

SCIENCE BEHIND THE STUDY

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Antagonizing the Leptin Receptor in Obesity

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Childhood obesity is a challenging clinical condition. Secondary causes of obesity are often sought but rarely found, and few can be addressed by successful therapeutic interventions. Leptin was once hailed as a treatment for most cases of childhood obesity but quickly lost favor when resistance to leptin was noted. In a Brief Report in this issue of the *Journal*, Funcke et al.¹ describe etiologic variants in the leptin gene (*LEP*) in two severely overweight children whose conditions were resistant to treatment with metreleptin (a pharmacologic substitute for leptin) and biochemical experiments that informed a successful treatment strategy. This study has implications for treating obesity more generally.

WHAT IS LEPTIN AND HOW DOES IT WORK?

Leptin is a peptide hormone and is made predominantly by adipose tissue. Storage of excess triglycerides leads to expansion of lipid droplets during feeding; as a result, adipocytes secrete leptin into the circulation (Fig. 1). After crossing the blood–brain barrier, leptin inhibits orexigenic neurons in the hypothalamus by binding to the long form of the leptin receptor, which is present on the surface of these neurons. Leptin thereby has the effect of increasing energy expenditure and decreasing food intake.^{2,3} However, as levels of circulating leptin increase, the hormone somehow becomes less effective at inhibiting these orexigenic neurons.²

HOW WAS LEPTIN DISCOVERED?

A strain of obese mice, first described in 1950, opened the door to our understanding of genetically acquired obesity. In 1973, Doug Coleman at the Jackson Laboratory found that there was a genetic basis for the obese phenotype of these mice (dubbed “ob/ob” mice).³ Two decades later, the causative gene was discovered: *Lep*, encoding leptin.⁴ In humans, congenital leptin deficiency is an autosomal recessive disorder in which genetic loss-of-function variants in *LEP* result in the complete absence of leptin and thereby cause severe, early-onset obesity.³

Another strain of mutant mice, also discovered more than 70 years ago, models both obesity and type 2 diabetes. This mouse has inactivating variants in the gene encoding the leptin receptor.⁵ There are 38 known variants in the leptin receptor gene (*LEPR*) in humans that cause severe, early-onset obesity and type 2 diabetes.⁶ In these persons, very high levels of circulating leptin are present; these levels are indicative of leptin resistance.

HOW DOES RESISTANCE TO LEPTIN DEVELOP?

Acquired leptin resistance due to obesity without a known genetic cause is characterized by increased levels of serum leptin (Fig. 2). Persistently high leptin levels lead to partial antagonism and reduced bioactivity. A similar phenomenon occurs in most patients with obesity who are treated with metreleptin. Here, too, partial antagonism between endogenous leptin and metreleptin is thought to cause resistance to metreleptin, although the mechanism of partial antagonism is not clear. There may be post-translational changes in the leptin molecule or altered leptin transport across the blood–brain barrier. Theoretically, lowering leptin levels (to reduce the partial antagonism) could reduce leptin resistance.

CAN A NATURAL MOLECULE ANTAGONIZE AN ENDOGENOUS HORMONE?

Yes. In 1996, Takahashi et al. reported the case of a patient with short stature who had a point mutation in the growth hormone gene. This point mutation resulted in a variant growth hormone that “outcompeted,” in vitro, the nonvariant growth hormone (encoded by the other, nonmutated copy of the growth hormone gene).⁷ However, the authors never conclusively proved interference with growth-hormone signaling, leading some to doubt the existence of any naturally occurring competitive antagonists to an endogenous hormone. The severe obesity, hyperphagia, and high levels of circulating leptin in the children described by Funcke et al. were

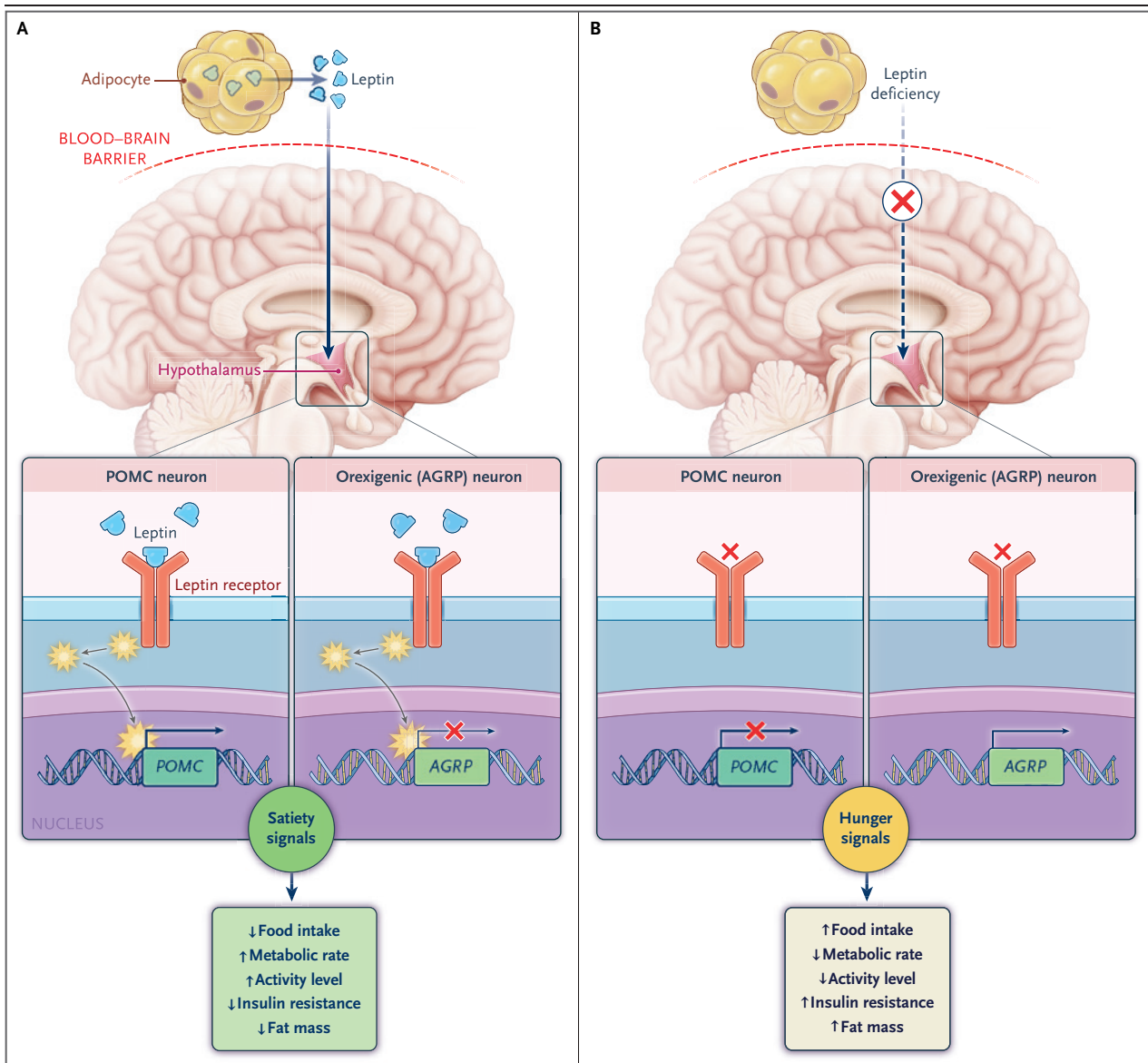


Figure 1. Leptin Signaling, Metabolism, and Obesity.

Leptin is made by adipocytes and is secreted into the circulation (Panel A). It crosses the blood–brain barrier and binds to the leptin receptor in the hypothalamus, which stimulates proopiomelanocortin (POMC) and inhibits orexigenic neurons and thus the production of agouti-related protein (AGRP). These changes result in suppression of appetite and enhanced energy expenditure. A lack of leptin leads to obesity, increased food intake, reduced energy metabolism, and ultimately left ventricular hypertrophy (Panel B).

caused by antagonistic leptin proteins that bound to the leptin receptor but triggered marginal, if any, signaling. In the presence of the nonvariant leptin, these proteins acted as competitive antagonists, the authors found.

WHAT IS THE MECHANISM OF ACTION?

To understand the molecular mechanism of the *LEP* variants described by Funcke et al., it is worth

reviewing some basic concepts in pharmacology.⁸ Agonism is the binding of an agent to a receptor that mimics the full activity of the endogenous compound, whereas partial agonism denotes only a portion of the signaling activity of that compound (Fig. 2). Competitive antagonism occurs when there is competition for the same binding site on the receptor as the agonist. Funcke et al. found that neither of the variant

leptin proteins initiated signaling through the leptin receptor *in vitro*, even though binding affinities between these proteins and the leptin receptor were similar to that of native leptin. In competitive binding assays, however, each variant leptin suppressed signaling by native leptin, so each acted as a competitive antagonist with leptin. In the absence of nonvariant leptin (as was the case in the patients, each of whom carried two variant alleles), each variant had partial agonist activity.

AND THE TREATMENT OF THE PATIENTS?

Initially, they were unsuccessfully treated with conventional doses of metreleptin. Guided by the results of their biochemical experiments, Funcke et al. markedly increased the dose to overcome the effects of the endogenous antagonist leptin. In addition, the patients participated in fasting and exercise programs to lower the production of endogenous antagonist leptin. Both patients lost a great deal of weight, and metreleptin doses were reduced.

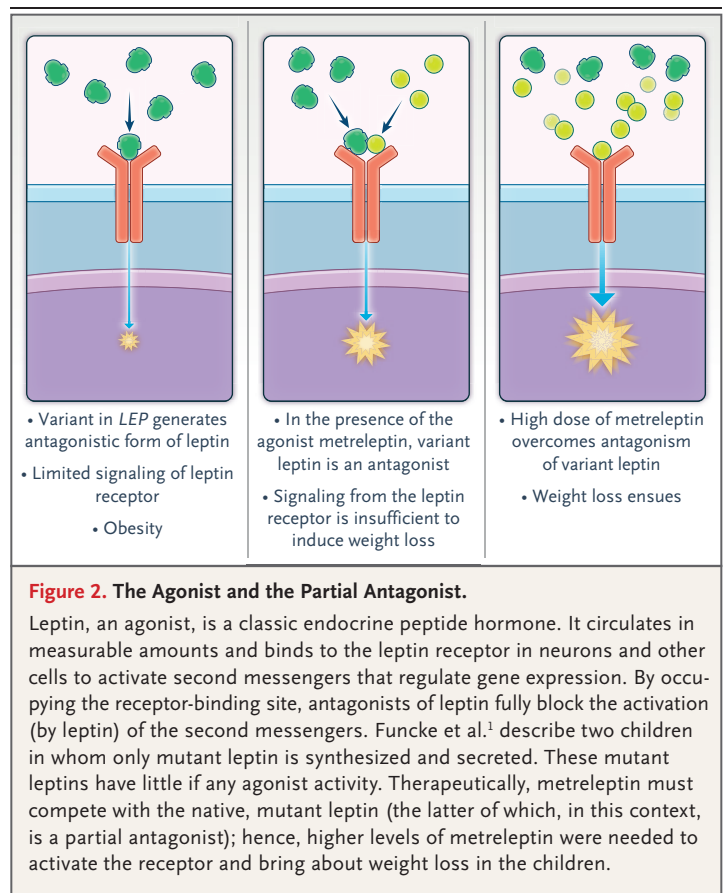
WHAT DOES THIS STUDY TELL US?

First, circulating, endogenous variant hormone can competitively antagonize nonvariant hormone (or its therapeutic substitute — in this case, metreleptin). Second, other treatment strategies for diet-induced obesity involving leptin might be considered. For example, Zhao et al. studied mice with only one intact copy of the leptin gene that were receiving a high-fat diet. In these mice, leptin levels did not rise in response to the diet, yet obesity, fatty liver, and metabolic dysregulation did not develop, which implies that comparatively low leptin levels may be critical to maintaining sensitivity to leptin.⁹ It is apparent that there is a narrow appropriate dose–response effect of leptin on leptin-receptor signaling in the hypothalamus. Further research into the use of monoclonal antibodies as a potential therapeutic tool for obesity is warranted.¹⁰

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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