

A case for new therapy for diabetes, is it leptin?

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Since its discovery, insulin and/or insulin mimetics have been the therapy of choice to alleviate hyperglycemia in patients suffering from either type 1 diabetes (T1D) or type 2 diabetes (T2D). These endeavors, spanning over several decades, however, have also documented the inability of this monotherapy to sustain stable glycemia on a minute-to-minute basis, decelerate the attendant metabolic and neural comorbidities and the impending adverse impact on life span.^[1-4] Recent multidisciplinary research devoted to gaining a deeper understanding of the neurobiology of the adipocyte hormone leptin in the integration of energy balance has, quite unexpectedly, not only enforced a re-evaluation of the etiology of diabetes, but also has unraveled potential targets for a novel durable therapy for these two afflictions.^[5-8] Additionally in the process, this insight dispelled the long-held but poorly substantiated presumptions by prominent investigators and diabetologists that T1D and T2D are distinct disorders resulting primarily from either a lack of pancreatic insulin in the former or due to development of insulin's ineffectiveness to maintain blood glucose within the physiologic norm in the latter.

NEW CONCEPTUAL ADVANCE

Instead, it is now apparent that optimal operation of leptin-brain feedback signaling is the obligatory final common hormonal–neural pathway for sustenance of glucose homeostasis through the lifetime.^[6] Indeed, disruption in this feedback relay resulting from leptin insufficiency in the hypothalamus due to either leptinopenia in T1D patients, or to hyperleptinemia-induced development of imperviousness of the blood–brain barrier (BBB) to leptin in T2D patients,

has been shown experimentally to be a primary underlying cause of derangement in glucose homeostasis.^[6-12] This conceptual advance implying a suboptimal leptin-driven signal outflow from the hypothalamus is affirmed by findings that reinstatement of leptin signaling solely in the hypothalamus readily restored glucose homeostasis and kept at bay the metabolic comorbidities for the lifetime in various clinical and experimental paradigms of T1D and T2D.^[2,6,7,9,13,14] Remarkably, however, recognition and acceptance of this novel insight in the etiology of diabetes have been slow among the scientific community largely because of the deeply held assumptions (enumerated below) based on weak and questionable evidence over several decades, combined with inattention to those discoveries in leptin neurobiology that shed new light on the etiology of metabolic diseases.

1. Insulin is the only hormonal signal needed to maintain glucose homeostasis involving multiple targets in the periphery alone, and hormonal signals generated by insulin have little neurally mediated role in imposing glucose homeostasis.
2. It is the obesity, dietary or age-related, and not the antecedent hyperinsulinemia, the earliest etiologic factor that disrupts insulin signaling at the molecular level by insulin receptor downregulation, receptor insensitivity to diminished rates of glucose disposal that progressively inflict hyperglycemia, accompanied by accelerated adipogenesis, hyperleptinemia, abnormal rate of fat deposition, and obesity.
3. Hyperinsulinemia in T2D patients is believed to result from persistent elevated circulating glucose concentrations orchestrated by excessive dietary signals, and not due to the loss of a mandatory hypothalamic regulatory restraint on pancreatic insulin secretion caused by leptin insufficiency in the brain of these patients (see below).
4. New information that has not yet been incorporated into the overall roadmap of the etiology of diabetes includes (i) a tonic restraint on insulin secretion is exerted by leptin-induced signal relay from the hypothalamus to the pancreas,^[15-17] (ii) leptin entry

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into the brain across the BBB is physiologically governed by receptor-mediated regulatory processes that dynamically monitor leptin passage into the brain, strictly in accordance with the degree of hyperleptinemia,^[18-20] and (iii) leptin insufficiency, induced by excessive circulating leptin concentration, curtails hypothalamic restraint on insulin secretion that, in turn, destabilizes glucose homeostasis. This is readily correctable by reinstating leptin sufficiency by circumventing BBB with replenishment directly in the hypothalamus.^[2,6,21]

NEUROBIOLOGY OF LEPTIN AND GLUCOSE HOMEOSTASIS

Multidisciplinary approaches undertaken to investigate the mechanism of action of leptin in hypothalamic regulation of energy intake and expenditure, quite unexpectedly, uncovered the existence of a distinct neuroendocrine axis intimately involved in the control of glucose homeostasis on a minute-to-minute basis.^[5,7,8] Seemingly, leptin mobilizes three distinct circuitries emanating from the leptin receptor-expressing hypothalamic neurons that employ diverse neurotransmitters for cross talk locally and for signal relay to peripheral organs involved in glucose disposal and energy expenditure. Whereas the appetite regulating network (ARN) resident within the hypothalamus acts locally to control energy intake, the energy expenditure network (EEN) projects to brown adipose tissue (BAT) to regulate nonthermogenic energy expenditure and glucose disposal, and the fat accrual network (FAN) regulates fat deposition in the body by coordinating pancreatic insulin secretion needed for disposal and storage of glucose in skeletal muscle, liver, and white adipose tissue (WAT).^[7,22-25] Subsequent observations showing that interruption of the leptin-directed neural relay to the periphery results in hyperphagia and in those multiple metabolic disturbances, such as attenuated nonthermogenic energy expenditure, unremitting hyperinsulinemia, insulin insensitivity, and hyperglycemia, that subsequently promote adipogenesis and abnormal rate of fat accrual have validated the obligatory participation of the ARN, EEN, and FAN descending pathways in weight and glucose homeostasis.^[7] That the hypothalamus is the singular site of leptin action in the central nervous system is further affirmed by demonstrations that either complete absence of leptin availability or deletion of leptin receptors selectively in the hypothalamus reproduces these very metabolic disruptions while restoration of leptin supply or instillation of leptin receptors locally in the hypothalamus alone reverses these afflictions.^[7,10,26-28]

Perhaps the two most unanticipated additional findings uncovered by concerted research in the neurobiology of leptin were the discovery of leptin's ability to elicit unvarying, stable glycemia to enhance glucose disposal by attenuating insulin resistance in the periphery. For instance, leptin infusion intraventricularly or leptin supply selectively in the hypothalamus by gene therapy conferred euglycemia and increased insulin sensitivity peripherally in several models of T1D and T2D.^[7,8,13,14,29] Although the precise mechanism remains to be delineated, these unique ways of leptin's participation in glucose homeostasis reinforced the emerging notion that leptin engages multiple hypothalamic relays to regulate glucose homeostasis on a minute-to-minute basis.^[7]

A PERSPECTIVE

Leptin therapy for diabetes

Convergence of evidence convincingly endorses the implication that defective leptin-induced signal relay from the hypothalamus constitutes the key common pathway in the genesis of pathophysiologic sequelae that culminate in T1D and T2D. The potential for harnessing this new breakthrough is underscored by numerous preclinical and clinical investigations already underway to assess the efficacy and safety of leptin therapy for T1D and T2D. Restoration of leptin signal relay by supplying leptin selectively in the hypothalamus with gene therapy in T1D models of monogenic diabetic syndrome, the obese leptin mutant *ob/ob* mice displaying hyperglycemia along with hyperinsulinemia, and the insulin 2 gene (*Ins2*) mutant, insulin-deficient, nonobese hyperglycemic Akita mice, imposed long-lasting euglycemia and increased insulin sensitivity regardless of the marked diminution in circulating insulin seen in *ob/ob* mice, or in the complete absence of biologically active insulin as observed in Akita mice.^[13,14] Similarly, hyperglycemia evoked by streptozotocin-induced insulinitis in mice was remedied in favor of stable euglycemia for the one-year duration of the experiment when leptin was supplied in the hypothalamus alone by gene therapy.^[30] It is important to note that stable euglycemia in these paradigms was manifested in response to increased neural outflow along EEN and FAN with or without affecting signaling along the ARN. Further, leptin delivery through systemic routes by either daily injections or by leptin gene therapy also reproduced these benefits in these mouse models of T1D.^[31,32] In leptinopenic clinical and animal lipodystrophic models exhibiting severe hyperglycemia, hyperinsulinemia, and insulin resistance, leptin replacement alone by daily injections ameliorated these symptoms during the entire course of treatment, lasting longer than 6 months.^[11,33,34] Sparked by these demonstrations of the long-term efficacy and safety of systemic leptin administration to correct

diabetes, a clinical trial aimed at evaluating the application of leptin therapy in T1D patients is currently underway.^[35]

Predictably, due to the preexisting hyperleptinemia and increased imperviousness of the BBB to leptin entry in obese patients and in rodents with T2D, raising the circulating levels further by systemic administration is ineffective.^[5,7,18] However, circumventing the BBB by supplying leptin by either intraventricular infusion or with the aid of gene therapy selectively in the hypothalamus was highly beneficial in restoring euglycemia, concomitant with repressed hyperinsulinemia, insulin insensitivity, and adiposity, were reinstated for extended periods in both aging and high fat diet-fed obese rodents.^[7,10,26,36]

What's next?

In toto, the worldwide epidemic of diabetes and attending co-morbidities, together with the knowledge of the relatively higher rates of the incidence of diabetes in developing countries,^[2-4,21] should catalyze a global search for newer and unconventional therapeutic strategies that can curb this alarming pandemic without the well-known shortcomings of insulin therapy, such as its failure to reproduce and sustain normoglycemia over a 24-h period, roller coaster pattern of glycemia interspersed with episodes of severe hypoglycemia, attendant obesity, metabolic and neural comorbidities, and the sky-rocketing treatment costs.

Since substantial experimental evidence has now accumulated to support a unifying role of leptin-hypothalamus signaling in T1D and T2D, leptin therapy offers distinct advantages over insulin therapy at several fronts, notably the markedly reduced frequency of treatment and blood glucose monitoring because both peripheral and central routes of leptin administration produce extremely stable glycemia and prevent the comorbidities. In fact, leptin gene therapy consisting of a single peripheral, central, or site-specific hypothalamic injection of recombinant adeno-associated virus (rAAV) vector encoding the leptin gene is highly advantageous over other modes of delivery, because it can impose long-lasting euglycemia and mitigate comorbidities.^[9,10,21,26] rAAV is a relatively nonpathogenic and nonimmunogenic vector as amply documented by numerous ongoing clinical trials for various neural diseases.^[29,37,38] Consequently, leptin therapy is potentially a suitable new strategy for physicians that provide an additional armament to subserve as an efficient alternative or a supplement to the current insulin monotherapy. Since the clinical safety and benefits of leptin therapy for long-term amelioration of T1D and T2D have not yet been fully ascertained, it is timely and pertinent to undertake rigorous clinical trials to evaluate and refine the leptin treatment regimen, to determine the efficient mode of delivery—systemic, nasal, or central route—and to

assess the efficacy of a stable supply of biologically active leptin with the aid of gene therapy.^[21,29,39,40] A search for newer long-acting leptin mimetics that can cross the BBB and reinstate hypothalamic control of glucose homeostasis also has the potential to pave the way in providing new antidiabetic drugs.

REFERENCES

1. Banting FG, Best CH. Pancreatic extracts. 1922. *J Lab Clin Med* 1990;115:254-72.
2. Kalra SP. Central leptin gene therapy ameliorates diabetes type 1 and 2 through two independent hypothalamic relays; a benefit beyond weight and appetite regulation. *Peptides* 2009;30:1957-63.
3. Scully T. Diabetes in numbers. *Nature* 2012;485:S2-3.
4. Shetty P. Public health: India's diabetes time bomb. *Nature* 2012;485:S14-6.
5. Friedman JM. Leptin at 14 y of age: An ongoing story. *Am J Clin Nutr* 2009;89:973S-79S.
6. Kalra SP. Central leptin insufficiency syndrome: An interactive etiology for obesity, metabolic and neural diseases and for designing new therapeutic interventions. *Peptides* 2008;29:127-38.
7. Kalra SP, Kalra PS. Neuroendocrine control of energy homeostasis: Update on new insights. *Prog Brain Res* 2010;181:17-33.
8. Gautron L, Elmquist JK. Sixteen years and counting: An update on leptin in energy balance. *J Clin Invest* 2011;121:2087-93.
9. Kalra SP. Increased leptin supply to hypothalamus by gene therapy confers life-long benefits on energy homeostasis, disease cluster of metabolic syndrome-diabetes type 1 and 2, dyslipidemia and cardiovascular ailments and bone remodeling. In: Shioda S, Homma I, Kato N, editors. *Transmitters and Modulators in Health and Disease*. Tokyo: Springer; 2009. p. 19-30.
10. Boghossian S, Ueno N, Dube MG, Kalra P, Kalra S. Leptin gene transfer in the hypothalamus enhances longevity in adult monogenic mutant mice in the absence of circulating leptin. *Neurobiol Aging* 2007;28:1594-604.
11. Mantzoros CS, Magkos F, Brinkoetter M, Sienkiewicz E, Dardeno TA, Kim SY, *et al*. Leptin in human physiology and pathophysiology. *Am J Physiol Endocrinol Metab* 2011;301:E567-84.
12. Farooqi IS, O'Rahilly S. Leptin: A pivotal regulator of human energy homeostasis. *Am J Clin Nutr* 2009;89:980S-4S.
13. Ueno N, Dube MG, Inui A, Kalra PS, Kalra SP. Leptin modulates orexigenic effects of ghrelin and attenuates adiponectin and insulin levels and selectively the dark-phase feeding as revealed by central leptin gene therapy. *Endocrinology* 2004;145:4176-84.
14. Ueno N, Inui A, Kalra PS, Kalra SP. Leptin transgene expression in the hypothalamus enforces euglycemia in diabetic, insulin-deficient nonobese Akita mice and leptin-deficient obese ob/ob mice. *Peptides* 2006;27:2332-42.
15. Dhillon H, Kalra SP, Prima V, Zolotukhin S, Scarpace PJ, Moldawer LL, *et al*. Central leptin gene therapy suppresses body weight gain, adiposity and serum insulin without affecting food consumption in normal rats: A long-term study. *Regul Pept* 2001;99:69-77.
16. Otukonyong EE, Dube MG, Torto R, Kalra PS, Kalra SP. Central leptin differentially modulates ultradian secretory patterns of insulin, leptin and ghrelin independent of effects on food intake and body weight. *Peptides* 2005;26:2559-66.
17. Boghossian S, Dube MG, Torto R, Kalra PS, Kalra SP. Hypothalamic clamp on insulin release by leptin-transgene expression. *Peptides* 2006;27:3245-54.

18. Kastin AJ, Pan W. Dynamic regulation of leptin entry into brain by the blood-brain barrier. *Regul Pept* 2000;92:37-43.
19. Banks WA, DiPalma CR, Farrell CL. Impaired transport of leptin across the blood-brain barrier in obesity. *Peptides* 1999;20:1341-5.
20. Banks WA, Farr SA, Morley JE. The effects of high fat diets on the blood-brain barrier transport of leptin: Failure or adaptation? *Physiol Behav* 2006;88:244-8.
21. Kalra SP. Pivotal role of leptin-hypothalamus signaling in the etiology of diabetes uncovered by gene therapy: A new therapeutic intervention? *Gene Ther* 2011;18:319-25.
22. Bartness TJ, Kay Song C, Shi H, Bowers RR, Foster MT. Brain-adipose tissue cross talk. *Proc Nutr Soc* 2005;64:53-64.
23. Kreier F, Kap YS, Mettenleiter TC, van Heijningen C, van der Vliet J, Kalsbeek A, *et al.* Tracing from fat tissue, liver, and pancreas: A neuroanatomical framework for the role of the brain in type 2 diabetes. *Endocrinology* 2006;147:1140-7.
24. Uyama N, Geerts A, Reynaert H. Neural connections between the hypothalamus and the liver. *Anat Rec A Discov Mol Cell Evol Biol* 2004;280:808-20.
25. Buijs RM, Chun SJ, Nijima A, Romijn HJ, Nagai K. Parasympathetic and sympathetic control of the pancreas: A role for the suprachiasmatic nucleus and other hypothalamic centers that are involved in the regulation of food intake. *J Comp Neurol* 2001;431:405-23.
26. Boghossian S, Lecklin A, Torto R, Kalra PS, Kalra SP. Suppression of fat deposition for the life time with gene therapy. *Peptides* 2005;26:1512-9.
27. Cohen P, Zhao C, Cai X, Montez JM, Rohani SC, Feinstein P, *et al.* Selective deletion of leptin receptor in neurons leads to obesity. *J Clin Invest* 2001;108:1113-21.
28. Keen-Rhinehart E, Kalra SP, Kalra PS. AAV-mediated leptin receptor installation improves energy balance and the reproductive status of obese female Koletsky rats. *Peptides* 2005;26:2567-78.
29. Kalra SP, Kalra PS. Gene-transfer technology: A preventive neurotherapy to curb obesity, ameliorate metabolic syndrome and extend life expectancy. *Trends Pharmacol Sci* 2005;26:488-95.
30. Kojima S, Asakawa A, Amitani H, Sakoguchi T, Ueno N, Inui A, *et al.* Central leptin gene therapy, a substitute for insulin therapy to ameliorate hyperglycemia and hyperphagia, and promote survival in insulin-deficient diabetic mice. *Peptides* 2009;30:962-6.
31. Yu X, Park BH, Wang MY, Wang ZV, Unger RH. Making insulin-deficient type 1 diabetic rodents thrive without insulin. *Proc Natl Acad Sci U S A* 2008;105:14070-5.
32. Wang MY, Chen L, Clark GO, Lee Y, Stevens RD, Ilkayeva OR, *et al.* Leptin therapy in insulin-deficient type I diabetes. *Proc Natl Acad Sci U S A* 2010;107:4813-9.
33. Ogawa Y, Masuzaki H, Hosoda K, Aizawa-Abe M, Suga J, Suda M, *et al.* Increased glucose metabolism and insulin sensitivity in transgenic skinny mice overexpressing leptin. *Diabetes* 1999;48:1822-9.
34. Ebihara K, Kusakabe T, Hirata M, Masuzaki H, Miyanaga F, Kobayashi N, *et al.* Efficacy and safety of leptin-replacement therapy and possible mechanisms of leptin actions in patients with generalized lipodystrophy. *J Clin Endocrinol Metab* 2007;92:532-41.
35. Unger R. "Study to determine whether leptin helps type 1 diabetes patients." UT Southwestern Medical Center: Science Daily; 1 Oct 2010. Online Jul 2012.
36. Dube MG, Beretta E, Dhillon H, Ueno N, Kalra PS, Kalra SP. Central leptin gene therapy blocks high-fat diet-induced weight gain, hyperleptinemia, and hyperinsulinemia: Increase in serum ghrelin levels. *Diabetes* 2002;51:1729-36.
37. Mandel RJ, Burger C. Clinical trials in neurological disorders using AAV vectors: Promises and challenges. *Curr Opin Mol Ther* 2004;6:482-90.
38. Mueller C, Flotte TR. Clinical gene therapy using recombinant adeno-associated virus vectors. *Gene Ther* 2008;15:858-63.
39. Kastin AJ, Pan W. Intranasal leptin: Blood-brain barrier bypass (BBB) for obesity? *Endocrinology* 2006;147:2086-7.
40. Dhillon H, Kalra SP, Kalra PS. Dose-dependent effects of central leptin gene therapy on genes that regulate body weight and appetite in the hypothalamus. *Mol Ther* 2001;4:139-45.

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