Correction

MEDICAL SCIENCES

Correction for "Leveraging leptin for type I diabetes?" by Daniel Kraus, Mark A. Herman, and Barbara B. Kahn, which appeared in issue 11, March 16, 2010, of *Proc Natl Acad Sci USA* (107:4793–4794; first published March 8, 2010; 10.1073/pnas.1000736107).

Due to a printer's error, an uncorrected author proof of this manuscript appeared in Early Edition. The current online and print versions are correct.

www.pnas.org/cgi/doi/10.1073/pnas.1003961107

Leveraging leptin for type I diabetes?

Daniel Kraus, Mark A. Herman, and Barbara B. Kahn[1]

Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA 02215

The discovery of insulin in 1922 is one of the miracles of modern medicine, and it turned a once deadly disease—insulin-deficient (autoimmune) type 1 diabetes mellitus (T1DM)—into a manageable one. It is now clear that insulin is a key metabolic regulator that is vital to glucose and lipid homeostasis and affects many aspects of growth and development. Insulin's fundamental importance in biology is underscored by the conservation of insulin-like hormones and their receptors from flies and worms to humans. In PNAS, Wang et al. (1) extend previous findings (2–4) to suggest that another hormone, leptin, may substitute for or be used in combination with insulin to treat T1DM more effectively.

Leptin, a prototypic fat-secreted hormone, is also a master metabolic regulator. It is critical for control of appetite, body weight, energy homeostasis, and reproduction (5). Deficiency of leptin or its receptor in rodents and humans causes severe hyperphagia, obesity, insulin resistance, and neuroendocrine and reproductive dysfunction (6). Based on its ability to normalize body weight in massively obese *ob*/*ob* mice (which lack leptin) and reduce food intake in normal rodents, it was anticipated that leptin would curb the obesity pandemic. Unfortunately, common obesity is a state of leptin resistance rather than leptin deficiency, and leptin therapy alone is generally unsuccessful in clinical trials for obesity (7), although a small study suggests potential efficacy for leptin in combination with amylin (8). To date, efficacy of leptin monotherapy in humans is primarily limited to leptin-deficient states such as congenital leptin deficiency, lipoatrophy, hypothalamic amenorrhea with reduced adipose mass, and HIV lipodystrophy (9).

Is an Alternate or Adjunct Treatment for T1DM Needed?

With insulin therapy, T1DM is no longer a life-threatening disease, and the burden of diabetic complications including nephropathy, retinopathy, neuropathy, cardiovascular disease, and lower limb amputation has also been reduced. However, modern treatment of T1DM falls far short of eliminating morbidity and is accompanied by considerable risk of another life-threatening complication, hypoglycemia. This is because insulin secretion from pancreatic β cells is a finely tuned physiological process, exquisitely matching fuel availability to utilization on a minute-to-minute basis. Exogenous insulin administration cannot, thus far, mimic this with the necessary precision. Patients have hypo- or hyperglycemic episodes because of unavoidable mismatches of insulin doses with caloric intake, physical activity, and factors such as stress. Intensive insulin therapy in T1DM may also contribute to increased adiposity, hepatic steatosis, and adverse plasma lipoprotein profiles, although these effects are much more pronounced in type 2 diabetes. Treatment approaches are needed that closely mimic the rapid responsiveness of endogenous insulin secretion (Fig. 1*A*) and reduce the risk of hypoglycemia. Strategies being developed range from microprocessor-controlled closed-loop insulin delivery systems to pancreatic islet allografts and xenografts and stem cell engineering. However, these are not yet clinically available. Recent studies suggest leptin treatment might be beneficial because of its ability to normalize glycemia in insulin-deficient diabetic rats and mice (1–4).

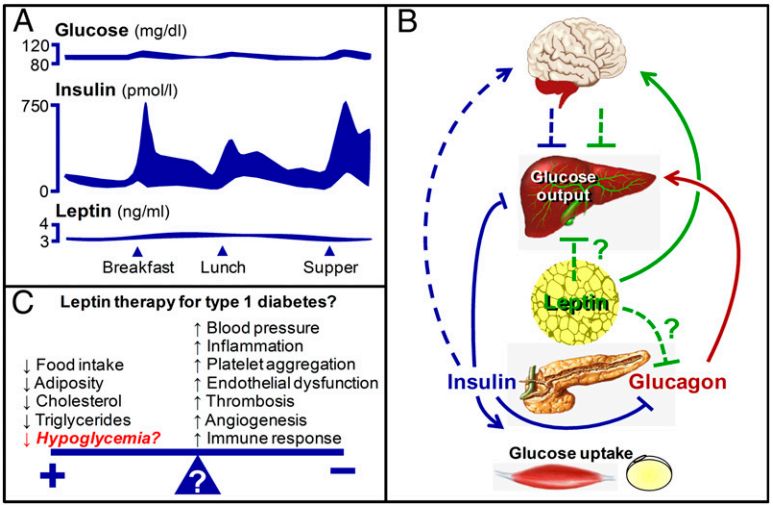

Fig. 1. Insulin, leptin, and the regulation of glucose homeostasis. (*A*) Plasma insulin levels vary widely in response to meals, whereas glucose is tightly controlled throughout the day (17). Leptin levels fluctuate much less (18). (*B*) Schematic representation of the convergence of insulin and leptin in a network that regulates glucose homeostasis. Solid lines indicate well-established effects. For clarity, not all connections are depicted. The question marks indicate two proposed interactions. The proposed effect of leptin to suppress glucagon may be direct or indirect. (*C*) Weighing the potential benefits and risks of leptin treatment for T1DM.

Potential Mechanisms for the Beneficial Effects of Leptin on Glucose Metabolism

Before the discovery of insulin, T1DM was managed by severely restricting caloric intake to reduce hyperglycemia. One might hypothesize that leptin normalizes glycemia in insulin-deficient models through its appetite-suppressant effects. However, reduction of food intake in a control group that was pair-fed to the leptin-treated group was not sufficient to normalize glycemia (1). Thus, reduced food intake alone does not explain the full effect of leptin to normalize glycemia in insulin-deficient rodents.

The majority of leptin's effects on appetite, energy balance, and reproductive function are mediated through the brain, particularly the hypothalamus. Leptin action in these neurons also regulates peripheral glucose metabolism and this is partly independent of its effects on food intake and adiposity (10). This may contribute to the efficacy of leptin treatment in insulin-deficient rodent models.

Wang et al. (1) hypothesize that leptin may control glycemia by suppressing secretion of glucagon (Fig. 1*B*), a hormone that potently stimulates glucose production by the liver. Indeed, leptin reduces plasma glucagon levels to a similar degree

Author contributions: D.K., M.A.H., and B.B.K. wrote the paper.

Conflict of interest statement: B.B.K. is on a scientific advisory board for Amylin Pharmaceuticals, Inc.

See companion article on page 4813.

[1]To whom correspondence should be addressed: bkahn@bidmc.harvard.edu.

as insulin therapy (1, 4). This may be mediated directly or through the central nervous system (11) (Fig. 1*B*). Glucagon action seems to be essential for the development of hyperglycemia in insulin-deficient mice, because mice lacking glucagon receptors do not become hyperglycemic after induction of insulin deficiency (1). However, whether leptin-mediated suppression of glucagon is essential for leptin's ability to normalize glycemia in T1DM has not been tested.

Recently, an alternative mechanism was proposed. Leptin was found to regulate insulin-like growth factor-binding protein 2 (IGFBP2) expression in liver, and pharmacologic IGFBP2 levels reversed both type 1 and type 2 diabetes in mice (12). Whether IGFBP2 induction is necessary for leptin's action on glucose homeostasis or to normalize glycemia in insulin-deficient states is unknown.

Theoretical Advantages of Leptin Therapy for T1DM

Because hypoglycemia is the most serious complication of insulin therapy, a critical question is whether adjunct leptin treatment might reduce the incidence or severity of hypoglycemic episodes in human T1DM. Leptin-insulin combination in T1DM mice improved glycemic stability compared with insulin alone (1). This may occur because mice eat throughout the day and night albeit with a diurnal pattern. It is easier to improve glycemic stability in the absence of insulin when caloric intake is relatively constant. It is not clear that leptin would be effective in humans who generally eat a few defined meals requiring rapid responses by glucose regulatory hormones (Fig. 1*A*).

While both leptin and insulin treatment normalized glycemia in T1DM mice, leptin also reduced food intake, leading to leanness, whereas insulin increased adiposity (1). Although leptin does not effectively reduce food intake in the majority of obese humans, it could be effective in nonobese individuals who are not leptin resistant (13). This alone could improve glucose control in T1DM (Fig. 1*C*). If the insulin dose could be reduced as a result of leptin adjunctive therapy, the lipogenic effects of insulin might decrease. Additionally, leptin's effects to reduce hepatic lipogenesis and cholesterol synthesis below nondiabetic levels might also be beneficial (1). This may improve outcomes because overweight and obesity and their associated comorbidities confer the same increased mortality risk in T1DM as in the nondiabetic population (14).

Is Leptin Therapy Likely to Be Effective in Type 1 Diabetic Humans?

There are important differences between T1DM mice and humans that may affect the efficacy of leptin treatment. T1DM mice are leptin deficient due to reduced fat mass resulting from uncontrolled diabetes unlike human T1DM that receive insulin therapy. Leptin supplementation in leptin-sufficient T1DM humans may not have the same glycemic effects as leptin replacement in a leptin-deficient state (mouse T1DM). Most likely leptin levels would need to be increased above normal in T1DM humans, which may not be effective because of leptin receptor down-regulation (15), and could also lead to adverse effects (Fig. 1*C* and see below).

Timing is also a concern: insulin levels are regulated minute-to-minute to permit precise glycemic control in the setting of unpredictable caloric intake and utilization (Fig. 1*A*). Leptin levels are regulated over the course of hours, days, or weeks. Can leptin, a hormone that seems to have evolved to signal nutritional status over the long term (5), regulate glucose homeostasis in the short term?

Potential Adverse Effects of Leptin Therapy

In addition to efficacy, potential adverse effects need to be considered (Fig. 1*C*). Leptin can raise blood pressure; promote platelet aggregation, which could cause thrombosis; impair endothelial function; increase immune function; and foster inflammation and angiogenesis (16) (Fig. 1*C*), all of which could produce or worsen diabetic complications or other diseases. To date, such adverse effects have not been reported in leptin-deficient lipodystrophic patients treated with replacement doses of leptin. However, if higher than normal leptin levels are needed to effectively lower glycemia in T1DM humans (because they are not leptin deficient), leptin's potentially adverse effects may become significant. Furthermore, leptin's effect to suppress glucagon may place T1DM patients at increased risk for severe hypoglycemic episodes by impairing the counterregulatory response necessary to restore glycemia.

Summary

Recent data provide convincing evidence that leptin has beneficial effects on glucose homeostasis in mouse models of insulin-deficient T1DM and demonstrate the feasibility of low-dose insulin and leptin combination therapy in mice (1–4). While there are many important considerations, carefully designed trials in T1DM humans to determine whether leptin adjunct therapy would allow significant reductions in insulin doses and/or improve glycemic stability without adverse effects are warranted. Safety evaluation should include careful assessment of effects of this combination therapy on the counterregulatory response to hypoglycemia. Extensive studies will be needed to determine long-term safety and efficacy.

ACKNOWLEDGMENTS. We acknowledge the following grant support: National Institutes of Health Grants P01 DK56116 (to B.B.K.) and K08 DK076726 (to M.A.H.) and a fellowship from the American Heart Association (to D.K.).

1. Wang M, et al. (2010) Leptin monotherapy in insulin deficient type 1 diabetes. *Proc Natl Acad Sci USA* 107: 4813–4819.
2. Chinookoswong N, Wang JL, Shi ZQ (1999) Leptin restores euglycemia and normalizes glucose turnover in insulin-deficient diabetes in the rat. *Diabetes* 48:1487–1492.
3. Miyanaga F, et al. (2003) Leptin as an adjunct of insulin therapy in insulin-deficient diabetes. *Diabetologia* 46: 1329–1337.
4. Yu X, Park BH, Wang MY, Wang ZV, Unger RH (2008) Making insulin-deficient type 1 diabetic rodents thrive without insulin. *Proc Natl Acad Sci USA* 105:14070–14075.
5. Ahima RS, Flier JS (2000) Leptin. *Annu Rev Physiol* 62: 413–437.
6. Farooqi IS, O'Rahilly S (2005) Monogenic obesity in humans. *Annu Rev Med* 56:443–458.
7. Chicurel M (2000) Whatever happened to leptin? *Nature* 404:538–540.
8. Roth JD, et al. (2008) Leptin responsiveness restored by amylin agonism in diet-induced obesity: Evidence from nonclinical and clinical studies. *Proc Natl Acad Sci USA* 105:7257–7262.
9. Kelesidis T, Kelesidis I, Chou S, Mantzoros CS (2010) Narrative review: The role of leptin in human physiology: Emerging clinical applications. *Ann Intern Med* 152:93–100.
10. Kalra SP (2009) Central leptin gene therapy ameliorates diabetes type 1 and 2 through two independent hypothalamic relays; a benefit beyond weight and appetite regulation. *Peptides* 30:1957–1963.
11. Tudurí E, et al. (2009) Inhibitory effects of leptin on pancreatic alpha-cell function. *Diabetes* 58:1616–1624.
12. Hedbacker K, et al. (2010) Antidiabetic effects of IGFBP2, a leptin-regulated gene. *Cell Metab* 11:11–22.
13. Heymsfield SB, et al. (1999) Recombinant leptin for weight loss in obese and lean adults: A randomized, controlled, dose-escalation trial. *JAMA* 282:1568–1575.
14. Conway B, et al. (2009) Adiposity and mortality in type 1 diabetes. *Int J Obes (Lond)* 33:796–805.
15. Wang MY, Orci L, Ravazzola M, Unger RH (2005) Fat storage in adipocytes requires inactivation of leptin's paracrine activity: Implications for treatment of human obesity. *Proc Natl Acad Sci USA* 102:18011–18016.
16. Koh KK, Park SM, Quon MJ (2008) Leptin and cardiovascular disease: Response to therapeutic interventions. *Circulation* 117:3238–3249.
17. Jacobs MA, et al. (1997) Metabolic efficacy of preprandial administration of Lys(B28), Pro(B29) human insulin analog in IDDM patients. A comparison with human regular insulin during a three-meal test period. *Diabetes Care* 20:1279–1286.
18. Gavrila A, et al. (2003) Diurnal and ultradian dynamics of serum adiponectin in healthy men: Comparison with leptin, circulating soluble leptin receptor, and cortisol patterns. *J Clin Endocrinol Metab* 88:2838–2843.