Introduction to the symposium\textsuperscript{1,2}

Emanuel Lebenthal

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 \textit{(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 \textit{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 from the adipocyte, or they were homozygous for a missense mutation in the gene. As was the case in \textit{ob/ob} mice, treatment with recombinant human leptin reduced weight and food intake dramatically. Despite such initial successes, the hope that leptin administration might be an effective mode of therapy in the more garden variety obesity phenotypes was not successful, because the common forms of human obesity are not due to single-gene defects and are associated with hyperleptinemia and leptin resistance, rather than with hypo.leptinemia.

As discussed by Elmquist at the symposium, the main target of leptin’s action on energy regulation is the central nervous system. Leptin receptors in the mediobasal hypothalamus are critically important signal transducers that modulate neuronal activity via local neuronal circuits. On the basis of insulin-signaling pathways that mirror those activated by leptin in the central nervous system, Elmquist et al (4) further suggested that hypothalamic leptin action is critical for maintaining glucose and metabolic homeostasis via crosstalk between leptin and insulin. Their work makes it apparent that 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.

Elmquist et al (4) emphasized that, in addition to the hypothalamus, other brain centers such as the brainstem midbrain and hindbrain might also be regulated by leptin and thus also affect food intake and body weight, and they provided several lines of thought on various mechanisms. Varying isoforms of leptin receptors may convey different biological activities and thus may play a role in leptin tolerance or leptin resistance. Alternatively, interference in leptin signaling through tyrosine phosphatase 1B and/or altered leptin transport through the blood-brain barrier may contribute to leptin tolerance or resistance.

Blüher and Mantzoros (5) discussed important issues regarding leptin turnover and implications for leptin therapy, particularly in the area of reproduction. For example, they noted that, in addition to adipose tissue, leptin is also present in the placenta, mammary gland, testes, ovary, endometrium, and other organs involved in reproduction. They also describe leptin’s critical role in the regulation of reproduction, a function that is clearly evident from the hypogonadotropic hypogonadism found in individuals who are leptin deficient. From these observations, the authors speculate that recombinant leptin and/or 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.

Finally, both Farooqi and O’Rahilly (3) and Blüher and Mantzoros (4) discuss the multiple effects of leptin on innate and adaptive immunity. These functions suggest that immunomodulation with the use of leptin may have therapeutic potential in a range of human diseases. To exemplify this point, Blüher and Mantzoros pointed out that congenital leptin deficiency is associated with a predominant Th2 cytokine response that switches to a Th1 response after leptin therapy.

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

\textsuperscript{1}From the International Institute for Pediatric Nutrition and Gastroenterology, Department of Pediatrics, International Institute for pediatric Nutrition

\textsuperscript{2}Reprints not available. Address correspondence to E Lebenthal, International Institute for Pediatric Nutrition and Gastroenterology, Department of Pediatrics, Hadassah-Hebrew University Medical Center, Mount Scopus, Jerusalem, Israel. E-mail: elebenthal@yahoo.com.

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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