyperphagia, as well as efficient metabolism (e.g., it gets fat even when ingesting the same number of calories as lean litter mates). The product of the *ob* gene is the peptide leptin, a name derived from the Greek root *leptos*, meaning thin. Leptin is secreted by adipose cells and acts primarily through the hypothalamus. Its level of production provides an index of adipose energy stores (Fig. 415e-4). High leptin levels decrease food intake and increase energy expenditure. Another mouse mutant, *db/db*, which is resistant to leptin, has a mutation in the leptin receptor and develops a similar syndrome. The *ob* gene is present in humans where it is also expressed in fat. Several families with morbid, early-onset obesity caused by inactivating mutations in either leptin or the leptin receptor have been described, thus demonstrating the biologic relevance of the leptin pathway in humans. Obesity in these individuals begins shortly after birth, is severe, and is accompanied by neuroendocrine abnormalities. The most prominent of these is hypogonadotropic hypogonadism, which is reversed by leptin replacement in the leptin-deficient subset. Central hypothyroidism and growth retardation are seen in the mouse model, but their occurrence in leptin-deficient humans is less clear. Mutations in the leptin or leptin receptor genes do not play a prominent role in common forms of obesity.

Mutations in several other genes cause severe obesity in humans (Table 415e-1); each of these syndromes is rare. Mutations in the gene encoding proopiomelanocortin (POMC) cause severe obesity through failure to synthesize α -MSH, a key neuropeptide that inhibits appetite in the hypothalamus. The absence of POMC also causes secondary adrenal insufficiency due to absence of adrenocorticotropic hormone (ACTH), as well as pale skin and red hair due to absence of α -MSH. Proenzyme convertase 1 (PC-1) mutations are thought to cause obesity by preventing synthesis of α -MSH from its precursor peptide, POMC. α -MSH binds to the type 4 melanocortin receptor (MC4R), a key hypothalamic receptor that inhibits eating. Heterozygous loss-of-function mutations of this receptor account for as much as 5% of severe obesity. Loss of function of MRAP2, a protein required for normal MC4R signaling, has been found in rare cases of severe obesity. These six genetic defects define a pathway through which leptin (by stimulating POMC and increasing α -MSH) restricts food intake and limits weight