Chapter 4

LEPTIN AND NEUROENDOCRINOLOGY

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Abstract: The hormone leptin, a long sought satiety factor secreted mainly from adipocytes that relays the status of fat store to the hypothalamus, has emerged as one of the most important peripheral signals involved in the variety of neuroendocrine functions, including the regulation of food intake and body weight. Because the hypothalamus is a major site for integration of central and peripheral signals for the maintenance of energy homeostasis and many other physiological functions, most if not all, of the neuroendocrine functions of leptin are transduced primarily at the level of the hypothalamus. Leptin action in the hypothalamus for the maintenance of body weight is mediated by several orexigenic and anorectic signal producing neurons residing in the arcuate-paraventricular-lateral hypothalamus axis. Leptin not only modifies gene expression and release of the neuropeptides, but also modifies post- synaptic action of the neural signals and synaptic plasticity in the hypothalamus. In addition to the classical JAK2 (Janus kinase2)-STAT3 (signal transducer and activator of transcription 3) pathway, the phosphatidylinositol-3-kinase (PI3K)-phosphodiesterase-3B (PDE3B)-cAMP pathway plays a critical role in mediating leptin receptor signaling in the hypothalamus. A crosstalk between these two pathways may be important in leptin signaling in the hypothalamus. Defective hypothalamic STAT3 signaling, most likely due to an increase in suppressor of cytokine signaling-3, appears to play a role in the development of central leptin resistance in diet-induced obese (DIO) animals. Leptin signaling in the hypothalamus via STAT3 is also important in glucose homeostasis and reproduction. However, the development of leptin resistance in the neuropeptide Y, proopiomelanocortin and neurotensin neurons following chronic central leptin infusion is associated with normal STAT3, but a defective PI3K-PDE3B-cAMP pathway of leptin signaling in the hypothalamus. Future investigations on the role of the PI3K-PDE3B-cAMP pathway and its interaction with STAT3 and other pathways of leptin signaling in mediating various neuroendocrine functions are of significant importance to further our understanding on leptin biology.

Key words: Leptin, hypothalamus, energy homeostasis, leptin resistance, STAT3, PI3K, PDE3B, cAMP, feeding, obesity
1. INTRODUCTION

The discovery of the hormone leptin, which is mainly produced by adipocytes, has greatly enhanced our understanding on neuroendocrine mechanisms involved in various physiological functions including reproduction, food intake and body weight regulation. Most importantly, we are beginning to understand the complex neuroendocrine mechanisms underlying the development of obesity. Obesity is a major health hazard in humans. It is not restricted to the western societies anymore, but it qualifies as a worldwide health epidemic. Various genetic (monogenic, susceptible gene) and environmental (diet, exercise, social factors, chemicals, etc) factors are involved in the development of obesity. Remarkably, in most humans body weight is maintained in stable condition. Positive energy balance as a result of less energy expenditure as compared to energy intake leads to the storage of energy in the form of fat. Continuous increases in fat mass eventually lead to obesity. Although energy homeostasis is maintained by multiple mechanisms including that which gathers the body’s nutritional status and make appropriate behavioral and metabolic responses, it is widely accepted that a complex circuitry involving both central and peripheral factors working primarily in the brain, particularly in the hypothalamus, regulates body weight. In fact, the idea that some factors originating in the periphery relay the status of body fat stores to the brain originated with Kennedy, almost 50 years ago. The findings that lesions in the hypothalamic ventromedial (VMH) and paraventricular (PVN) nuclei caused hyperphagia and obesity, and that in the lateral hypothalamus (LH) resulted in hypophagic response in rat, prompted Kennedy in 1953 to hypothesize that the hypothalamus senses some peripheral factors that provide the information about the body fat stores, and the hypothalamus would then transduce this information to change food intake to compensate for changes in body fat content. Subsequent demonstration by Hervey using parabiosis experiments in rats that, when one of the parabiotic partners was made obese by a lesion in the VMH, the intact partner became anorexic and lean, suggesting that some blood-borne factor produced by the increased fat mass acted to induce satiety in the intact partner. In addition, its lack of effect in the lesioned animals also suggested that the action of this factor(s) in the hypothalamus was essential for the maintenance of normal body weight.

In the 1970s, using parabiosis experiments with ob/ob and db/db mice, Douglas Coleman concluded that the blood-borne factor was encoded in the ob gene and the receptor for this factor was encoded in the db gene. Finally in 1994, Jeffrey Friedman’s team discovered the product of the ob gene as a 16 kD protein and it was named leptin. Subsequently, in 1995, Tartaglia’s group cloned the leptin receptor. Expectedly, leptin signals nutritional status to key regulatory centers in the hypothalamus and it has emerged as an