Chapter 17

CLINICAL APPLICATIONS OF LEPTIN

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Abstract: The discovery of the adipocyte hormone leptin has had a profound impact on our understanding of obesity and the role of the adipose tissue as an endocrine organ. Due primarily to the weight reducing effect of leptin in the ob/ob mouse, the initial enthusiasm for leptin clinical investigation was in human obesity. This review will trace the clinical studies from states of leptin deficiency (‘Ob/Ob’, lipodystrophy, hypothalamic amenorrhea), a physiological replacement paradigm, to the pharmacological applications in obesity (a purported state of leptin insensitivity). This chapter reviews the clinical applications of two leptin analogs for which there is relevant clinical data available (A-200, a long acting analog, will not be discussed, as there is little available data). Both animal and clinical data in multiple disease states provide strong support for a leptin analogue as a potent physiological replacement therapy in states of ‘leptin deficiency’. The pharmacological applications in obesity will require further work to identify populations that might respond to leptin alone or in combination with agents impacting other pathways. The available clinical studies provide invaluable insights into furthering our understanding of the relevance of this hormone in health and disease states. Future studies are needed to explore the many potential applications of this remarkable cytokine hormone.

Key words: obesity; lipodystrophy; insulin resistance; dyslipidemia; adipocytokines; reproductive endocrinology; hypothalamic amenorrhea, neuroendocrine; therapeutics
INTRODUCTION

The discovery of leptin and other adipocyte-derived hormones has completely changed our view of the adipocyte as a cell with an important role in the regulation of metabolism. We now know that the fat cells have an endocrine function and can secrete a variety of proteins including leptin, adinopectin\(^1\), resistin\(^2\), TNF\(\alpha\)\(^3\), and IL-6 \(^4,5\). This list has grown to include other secreted factors such as adiponutrin, visfatin\(^6,7\), omentin\(^8\), etc. Leptin, by virtue of its rapid development for therapeutic applications and its projected therapeutic potential in obesity, has received the most attention. In addition to its regulatory effect in energy homeostasis and metabolism, there is a growing body of evidence that suggests involvement of leptin in the regulation of the immune system \(^9\), reproduction \(^10\), coagulation, sympathetic nervous system \(^11,12\), blood pressure \(^12\), growth \(^13\), steroid hormone production, fetal development \(^14\), hematopoiesis \(^15\), angiogenesis \(^4,5,14,16-19\) and wound repair \(^20,21\). When the effects of a cytokine hormone are so diverse, finding its clinical utility becomes challenging. A logical approach toward developing clinical uses of the pathway begins with the lessons from the knockout ob/ob mouse. Since the most obvious effect observed in the ob/ob mouse was dramatic weight loss, the drug was quickly embraced as the potential “magic bullet” for the rising epidemic of obesity in the Western World.

Since the story originates from the ob/ob mouse and begins with the discovery of leptin, it is useful to briefly review the physiology of leptin. Leptin is a protein structurally similar to cytokines \(^22,25\). It is the protein product of the ob gene in mice and humans \(^24,25\). The main site of leptin synthesis is adipose tissue (white more than brown) and blood levels of leptin correlate with total body fat; the circulating leptin level is elevated in obese rodents and humans \(^26,27,28\) and lower in lean subjects. Its main function is thought to be as an energy sensor via informing the brain of the energy storage level of the body \(^16,29,30\). In response to this signal, the brain makes appropriate adjustments to change food intake and energy expenditure to reestablish the energy homeostasis \(^16,29-34\). The ob/ob mouse, which has complete deficiency of leptin, are hyperphagic, hypothermic and morbidly obese, marked by increased energy intake with reduced energy expenditure \(^16,35,36,37\). Treatment of ob/ob mice with leptin causes a decrease in appetite and promotes weight loss, the majority of which is the body fat \(^35-37\). These mice also have a marked hepatic steatosis coupled with hepatic insulin resistance and hyperglycemia. In addition, the ob/ob mice are infertile and have a number of other hypothalamic-pituitary axes abnormalities such as central hypothyroidism, hypercorticosteronemia due to central CRF neuron activation, and linear growth impairment. More recently, immunological