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The Role of Leptin in Maintaining Plasma Glucose During Starvation

Rachel J. Perry[1] and Gerald I. Shulman[1-3]

Departments of [1]Internal Medicine and [2]Cellular & Molecular Physiology
Yale University School of Medicine
[3]Howard Hughes Medical Institute

Abstract
For 20 years it has been known that concentrations of leptin, a hormone produced by the white adipose tissue (WAT) largely in proportion to body fat, drops precipitously with starvation, particularly in lean humans and animals. The role of leptin to suppress the thyroid and reproductive axes during a prolonged fast has been well defined; however, the impact of leptin on metabolic regulation has been incompletely understood. However emerging evidence suggests that, in starvation, hypoleptinemia increases activity of the hypothalamic-pituitary-adrenal axis, promoting WAT lipolysis, increasing hepatic acetyl-CoA concentrations, and maintaining euglycemia. In addition, leptin may be largely responsible for mediating a shift from a reliance upon glucose metabolism (absorption and glycogenolysis) to fat metabolism (lipolysis increasing gluconeogenesis) which preserves substrates for the brain, heart, and other critical organs. In this way a leptin-mediated glucose-fatty acid cycle appears to maintain glycemia and permit survival in starvation.
Keywords Starvation, leptin, HPA axis, glucocorticoids, gluconeogenesis, lipolysis

Introduction: leptin and starvation

Leptin, a peptide hormone produced by the white adipose tissue which has been suggested to exert effects on the hypothalamus, hippocampus, brainstem, and gonadal tissue, the receptor for which was cloned in 1994 by Jeffrey Friedman and colleagues, who named it the "obese" receptor (1), is known to play a significant role in food intake: rodents and humans lacking this protein or its receptor are insatiably hungry and, without medical intervention, consequently develop obesity, metabolic syndrome and type 2 diabetes. In addition, leptin may play a role in the starved state, with prolonged fasting resulting in reductions in plasma leptin concentrations in multiple species. Evolutionary pressures have required animals and humans to develop mechanisms to survive the feast-famine cycles that have occurred throughout history. Tissues critical for survival – most importantly, brain and heart, but also erythrocytes and the renal medulla – require an adequate supply of glucose to function, without which survival would not be possible. Thus there has been longstanding interest in understanding the mechanisms by which euglycemia is maintained in the starved state and whether leptin plays any role in these homeostatic mechanisms. Based largely upon measurements of plasma fatty acid concentrations, it has long been believed that white adipose tissue (WAT) lipolysis is increased in starvation (2-20). As WAT lipolysis generates both glycerol and fatty acids, thereby increasing hepatic concentrations of acetyl-CoA, an activator of the gluconeogenic enzyme pyruvate carboxylase (PC) (21-24), as well as supply of a gluconeogenic substrate (glycerol) (25) it would stand to reason that increased lipolysis may be important for glucose maintenance in the starved state; therefore understanding why lipolysis is increased in starvation is of great interest. Canonical wisdom has held that fasting-induced insulinopenia (20, 26-35) – perhaps with superimposed WAT insulin resistance (13, 30, 36-38) and/or an increased WAT lipolytic response to catecholamine stimulation (12, 13, 39) – is responsible for the well-documented increases in WAT lipolysis in the fasting state.

However, in contrast to the conventional theory of leptin's role in the fasting state, we have recently demonstrated that insulinopenia is <u>not sufficient</u> to promote large increases in lipolysis in a related rodent model, insulin-deficient type 1

diabetes (T1D). In this model, increased hypothalamic-pituitary-adrenal axis activity, which occurs secondary to an acquired leptin deficiency, is also necessary (40-44). In our hands (45) and others' (8, 46-68), plasma leptin concentrations and WAT leptin expression have been shown to drop quickly with starvation. To understand the role of this reduction in plasma leptin, Ahima et al. performed a classic study in which they performed an intraperitoneal injection of leptin resulting in plasma leptin concentrations initially 100 times normal, and examined various physiologic parameters twelve hours later. They concluded that leptin modulates the responses of the reproductive, adrenal, and thyroid axes to starvation, but that it has little to nothing to do with regulation of glycemia or ketosis (60). Primarily due to these negative results with regard to leptin's impact on glucose in fasted rodents, leptin has been largely disregarded as a modulator of glycemia in the starved state in subsequent years. However we recently demonstrated that physiologic leptin replacement suppresses the increases in HPA axis-driven WAT lipolysis, hepatic gluconeogenesis, and plasma glucose concentrations observed in T1D rats, which are in a pseudo-starved state due to insulinopenia and resulting impairments in tissue glucose uptake despite hyperglycemia (42, 43). Therefore we decided to revisit the role of leptin in glycemic regulation in fasting rats. When we infused a physiologic replacement dose of leptin in 48 hr fasted animals, this intervention caused a rapid reduction in HPA axis activity, suppressing WAT lipolysis and gluconeogenesis, and necessitating infusion of glucose to avoid symptomatic hypoglycemia. We then demonstrated that increases in HPA axis activity, lipolysis, and hepatic acetyl-CoA content – all of which are negatively regulated by leptin – are not only associated but are required for glucose maintenance in starvation: treatment with inhibitors of fat oxidation (etomoxir) and lipolysis (atglistatin) or with an inhibitor of glucocorticoid receptor activity (mifepristone) all resulted in suppression of hepatic glucose production and reductions in plasma glucose and insulin concentrations in starved rats (45). Given the key role of hypoleptinemia and resulting increases in HPA axis activity, lipolysis, hepatic acetyl-CoA, and gluconeogenesis in maintaining plasma glucose concentrations in the starved state, we next sought to determine the signal to the adipocyte to reduce leptin concentrations. Treatment with an inhibitor of glycogen phosphorylase – and thus of glycogenolysis – demonstrated that depletion of hepatic glycogen and resulting reductions in plasma glucose and insulin concentrations could explain reductions in plasma leptin concentrations in fasting rats, whereas infusion of glucose in 48 hr fasted rats to cause modest increases in plasma glucose (5 to 6 mM) and insulin (60 to 100 pM) similar to what was measured in the 16 hr fasted state increased leptin and suppressed corticosterone to concentrations measured in 16 hr fasted rats. Finally, in order to place these findings in the broader physiological context, we performed, to our knowledge, the first assessment of how tissue-specific glucose versus fat/ketone oxidation changes between 0 and 48 hrs of fasting, and demonstrate that all tissues examined (brain, heart, liver, kidney, brown adipose tissue, WAT, and skeletal muscle) shift to varying extents from glucose to fat metabolism as the duration of fasting increases (45). These data demonstrate that starvation induces a shift from glucose to fat metabolism which permits survival by allowing the liver to produce adequate glucose through gluconeogenesis to maintain plasma glucose concentrations within the normal range, thereby preserving glucose supply to the heart, brain, and other tissues critical for survival.

Dose-dependent variations in leptin's physiologic effects

In our hands, leptin plays a key role for glucose maintenance in survival. These data beg the question of why previous studies of the role of leptin under fasting conditions have not elucidated this mechanism. We hypothesized that the failure of some previous studies to elucidate an acute effect of leptin to rapidly lower plasma glucose concentrations in starvation (60) and in T1D (69-71) may be related to the pharmacokinetics of the leptin administration: typically studies examining the impact of leptin have increased plasma leptin concentrations 10-100 times normal. To test the

physiologic impact of supraphysiologic leptin concentrations, we infused stepwise increasing doses of leptin in separate groups of 48 hr fasted and T1D rats and found that while supraphysiologic leptin had no impact on HPA axis activity, which was suppressed by all doses of leptin, high-dose leptin infusion promoted sympathetic activation, increasing WAT lipolysis, hepatic acetyl-CoA content, and gluconeogenesis (45). These data corroborate previous studies in which high concentrations of leptin were shown to cause sympathetic activation by promoting catecholamine synthesis (72) and responsiveness (73), which is reflected in increases in energy expenditure (60, 74-78). Consistent with our findings of the metabolic impact of leptin in the fasted state, whereas Chan et al. found that increasing leptin only to normal fed levels does not affect sympathetic activity in fasting humans (79), Ahrén and Havel have shown that high dose leptin increases plasma glucose and insulin concentrations in 24 hr fasted intact mice, but not in mice that had undergone a chemical sympathectomy. Taken together these data highlight the critical importance of careful selection of a physiological dose and continuous route of administration when testing the physiologic impact of leptin on metabolism.

Physiologic regulation of leptin concentrations

The finding that leptin plays a key role in the maintenance of euglycemia in the prolonged fasted state begs the question of how leptin concentrations are regulated physiologically. To a first approximation, leptin concentrations are typically proportional to fat mass (80-84); however the rapid reductions in leptin observed with starvation, which occur out of proportion to body weight changes (45, 52, 53, 55, 58, 60, 67, 85-88), suggest that an additional regulator beyond simply body fat mass may regulate leptin secretion and in particular its alterations with fasting. Several studies have shown that the combination of hyperglycemia and hyperinsulinemia – as occurs in the postprandial period – increases leptin secretion (54, 89-91), though other reports have failed to demonstrate any effect of feeding or short-term hyperglycemia-hyperinsulinemia on leptin concentrations (92-96). Similarly some (90, 97-108) but not all (94, 96, 109-114) studies indicate that prolonged euglycemic hyperinsulinemia may be sufficient to promote leptin expression or secretion, an effect partially mitigated under hypoglycemic hyperinsulinemic conditions (101, 115). These data led us to hypothesize that reductions in plasma glucose and insulin concentrations in 48 hr fasted rats may explain their reductions in plasma leptin concentrations. Consistent with that hypothesis, infusing 48 hr fasted rats with a low dose of glucose to raise plasma glucose concentrations modestly from 5 to 6 mM, with a consequent 75% increase in plasma insulin concentrations, doubled plasma leptin concentrations and halved plasma corticosterone (45). These data demonstrate that progressive reductions in plasma glucose concentrations signal the adipocyte to reduce leptin secretion, thereby increasing HPA axis activity and WAT lipolysis, both of which are necessary to avoid hypoglycemia in the prolonged fasted state.

Impact of glycogen depletion and substrate limitation in a prolonged fast

Hypoleptinemia resulting from reductions in plasma glucose and insulin concentrations is clearly required for the maintenance of euglycemia in starvation (45). Therefore, it becomes important to understand why plasma glucose – and therefore insulin – concentrations fall as the fasting period progresses, provoking this hypoleptinemia. Using ^{13}C nuclear magnetic resonance (NMR) spectroscopy, Rothman et al. have shown that a 72 hr fast causes progressive reductions in rates of hepatic glycogenolysis in humans, whereas rates of gluconeogenesis remain relatively constant over this three-day period (116). However, neither rates of hepatic glycogenolysis nor substrate contributions to gluconeogenesis had been measured during a prolonged fast in rodents. To that end, we developed a Positional Isotopomer NMR Tracer Analysis (PINTA) method (117) in which a steady-state infusion of [3-^{13}C] lactate and [$^{2}H_7$] glucose is performed, and the positional enrichment of each carbon of plasma or liver glucose is measured by ^{13}C NMR. This method allows investigators to differentiate between rates of each of the pathways contributing to endogenous glucose production: hepatic glycogenolysis and gluconeogenesis from both glycerol and oxaloacetate (i.e. pyruvate carboxylase flux, V_{PC}). In

our recent study, PINTA revealed a progressive decline in rates of hepatic glycogenolysis, with glycogen entirely depleted by 48 hr of fasting. Given the key role of hypoleptinemia and resulting increases in HPA axis activity, lipolysis, hepatic acetyl-CoA, and gluconeogenesis in maintaining plasma glucose concentrations in the starved state, we next sought to determine the signal to the adipocyte to reduce leptin concentrations. Treatment with an inhibitor of glycogen phosphorylase – and thus of glycogenolysis – demonstrated that depletion of hepatic glycogen and resulting reductions in plasma glucose and insulin concentrations could explain reductions in plasma leptin concentrations in fasting rats, whereas infusion of glucose in 48 hr fasted rats to cause modest increases in plasma glucose (5 to 6 mM) and insulin (60 to 100 pM) similar to what was measured in the 16 hr fasted state increased leptin and suppressed corticosterone to concentrations measured in 16 hr fasted rats. Finally, in order to place these findings in the broader physiological context, we performed, to our knowledge, the first assessment of how tissue-specific glucose versus fat/ketone oxidation changes between 0 and 48 hrs of fasting, and demonstrate that all tissues examined (brain, heart, liver, kidney, brown adipose tissue, WAT, and skeletal muscle) shift to varying extents from glucose to fat metabolism as the duration of fasting increases (45). These data demonstrate that starvation induces a shift from glucose to fat metabolism which signals the white adipocyte that the body is running out of energy stores, thus provoking hypercorticosteronemia which in turn stimulates fat mobilization through increases in WAT lipolysis. These increases in lipolysis allow the liver to produce adequate glucose through gluconeogenesis to maintain plasma glucose concentrations within the normal range, thereby preserving glucose supply to the heart, brain, and other tissues critical for survival.

Based on the progressive increases in WAT lipolysis with starvation (2-20), one would predict that rates of gluconeogenesis would progressively increase in the starved state; however, we found the opposite: while V_{PC} increased between short- and moderate-term fasted rats (8 vs. 16 hr), we observed a 50% reduction in hepatic V_{PC} flux between 16 and 48 hr fasting, suggesting that an additional regulator may limit hepatic gluconeogenesis in the starved state. Several groups have observed reductions in alanine release from prolonged fasted humans (118-122), suggesting reductions in whole-body alanine turnover which have been documented in fasting rats (123) and humans (124). We confirmed this reduction in alanine turnover as well as lactate turnover and amino acid concentrations with starvation (45) and hypothesized that substrate limitation may reduce V_{PC} flux in a prolonged fast. Consistent with that hypothesis, alanine replacement increased V_{PC} rates to those measured in recently fed animals. In addition, we observed a substrate-dependent limitation on mitochondrial oxidation rates in starvation: while 48 hr fasted rats exhibited a 50% reduction in hepatic citrate synthase flux (V_{CS}), alanine replacement normalized this flux to rates that were not different from 8 or 16 hr fasted animals (45). These data argue against the well-documented starvation-induced suppression of thyroid function (3, 45, 60, 125-142) as a potential explanation for the reduced energy expenditure that has been observed in periods of fasting or severe caloric restriction (142-152) and instead demonstrate that substrate limitation suppresses rates of hepatic mitochondrial oxidation in the starved state, thereby reducing the body's total energy demands and preserving fuel for the brain, heart, and other organs which are required to function continuously to permit survival.

Role of leptin in starvation in obese individuals

The recent observation that hypoleptinemia is required to drive a glucose-fatty acid cycle that maintains adequate plasma glucose concentrations in fasting rats (45) has also been explored to an extent in humans. While leptin clearly falls with fasting in humans (8, 51-59, 61-65, 68), plasma cortisol data in fasting humans are variable, with some studies demonstrating increases in cortisol with fasting or severe caloric restriction (68, 153-161), while others failed to observe any increase in glucocorticoid concentrations associated with caloric deprivation (58, 137, 152, 162). Variable leptin responses to fasting in human studies may result

from the higher adipose tissue mass that is typical in humans: whereas young, lean rodents almost entirely deplete their subcutaneous adipose tissue after several days of fasting, thereby lowering leptin concentrations below a threshold capable of stimulating the HPA axis, a much longer fast may be required to reduce leptin below this critical threshold in humans. Consistent with this hypothesis, individuals with anorexia exhibit both hypoleptinemia and hypercortisolemia (163-176), whereas obese subjects exhibit a blunting of the reductions in leptin (45, 52, 53, 55, 56, 109, 177, 178) and increases in glucocorticoids (45, 179, 180) generated by hypocaloric feeding. These findings have led investigators to formulate the concept of "leptin resistance" in obesity (181-183). However this hypothesis is largely based on the increased circulating leptin concentrations observed in obesity – which may be the result of expanded fat mass in the obese state – as the lack of a physiologic response to leptin in the obese state may in many cases simply reflect the inability of appetite regulatory mechanisms to respond to changes from high leptin (typical of obesity) to even higher leptin during leptin treatment. In addition, further studies would be needed to determine whether there is a threshold for plasma leptin concentrations below which the HPA axis is stimulated, what this is, and how it relates to weight loss in fasting human subjects.

Conclusion

Twenty-four years after the discovery of leptin, despite thousands of studies and hundreds of reviews on its function, the precise role of leptin in starvation remains a topic of active investigation. Recent work suggests that leptin plays a pleiotropic role in regulation of physiologic homeostasis in starvation, modulating the adrenal, thyroid, and gonadal responses to starvation by divergent mechanisms. With regard to metabolic regulation, hypoleptinemia resulting from reductions in plasma glucose and insulin concentrations and consequent suppression of WAT glucose uptake triggers a glucose-fatty acid cycle that promotes increased lipolysis, hepatic acetyl-CoA, and pyruvate carboxylase flux in starvation. Therefore, leptin may be a key signal which reflects hepatic glycogen stores and signals the adipocyte when glycogen is depleted, requiring a shift from glucose to fat metabolism in order to maintain glucose supply for the brain, heart, and other obligate glucose-utilizing organs, permitting survival in starvation.

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