Review Article

Should leptin replace insulin as a lifetime monotherapy for diabetes type 1 and 2?

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ABSTRACT

Evidence accumulated during the last decade has affirmed that adipocyte leptin insufficiency in the hypothalamus is the primary etiological factor in the pathogenesis of diabetes type 1 and 2 and related metabolic morbidities. Leptin insufficiency disrupts the relay of hypothalamic regulatory information along three descending pathways to the organs in the periphery that normally participate in maintenance of glucose homeostasis on a minute-to-minute basis throughout lifetime. Reinstatement of leptin sufficiency in the hypothalamus by either systemic or central injections, or its provision selectively in the hypothalamus with the aid of gene therapy extinguished hyperglycemia and normalized blood glucose stably during the entire course of treatment in a variety of animal models of diabetes type 1 and 2. In follow-up clinical trials, twice daily leptin treatment in leptinopenic and insulinopenic type 1 diabetics and leptinopenic and hyperinsulinemic type 2 diabetics with congenital lipodystrophy or acquired lipoatrophy normalized blood glucose without any discernible adverse effects during the extended course of treatment. Taken together, these findings have amply endorsed the efficacy of leptin therapy to restore glucose homeostasis in insulin-deficient as well as hyperinsulinemic diabetic patients. Consequently, restoration of optimal hypothalmic signaling to reinstate glucose homeostasis with leptin is a highly suitable new therapeutic strategy to ameliorate diabetes type 1 and 2 for the lifetime and to replace the currently in vogue insulin monotherapy. In view of the relentless challenges posed by the worldwide epidemic of diabetes and soaring treatment costs, taken together with the well-known shortcomings of therapies based on restoring insulin signaling, it is highly critical and timely to undertake new clinical trials that ascertain appropriate dosage and route of leptin delivery to the hypothalamus capable of safely sustaining stable glycemia for lifetime.

Key words: Brain, diabetes, leptin

The isolation, structure and synthesis of leptin, a 16 kDa protein secreted primarily by white adipocyte tissue (WAT) was published in 1994. Research since then has focused mainly on elucidating the mechanisms that regulate leptin synthesis and secretion from WAT, and the sites and mode of its action at cellular and molecular levels in facilitating energy homeostasis in response to the ever changing internal and external environments. Perhaps the most novel insights from these extensive investigations of the last decade are the serendipitous revelations that insulin is obesogenic and stimulates leptin secretion from fat cells, and that leptin, not insulin, is the singular obligatory signal to the hypothalamus that maintains glucose homeostasis. Further, a breakdown in the optimal leptin signaling to central targets inflicted by either insulinopenia or hyperinsulinemia, results in a loss of hypothalmic control on blood glucose homeostasis culminating in hyperglycemia, diabetes, and related morbidities. This recognition of the central role of leptin propelled research endeavors towards gaining a deeper understanding of the dynamics of insulin-leptin relationship in the periphery, and the mode of neural action of leptin in directing glucose homeostasis. Multidisciplinary approaches were undertaken to unravel these underlying mechanisms. Diverse pharmacological and genetic animal and human paradigms of diabetes type 1 and 2 were employed along with novel gene therapy to deliver an uninterrupted supply of leptin peripherally and centrally in specific hypothalmic locations. The outcome of these studies on the dynamic operation of the WAT-hypothalamus feedback conversation in imparting glucose homeostasis

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was compiled in recent review articles[1-3] and is briefly enumerated below:

1. Insulin stimulates the secretion of leptin from adipocytes and leptin, in turn, imposes regulatory restraint on insulin secretion via neural relays to pancreatic beta cells. Thus, a tight feedback control sustains an optimal pattern of circulating concentrations of the two hormones to preserve glucose homeostasis.
2. Entry of leptin in optimal amounts into the brain is regulated by the blood brain barrier (BBB), a receptor mediated process of endothelial cells. Hyperinsulinemia-induced adiposity and the resultant hyperleptinemia lead to a proportional downregulation of leptin receptors. Quantitatively, leptin entry across BBB is proportional to this receptor downregulation. The resultant leptin insufficiency at neural targets in the hypothalamus disrupts efferent relays to those peripheral targets that are intimately involved in glucose disposal and restraint on insulin efflux. Thus, in keeping with the well-documented observations, hyperleptinemia, a concomitant of obesity, invariably eventuates into a persistent state of hyperglycemia and diabetes type 2.
3. Similarly, leptinopenia due to a lack of endogenous insulin stimulus as in type 1 diabetics, and congenital and acquired lipoatrophy in humans and rodent models; imparts leptin insufficiency in hypothalamic targets to engender similar sequential events, disruption in neural relay to target organs in the periphery, loss of glucose homeostasis, and persistent hyperglycemia.
4. Descending neural relay from three discrete hypothalamic networks; the appetite regulating network operating locally in the basal hypothalamus, the energy expending network linked to brown adipose tissue, and the fat accrual network linked to pancreas, skeletal muscles, liver, and WAT; have been identified as obligatory in the regulation of glucose homeostasis by leptin. This is in accord with the findings showing that interruption of signal relays surgically, pharmacologically, or by genetic manipulations along any of these efferent pathways, orchestrates the loss of glucose homeostasis and diabetes, similar to that conferred by leptin insufficiency in the hypothalamus.
5. Gene therapy to replenish leptin selectively in the hypothalamus, without entry into the peripheral circulation, has provided unequivocal experimental evidence that endorses leptin as the key obligatory hormonal signal regulating glucose homeostasis via mobilization of these descending hypothalamic neural relays to peripheral organs. A series of experiments disclosed that leptin delivery directly to hypothalamic targets, with the aid of a single injection of nonpathogenic and nonimmunogenic recombinant adeno-associated virus (rAAV) vector encoding leptin gene, evoked stable glycemia lasting for the duration of the experiments in all type 1 and 2 diabetes animal models. Further, these benefits were similar to those engendered when the efficacy of leptin was examined after systemic delivery of leptin in humans and animal.
6. Additional unanticipated findings emanating from the experiments designed to ameliorate diabetes type 1 and 2 with central or peripheral leptin treatment are that it readily conferred stable glycemia by concurrently augmenting insulin sensitivity and glucose metabolism with treatment paradigms limited to only 1-2 injections over a 24 h period. These revelations markedly contrast the well-documented shortcomings of the currently in vogue insulin monotherapy requiring multiple injections, characterized by the roller coaster pattern of glycemia interspersed with episodes of hypoglycemia, and accelerated rates of adiposity and metabolic comorbidities.

In aggregate, it is now obvious that extensive compelling experimental evidence exists in support of the implication that diabetes is a neural affliction resulting from imprecise communication between adipocytes and the hypothalamus; and leptin replacement therapy is a promising, durable, and safe strategy to alleviate type 1 and 2 diabetes for lifetime. This radically new insight should catalyze clinical trials to replace and/or complement insulin therapy with a focus on establishing optimal dosage and route of leptin administration. Moreover, it establishes the impetus to devise long-acting leptin mimetics that can cross the BBB with marked facility in order to optimally sustain the hypothalmic control on glucose homeostasis; and thereby, serve as reliable and safe antidiabetic drugs.

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