New Prospects for the Treatment of Obesity
—Leptin and the discovery of anti-obesity drugs—

JMAJ 48(2): 64–67, 2005

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Abstract: Obesity is a typical multifactorial disease that results from complex interactions between hereditary predisposition and environmental factors, making it extremely difficult to approach from a molecular level. At the end of 1994, an obese gene product, leptin, was discovered, and, since then, obesity research has produced a variety of new findings. Leptin is secreted from the adipose tissue and to act directly on the hypothalamus, causing appetite suppression and accelerated energy metabolism, thereby denoting a relationship to obesity and weight gain. A number of hypothalamic appetite regulators have been found, and it has recently become apparent that many of these regulators are controlled by leptin. In contrast, many genes that are known to cause human obesity and to develop from single-gene mutations regulate energy metabolism by leptin, and they have attracted attention as possible anti-obesity drugs. This paper outlines new anti-obesity drug research and development that have emerged since the discovery of leptin.

Key words: Leptin; Hypothalamus; Development of anti-obesity drugs; Neuropeptides

Introduction

Obesity is a typical multifactorial disease that results from complex interactions between hereditary predisposition and environmental factors, making it extremely difficult to approach from a molecular level. After leptin, which causes obesity in the ob/ob mouse when it mutates, was found at the end of 1994, research on obesity took a new direction. It is speculated that leptin is released from the adipose tissue and acts directly on the hypothalamus to control various appetite regulators, leading to strong suppression of the appetite and increased energy metabolism. Thus, leptin is considered to be involved in the control of obesity and weight gain. Although various appetite regulators have been uncovered, it has recently become apparent that many are controlled by leptin, causing leptin to become the target of
potential new anti-obesity drugs (Fig. 1).

This paper outlines potentially new anti-obesity drugs that have become apparent as a result of leptin’s discovery, and describes future prospects in the treatment of obesity.

**Leptin**

In *ob/ob* mice, which are devoid of leptin, and in patients with leptin-deficient obesity, leptin selectively decreases body fat, inducing prominent weight loss. Therefore, leptin was heralded as a new anti-obesity drug almost as soon as it was discovered. However, many cases of obesity are considered leptin-resistant because blood concentrations of leptin increase in proportion to weight gain. The brain delivery of leptin and abnormalities of the leptin receptor or post-leptin-receptor hypothalamic neuronal pathways, have been cited as leptin resistance molecular mechanisms, although the details remain unclear.

The interim report of a clinical trial of leptin in non-obese and simple obese subjects showed weight reduction as a result of 20- to 30-fold higher blood concentrations of leptin than normal in some obese subjects, demonstrating the efficacy of mass administration of leptin even in patients with leptin-resistant obesity. In contrast, about 5–10% of patients with obesity have decreased blood concentrations of leptin; thus, leptin compensatory therapy may be promising in such subjects. It has recently been reported that compensation for decreased leptin caused by diet therapy prevents oxygen consumption from decreasing during the weight-loss process, suggesting the possibility that diet therapy combined with compensatory leptin administration produces efficient weight loss.

Possible anti-obesity drugs targeting leptin include leptin analogues, leptin agonists, and leptin resistance-improving agents.

**Hypothalamic Neuropeptides**

The production of many neuropeptides in the hypothalamus is reported to be regulated by leptin. These neuropeptides have attracted attention as potential targets of new anti-obesity drugs.

1. **Neuropeptide Y (NPY)**

Neuropeptide Y (NPY) is a 36-amino acid peptide present in large quantities in the central nervous system. NPY administered into the cerebral ventricle of rodents causes strong appetite enhancement, and the administration of consecutive daily doses of NPY induces obesity in these animals. The NPY-containing neurons in the arcuate nucleus (Arc) of the hypothalamus suggests an important connection to appetite regulation, and leptin is known to decrease the NPY gene expression in the Arc.

The NPY receptor is a seven-transmembrane, G-protein-coupled receptor. Five subtypes (Y1, Y2, Y4, Y5, Y6) of this receptor are known to exist. Antagonists of the NPY Y1 receptor (Y1-R) and Y5 receptor (Y5-R), among other subtypes, are attracting attention as possible anti-obesity drugs. Several Y1-R antagonists have already been developed, and their appetite-suppressive effects have been noted in normal animals and Zucker (*fa/fa*) rats and *db/db* mice, which have leptin receptor gene muta-
3. Cocaine- and amphetamine-regulated transcript (CART)

CART-containing neurons are present in the Arc and dorsomedial hypothalamic nucleus (DMH). In the Arc, CART is present in the same neurons as those containing POMC. It has been demonstrated that the CART gene expression in the Arc is enhanced by leptin. Although no CART receptor has been identified to date, CART receptor agonists could have the potential to be anti-obesity drugs.

4. Melanin-concentrating hormone (MCH)

Melanin-concentrating hormone (MCH) in mammals is a cyclic 19-amino-acid peptide that has one disulfide bond in its molecule. MCH-containing neurons are present in the zona incerta and lateral hypothalamic area (LHA), and MCH gene expression in the hypothalamus is decreased by leptin. It has been reported that intraventricular administration of MCH caused no changes in total daily food intake, although food intake increased immediately after administration; consecutive daily intraventricular administration of MCH resulted in no weight gain. On the other hand, MCH-deficient mice exhibit decreases in food intake and body weight, showing increased basal metabolism.

Type-1 and type-2 MCH receptors (MCH-1R and MCH-2R) have been identified as human MCH receptors, but their respective functions in the regulation of energy metabolism remain unknown. When antagonists that are highly selective for the two receptor subtypes are developed and their properties are clarified, the development of new anti-obesity drugs is anticipated.

5. Others

It has recently been reported that neurotrophic factors such as ciliary neurotrophic factor (CNTF) and brain-derived neurotrophic factor (BDNF) have anti-obesity activity. CNTF is known to activate the intracellular signaling pathway JAK-STAT, overlapping with those
pathways activated by leptin. CNTF and BDNF are also effective in high-fat diet-induced obesity model animals that are leptin resistant. Low-dose CNTF was indicated to be a potentially useful anti-obesity drug in a US phase-I clinical study.

Gene expression of these neurotrophic factors is not controlled by leptin. However, elucidation of the molecular mechanisms of appetite regulation by CNTF and BDNF may lead to clarification of the molecular mechanisms of leptin resistance and, eventually, to the discovery of new anti-obesity drugs.

**Conclusion**

The basics of obesity treatment include lifestyle modifications, particularly diet. However, following the discovery of leptin, there has been rapid progress in the development of new anti-obesity drugs that target various neuropeptide/receptor systems involved in the central regulation of appetite. This paper has outlined the targets of anti-obesity drug development that have come to light since the discovery of leptin. Readers are referred to other reviews for information that has not been included in this paper.

Obesity is a chronic disease that often requires long-term treatment. Ordinary obesity treatment often achieves temporary weight loss, but such weight loss can be difficult to maintain (rebound phenomenon). It is thus important to develop effective anti-obesity drug therapies with minimal side effects. The advent of new anti-obesity drugs and their clinical application are expected due to expanded research into obesity that has been fueled by the discovery of leptin.

**REFERENCES**