In 1994 Friedman et al (1) identified the hormone leptin in adipose tissue. This seminal discovery triggered the novel concept that adipose tissue functions as an endocrine organ and established the active role of the adipocyte in the regulation of food intake and energy expenditure. Friedman et al (2) further established that leptin deficiency is the cause of obesity in a classical rodent model of severe obesity, the obese (ob/ob) mouse, and that treatment of affected mice with recombinant leptin diminished excessive food intake, ameliorated obesity, and corrected the other metabolic abnormalities associated with the genetic defect.

In 1997 Farooqi et al (3) found the human counterpart to the ob/ob mouse when they discovered that some forms of severe obesity that are manifested early in life are due to congenital leptin deficiency. These individuals were homozygous for a frameshift mutation in the leptin gene, which resulted in a truncated protein that was not secreted. The altered leptin function in these obese individuals was manifested early in life and was due to congenital leptin deficiency. These observations supported the theory that congenital leptin deficiency is associated with a predominant Th2 cytokine profile. The authors raised the intriguing suggestion that pharmacologic agents that act as leptin sensitizers might become useful therapeutic tools for hypothalamic amenorrhea or for the amenorrhea accompanying anorexia nervosa. However, Blüher and Mantzoros (5) also highlighted the continued uncertainty about leptin’s precise role or roles in the regulation of the hypothalamic-pituitary-adrenal axis, the hypothalamic-pituitary-thyroid axis, and the hypothalamic-pituitary-growth hormone and insulin-like growth factor I axis.

Blüher and Mantzoros (5) also raised the interesting possibility that recombinant leptin may have therapeutic value under clinical conditions accompanied by relative leptin deficiency. They indicated, for example, that in patients with lipodystrophy and metabolic syndrome induced by antiretroviral therapy, leptin administration might improve insulin resistance and metabolic profile. The authors raised the intriguing suggestion that pharmacologic agents that act as leptin sensitizers may help to ameliorate the leptin resistance observed in the common forms of human obesity, in much the same way that pharmacologic agents improve insulin sensitivity in type 2 diabetes mellitus.

Overall, the reviews presented in this supplement (2–5) describe, in depth, core research that advances the frontiers of medicine. They contribute to the understanding of the role of leptin in the regulation and modulation of glucose metabolism, fat metabolism, energy expenditure, food intake, reproduction, and immunity. The diverse actions of leptin spotlight the search for additional, more detailed studies of the multiple signaling cascades that follow leptin action are required to fully define the role of leptin regulation in energy balance.
for new and exciting therapeutic uses of this hormone that extend beyond the initial focus of its use in treating obesity.

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REFERENCES


