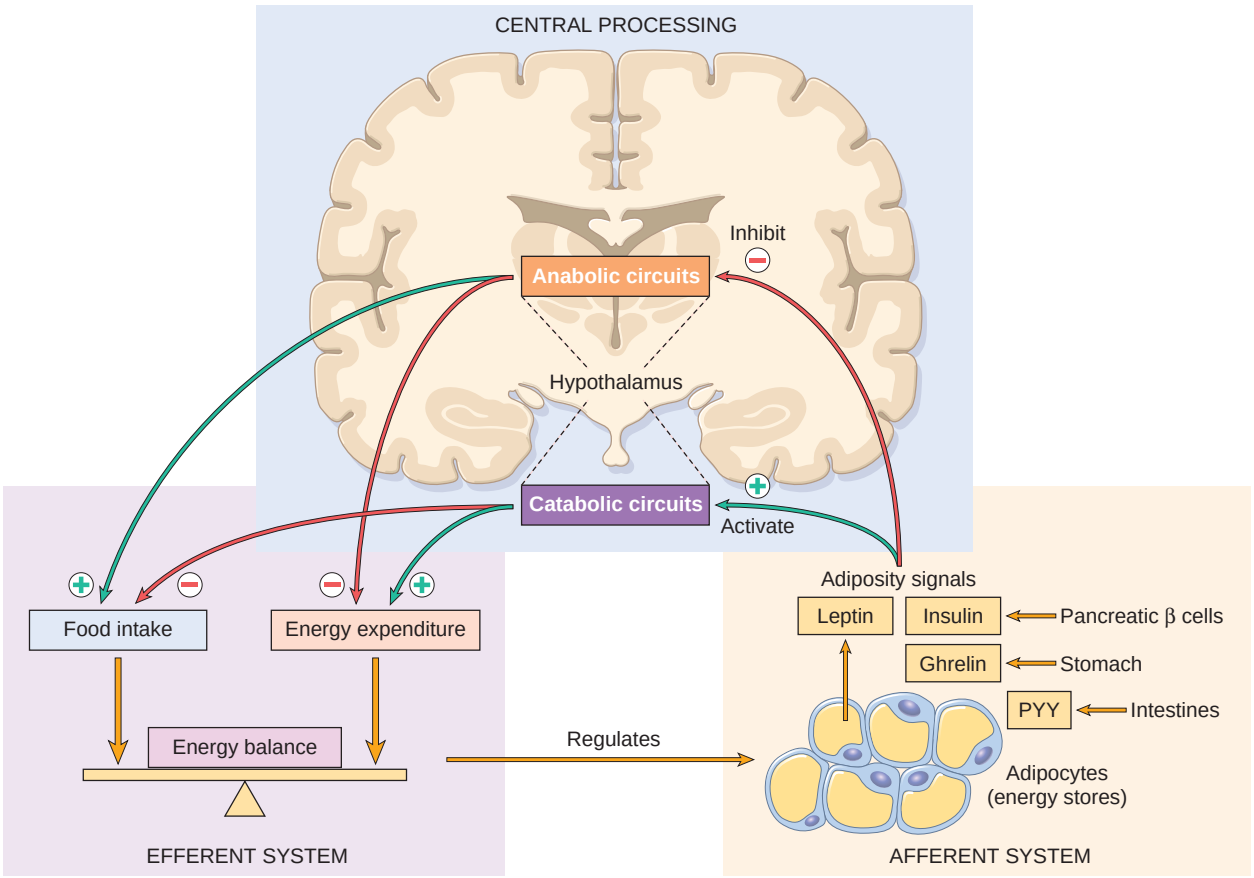

Figure 9-30 Regulation of energy balance. Adipose tissues generate afferent signals that influence the activity of the hypothalamus, which is the central regulator of appetite and satiety. These signals decrease food intake by inhibiting anabolic circuits, and enhance energy expenditure through the activation of catabolic circuits. PYY, Peptide YY. See text for details.

lack of the signal for energy sufficiency that is normally provided by leptin.

While the precise mechanisms that regulate the output of leptin from adipose tissue have not been completely defined, it has been established that leptin secretion is stimulated when fat stores are abundant. It is believed that insulin-stimulated glucose metabolism is an important factor in the regulation of leptin levels. Leptin levels are also regulated by multiple additional posttranscriptional mechanisms that affect its synthesis, secretion, and turnover. In the hypothalamus, leptin stimulates POMC/CART neurons that produce anorexigenic neuropeptides (primarily melanocyte-stimulating hormone) and inhibits NPY/AgRP neurons that produce feeding-inducing (orexigenic) neuropeptides (Figs. 9-30 and 9-31). In individuals with stable weight, the activities of the opposing POMC/CART and NPY/AgRP pathways are properly balanced. However, when there are inadequate stores of body fat, leptin secretion is diminished and food intake is increased.

Humans with loss-of-function mutations in the leptin system develop early-onset severe obesity, but this is a rare condition. Mutations of melanocortin receptor 4 (MC4R) and its downstream pathways are more frequent, being responsible for about 5% of massive obesity. In these individuals, sensing of satiety (anorexigenic signal) is not generated, and hence they behave as if they are undernourished. Haploinsufficiency of brain-derived neurotrophic factor (BDNF), an important component of signaling downstream of MC4R in the hypothalamus, is associated with obesity in patients with the WAGR syndrome (a very rare condition that includes Wilms tumor, aniridia, genitourinary defects, and mental retardation in addition to obesity, Chapter 10). Although the defects in leptin and MC4R detected so far are uncommon, they underscore the importance of these systems in the control of energy balance and body weight. Perhaps other genetic or acquired defects in these pathways may have pathogenic effects in more common forms of obesity. For instance, it has been proposed that leptin resistance is prevalent in humans; it has also been noted that obese children have lower circulating levels of BDNF.

Leptin regulates not only food intake but also energy expenditure, through a distinct set of pathways. Thus, an abundance of leptin stimulates physical activity, heat production, and energy expenditure. The neurohumoral mediators of leptin-induced energy expenditure are less well defined. *Thermogenesis*, an important catabolic effect mediated by leptin, is controlled in part by hypothalamic signals that increase the release of norepinephrine from sympathetic nerve endings in adipose tissue. In addition to these effects, leptin can function as a proinflammatory cytokine and participates in the regulation of hematopoiesis and lymphopoiesis. The OB-R receptor is similar structurally to the IL-6 receptor and activates the JAK/STAT pathway.