Published in final edited form as:

Postdoc J. 2018 March ; 6(3): 3–19. doi:10.14304/surya.jpr.v6n3.2.

The Role of Leptin in Maintaining Plasma Glucose During Starvation

Rachel J. Perry¹ and Gerald I. Shulman^{1,2,3}

¹Department of Internal Medicine, Yale University School of Medicine

²Department of Cellular & Molecular Physiology, Yale University School of Medicine

³Howard 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 not sufficient 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), Åhrén 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 $[3-^{13}\text{C}]$ lactate and $[2\text{H}_7]$ 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 hypercorticotestosterone 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.

Acknowledgments

The authors' work is funded by grants from the United States Public Health Service (K99 CA215315, R01 DK113984, R01 DK40936, P30 DK059635, T32 DK101019, UL1TR000142).

References

1. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature*. 1994; 372(6505):425–32. DOI: 10.1038/372425a0 [PubMed: 7984236]
2. Garber AJ, Menzel PH, Boden G, Owen OE. Hepatic ketogenesis and gluconeogenesis in humans. *The Journal of clinical investigation*. 1974; 54(4):981–9. DOI: 10.1172/JCI107839 [PubMed: 4430728]
3. Cahill GF Jr. Starvation in man. *Clin Endocrinol Metab*. 1976; 5(2):397–415. [PubMed: 182420]
4. Kerndt PR, Naughton JL, Driscoll CE, Loxterkamp DA. Fasting: the history, pathophysiology and complications. *West J Med*. 1982; 137(5):379–99. [PubMed: 6758355]
5. Soeters MR, Soeters PB, Schooneman MG, Houten SM, Romijn JA. Adaptive reciprocity of lipid and glucose metabolism in human short-term starvation. *American journal of physiology*

- Endocrinology and metabolism. 2012; 303(12):E1397–407. DOI: 10.1152/ajpendo.00397.2012 [PubMed: 23074240]
6. Viscarra JA, Vazquez-Medina JP, Rodriguez R, Champagne CD, Adams SH, Crocker DE, Ortiz RM. Decreased expression of adipose CD36 and FATP1 are associated with increased plasma non-esterified fatty acids during prolonged fasting in northern elephant seal pups (*Mirounga angustirostris*). *J Exp Biol*. 2012; 215(Pt 14):2455–64. DOI: 10.1242/jeb.069070 [PubMed: 22723485]
 7. Viscarra JA, Ortiz RM. Cellular mechanisms regulating fuel metabolism in mammals: role of adipose tissue and lipids during prolonged food deprivation. *Metabolism: clinical and experimental*. 2013; 62(7):889–97. DOI: 10.1016/j.metabol.2012.12.014 [PubMed: 23357530]
 8. Foo JP, Aronis KN, Chamberland JP, Paruthi J, Moon HS, Mantzoros CS. Fibroblast growth factor 21 levels in young healthy females display day and night variations and are increased in response to short-term energy deprivation through a leptin-independent pathway. *Diabetes care*. 2013; 36(4):935–42. DOI: 10.2337/dc12-0497 [PubMed: 23193213]
 9. Dias WJ, Baviera AM, Zanon NM, Galban VD, Garofalo MA, Machado CR, Bailao EF, Kettelhut IC. Lipolytic response of adipose tissue and metabolic adaptations to long periods of fasting in red tilapia (*Oreochromis sp.*, Teleostei: Cichlidae). *An Acad Bras Cienc*. 2016; 88(3 Suppl):1743–54. DOI: 10.1590/0001-3765201620150484 [PubMed: 27556329]
 10. Carlson MG, Snead WL, Campbell PJ. Fuel and energy metabolism in fasting humans. *The American journal of clinical nutrition*. 1994; 60(1):29–36. [PubMed: 8017334]
 11. Klein S, Young VR, Blackburn GL, Bistrian BR, Wolfe RR. Palmitate and glycerol kinetics during brief starvation in normal weight young adult and elderly subjects. *The Journal of clinical investigation*. 1986; 78(4):928–33. DOI: 10.1172/JCI112682 [PubMed: 3760192]
 12. Wolfe RR, Peters EJ, Klein S, Holland OB, Rosenblatt J, Gary H Jr. Effect of short-term fasting on lipolytic responsiveness in normal and obese human subjects. *The American journal of physiology*. 1987; 252(2 Pt 1):E189–96. DOI: 10.1152/ajpendo.1987.252.2.E189 [PubMed: 3548419]
 13. Jensen MD, Haymond MW, Gerich JE, Cryer PE, Miles JM. Lipolysis during fasting. Decreased suppression by insulin and increased stimulation by epinephrine. *The Journal of clinical investigation*. 1987; 79(1):207–13. DOI: 10.1172/JCI112785 [PubMed: 3540009]
 14. Klein S, Peters EJ, Holland OB, Wolfe RR. Effect of short- and long-term beta-adrenergic blockade on lipolysis during fasting in humans. *The American journal of physiology*. 1989; 257(1 Pt 1):E65–73. DOI: 10.1152/ajpendo.1989.257.1.E65 [PubMed: 2546438]
 15. Browning JD, Baxter J, Satapati S, Burgess SC. The effect of short-term fasting on liver and skeletal muscle lipid, glucose, and energy metabolism in healthy women and men. *Journal of lipid research*. 2012; 53(3):577–86. DOI: 10.1194/jlr.P020867 [PubMed: 22140269]
 16. Baba H, Zhang XJ, Wolfe RR. Glycerol gluconeogenesis in fasting humans. *Nutrition*. 1995; 11(2):149–53. Epub 1995/03/01. [PubMed: 7647479]
 17. Newman WP, Brodows RG. Insulin action during acute starvation: evidence for selective insulin resistance in normal man. *Metabolism: clinical and experimental*. 1983; 32(6):590–6. [PubMed: 6341773]
 18. Owen OE, Reichard GA Jr, Patel MS, Boden G. Energy metabolism in feasting and fasting. *Advances in experimental medicine and biology*. 1979; 111:169–88. [PubMed: 371355]
 19. Merimee TJ, Misbin RI, Pulkkinen AJ. Sex variations in free fatty acids and ketones during fasting: evidence for a role of glucagon. *The Journal of clinical endocrinology and metabolism*. 1978; 46(3):414–9. DOI: 10.1210/jcem-46-3-414 [PubMed: 752030]
 20. Brodows RG, Campbell RG, Al-Aziz AJ. Lack of central autonomic regulation of substrate during early fasting in man. *Metabolism: clinical and experimental*. 1976; 25(7):803–7. [PubMed: 781469]
 21. Perry RJ, Camporez JP, Kursawe R, Titchenell PM, Zhang D, Perry CJ, Jurczak MJ, Abudukadier A, Han MS, Zhang XM, Ruan HB, Yang X, Caprio S, Kaech SM, Sul HS, Birnbaum MJ, Davis RJ, Cline GW, Petersen KF, Shulman GI. Hepatic Acetyl CoA Links Adipose Tissue Inflammation to Hepatic Insulin Resistance and Type 2 Diabetes. *Cell*. 2015; 160(4):745–58. Epub 2015/02/11. DOI: 10.1016/j.cell.2015.01.012 [PubMed: 25662011]

22. Scrutton MC, Keech DB, Utter MF. Pyruvate Carboxylase. Iv. Partial Reactions and the Locus of Activation by Acetyl Coenzyme A. The Journal of biological chemistry. 1965; 240:574–81. Epub 1965/02/01. [PubMed: 14275106]
23. Utter MF, Keech DB. Formation of oxaloacetate from pyruvate and carbon dioxide. The Journal of biological chemistry. 1960; 235:PC17–8. Epub 1960/05/01. [PubMed: 13840551]
24. Utter MF, Keech DB, Scrutton MC. A possible role for acetyl CoA in the control of gluconeogenesis. Advances in enzyme regulation. 1964; 2:49–68. Epub 1964/01/01. [PubMed: 5863094]
25. Previs SF, Cline GW, Shulman GI. A critical evaluation of mass isotopomer distribution analysis of gluconeogenesis in vivo. The American journal of physiology. 1999; 277(1 Pt 1):E154–60. [PubMed: 10409139]
26. Froesch ER, Burgi H, Bally P, Labhart A. Insulin inhibition of spontaneous adipose tissue lipolysis and effects upon fructose and glucose metabolism. Mol Pharmacol. 1965; 1(3):280–96. [PubMed: 5842826]
27. Strubbe JH, Prins AJ. Reduced insulin secretion after short-term food deprivation in rats plays a key role in the adaptive interaction of glucose and free fatty acid utilization. Physiol Behav. 1986; 37(3):441–5. [PubMed: 3529144]
28. Yki-Jarvinen H, Taskinen MR. Interrelationships among insulin's antilipolytic and glucoregulatory effects and plasma triglycerides in nondiabetic and diabetic patients with endogenous hypertriglyceridemia. Diabetes. 1988; 37(9):1271–8. [PubMed: 3044892]
29. Horowitz JF, Coppack SW, Paramore D, Cryer PE, Zhao G, Klein S. Effect of short-term fasting on lipid kinetics in lean and obese women. The American journal of physiology. 1999; 276(2 Pt 1):E278–84. [PubMed: 9950787]
30. Soliman AT, ElZalabany MM, Salama M, Ansari BM. Serum leptin concentrations during severe protein-energy malnutrition: correlation with growth parameters and endocrine function. Metabolism: clinical and experimental. 2000; 49(7):819–25. DOI: 10.1053/meta.2000.6745 [PubMed: 10909989]
31. Navegantes LC, Sjostrand M, Gudbjornsdottir S, Strindberg L, Elam M, Lonnroth P. Regulation and counterregulation of lipolysis in vivo: different roles of sympathetic activation and insulin. The Journal of clinical endocrinology and metabolism. 2003; 88(11):5515–20. DOI: 10.1210/jc.2003-030445 [PubMed: 14602799]
32. Kershaw EE, Hamm JK, Verhagen LA, Peroni O, Katic M, Flier JS. Adipose triglyceride lipase: function, regulation by insulin, and comparison with adiponutrin. Diabetes. 2006; 55(1):148–57. [PubMed: 16380488]
33. Wang T, Zang Y, Ling W, Corkey BE, Guo W. Metabolic partitioning of endogenous fatty acid in adipocytes. Obes Res. 2003; 11(7):880–7. DOI: 10.1038/oby.2003.121 [PubMed: 12855758]
34. Wang B, Moya N, Niessen S, Hoover H, Mihaylova MM, Shaw RJ, Yates JR 3rd, Fischer WH, Thomas JB, Montminy M. A hormone-dependent module regulating energy balance. Cell. 2011; 145(4):596–606. DOI: 10.1016/j.cell.2011.04.013 [PubMed: 21565616]
35. Scherer T, Buettner C. Yin and Yang of hypothalamic insulin and leptin signaling in regulating white adipose tissue metabolism. Rev Endocr Metab Disord. 2011; 12(3):235–43. DOI: 10.1007/s11154-011-9190-4 [PubMed: 21713385]
36. Engfeldt P, Bolinder J, Ostman J, Arner P. Influence of fasting and refeeding on the antilipolytic effect of insulin in human fat cells obtained from obese subjects. Diabetes. 1985; 34(11):1191–7. [PubMed: 3899815]
37. Szkudelski T, Lisiecka M, Nowicka E, Kowalewska A, Nogowski L, Szkudelska K. Short-term fasting and lipolytic activity in rat adipocytes. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme. 2004; 36(10):667–73. DOI: 10.1055/s-2004-826012 [PubMed: 15523590]
38. Gjedsted J, Gormsen LC, Nielsen S, Schmitz O, Djurhuus CB, Keiding S, Orskov H, Tonnesen E, Moller N. Effects of a 3-day fast on regional lipid and glucose metabolism in human skeletal muscle and adipose tissue. Acta Physiol (Oxf). 2007; 191(3):205–16. DOI: 10.1111/j.1748-1716.2007.01740.x [PubMed: 17784905]

39. Klein S, Holland OB, Wolfe RR. Importance of blood glucose concentration in regulating lipolysis during fasting in humans. *The American journal of physiology*. 1990; 258(1 Pt 1):E32–9. DOI: 10.1152/ajpendo.1990.258.1.E32 [PubMed: 2405701]
40. Perry RJ, Petersen KF, Shulman GI. Pleiotropic effects of leptin to reverse insulin resistance and diabetic ketoacidosis. *Diabetologia*. 2016; 59(5):933–7. DOI: 10.1007/s00125-016-3909-4 [PubMed: 26961503]
41. Perry RJ. Pleiotropic Acute and Chronic Effects of Leptin to Reverse Type 1 Diabetes. *Postdoc J*. 2017; 5(1):3–11.
42. Perry RJ, Zhang XM, Zhang D, Kumashiro N, Camporez JP, Cline GW, Rothman DL, Shulman GI. Leptin reverses diabetes by suppression of the hypothalamic-pituitary-adrenal axis. *Nature medicine*. 2014 Epub 2014/06/16.
43. Perry RJ, Peng L, Abulizi A, Kennedy L, Cline GW, Shulman GI. Mechanism for leptin's acute insulin-independent effect to reverse diabetic ketoacidosis. *The Journal of clinical investigation*. 2017; 127(2):657–69. DOI: 10.1172/JCI88477 [PubMed: 28112679]
44. Perry RJ, Lee S, Ma L, Zhang D, Schlessinger J, Shulman GI. FGF1 and FGF19 reverse diabetes by suppression of the hypothalamic-pituitary-adrenal axis. *Nature communications*. 2015; 6:6980.doi: 10.1038/ncomms7980
45. Perry RJ, Wang Y, Cline GW, Rabin-Court A, Song JD, Dufour S, Zhang XM, Petersen KF, Shulman GI. Leptin Mediates a Glucose-Fatty Acid Cycle to Maintain Glucose Homeostasis in Starvation. *Cell*. 2018; 172(1–2):234–48e17. DOI: 10.1016/j.cell.2017.12.001 [PubMed: 29307489]
46. Trayhurn P, Thomas ME, Duncan JS, Rayner DV. Effects of fasting and refeeding on ob gene expression in white adipose tissue of lean and obese (ob/ob) mice. *FEBS letters*. 1995; 368(3): 488–90. [PubMed: 7635205]
47. MacDougald OA, Hwang CS, Fan H, Lane MD. Regulated expression of the obese gene product (leptin) in white adipose tissue and 3T3-L1 adipocytes. *Proceedings of the National Academy of Sciences of the United States of America*. 1995; 92(20):9034–7. [PubMed: 7568067]
48. Moinat M, Deng C, Muzzin P, Assimacopoulos-Jeannet F, Seydoux J, Dulloo AG, Giacobino JP. Modulation of obese gene expression in rat brown and white adipose tissues. *FEBS letters*. 1995; 373(2):131–4. [PubMed: 7589451]
49. Hardie LJ, Rayner DV, Holmes S, Trayhurn P. Circulating leptin levels are modulated by fasting, cold exposure and insulin administration in lean but not Zucker (fa/fa) rats as measured by ELISA. *Biochemical and biophysical research communications*. 1996; 223(3):660–5. DOI: 10.1006/bbrc.1996.0951 [PubMed: 8687452]
50. Igel M, Kainulainen H, Brauers A, Becker W, Herberg L, Joost HG. Long-term and rapid regulation of ob mRNA levels in adipose tissue from normal (Sprague Dawley rats) and obese (db/db mice, fa/fa rats) rodents. *Diabetologia*. 1996; 39(7):758–65. [PubMed: 8817099]
51. Sinha MK, Opentanova I, Ohannesian JP, Kolaczynski JW, Heiman ML, Hale J, Becker GW, Bowsher RR, Stephens TW, Caro JF. Evidence of free and bound leptin in human circulation. Studies in lean and obese subjects and during short-term fasting. *The Journal of clinical investigation*. 1996; 98(6):1277–82. DOI: 10.1172/JCI118913 [PubMed: 8823291]
52. Klein S, Horowitz JF, Landt M, Goodrick SJ, Mohamed-Ali V, Coppack SW. Leptin production during early starvation in lean and obese women. *American journal of physiology Endocrinology and metabolism*. 2000; 278(2):E280–4. [PubMed: 10662712]
53. Horowitz JF, Coppack SW, Klein S. Whole-body and adipose tissue glucose metabolism in response to short-term fasting in lean and obese women. *The American journal of clinical nutrition*. 2001; 73(3):517–22. [PubMed: 11237926]
54. Stefan N, Fritsche A, Haring H, Stumvoll M. Acute stimulation of leptin concentrations in humans during hyperglycemic hyperinsulinemia. Influence of free fatty acids and fasting. *International journal of obesity and related metabolic disorders: journal of the International Association for the Study of Obesity*. 2001; 25(1):138–42.
55. Haluzik M, Matoulek M, Svacina S, Hilgertova J, Haas T. The influence of short-term fasting on serum leptin levels, and selected hormonal and metabolic parameters in morbidly obese and lean females. *Endocrine research*. 2001; 27(1–2):251–60. [PubMed: 11428717]

56. Landt M, Horowitz JF, Coppack SW, Klein S. Effect of short-term fasting on free and bound leptin concentrations in lean and obese women. *The Journal of clinical endocrinology and metabolism*. 2001; 86(8):3768–71. DOI: 10.1210/jcem.86.8.7771 [PubMed: 11502809]
57. Sonnenberg GE, Krakower GR, Hoffmann RG, Maas DL, Hennes MM, Kissebah AH. Plasma leptin concentrations during extended fasting and graded glucose infusions: relationships with changes in glucose, insulin, and FFA. *The Journal of clinical endocrinology and metabolism*. 2001; 86(10):4895–900. DOI: 10.1210/jcem.86.10.7951 [PubMed: 11600559]
58. Chan JL, Heist K, DePaoli AM, Veldhuis JD, Mantzoros CS. The role of falling leptin levels in the neuroendocrine and metabolic adaptation to short-term starvation in healthy men. *The Journal of clinical investigation*. 2003; 111(9):1409–21. DOI: 10.1172/JCI17490 [PubMed: 12727933]
59. Chan JL, Bullen J, Lee JH, Yiannakouris N, Mantzoros CS. Ghrelin levels are not regulated by recombinant leptin administration and/or three days of fasting in healthy subjects. *The Journal of clinical endocrinology and metabolism*. 2004; 89(1):335–43. DOI: 10.1210/jc.2003-031412 [PubMed: 14715869]
60. Ahima RS, Prabakaran D, Mantzoros C, Qu D, Lowell B, Maratos-Flier E, Flier JS. Role of leptin in the neuroendocrine response to fasting. *Nature*. 1996; 382(6588):250–2. DOI: 10.1038/382250a0 [PubMed: 8717038]
61. Hoggard N, Johnstone AM, Faber P, Gibney ER, Elia M, Lobley G, Rayner V, Horgan G, Hunter L, Bashir S, Stubbs RJ. Plasma concentrations of alpha-MSH, AgRP and leptin in lean and obese men and their relationship to differing states of energy balance perturbation. *Clinical endocrinology*. 2004; 61(1):31–9. DOI: 10.1111/j.1365-2265.2004.02056.x [PubMed: 15212642]
62. Levitt Katz LE, Abraham M, Johansen L, Jawad AF. Leptin levels decline steadily during prolonged fasting in lean children. *The Journal of pediatrics*. 2006; 149(6):798–802. DOI: 10.1016/j.jpeds.2006.08.029 [PubMed: 17137895]
63. Chen H, Morris MJ. Differential responses of orexigenic neuropeptides to fasting in offspring of obese mothers. *Obesity*. 2009; 17(7):1356–62. DOI: 10.1038/oby.2009.56 [PubMed: 19282828]
64. Moragianni VA, Aronis KN, Chamberland JP, Mantzoros CS. Short-term energy deprivation alters activin a and follistatin but not inhibin B levels of lean healthy women in a leptin-independent manner. *The Journal of clinical endocrinology and metabolism*. 2011; 96(12):3750–8. DOI: 10.1210/jc.2011-1453 [PubMed: 21917874]
65. van Herpen NA, Sell H, Eckel J, Schrauwen P, Mensink RP. Prolonged fasting and the effects on biomarkers of inflammation and on adipokines in healthy lean men. *Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme*. 2013; 45(5):378–82. DOI: 10.1055/s-0032-1330015 [PubMed: 23235922]
66. Li Y, Li R, Chen W, Chen G. Vitamin A status and its metabolism contribute to the regulation of hepatic genes during the cycle of fasting and refeeding in rats. *The Journal of nutritional biochemistry*. 2016; 30:33–43. DOI: 10.1016/j.jnutbio.2015.11.012 [PubMed: 27012619]
67. Vujovic P, Lakic I, Laketa D, Jasnic N, Djurasevic SF, Cvijic G, Djordjevic J. Time-dependent effects of starvation on serum, pituitary and hypothalamic leptin levels in rats. *Physiological research/Academia Scientiarum Bohemoslovaca*. 2011; 60(Suppl 1):S165–70.
68. Gundersen Y, Opstad PK, Reistad T, Thrane I, Vaagenes P. Seven days' around the clock exhaustive physical exertion combined with energy depletion and sleep deprivation primes circulating leukocytes. *Eur J Appl Physiol*. 2006; 97(2):151–7. DOI: 10.1007/s00421-006-0150-8 [PubMed: 16506059]
69. Morton GJ, Meek TH, Matsen ME, Schwartz MW. Evidence against hypothalamic-pituitary-adrenal axis suppression in the antidiabetic action of leptin. *The Journal of clinical investigation*. 2015; 2015doi: 10.1172/JCI82723
70. Denroche HC, Kwon MM, Quong WL, Neumann UH, Kulpa JE, Karunakaran S, Clee SM, Brownsey RW, Covey SD, Kieffer TJ. Leptin induces fasting hypoglycaemia in a mouse model of diabetes through the depletion of glycerol. *Diabetologia*. 2015; 58(5):1100–8. DOI: 10.1007/s00125-015-3529-4 [PubMed: 25715699]
71. Denroche HC, Levi J, Wideman RD, Sequeira RM, Huynh FK, Covey SD, Kieffer TJ. Leptin therapy reverses hyperglycemia in mice with streptozotocin-induced diabetes, independent of hepatic leptin signaling. *Diabetes*. 2011; 60(5):1414–23. DOI: 10.2337/db10-0958 [PubMed: 21464443]

72. Shibuya I, Utsunomiya K, Toyohira Y, Ueno S, Tsutsui M, Cheah TB, Ueta Y, Izumi F, Yanagihara N. Regulation of catecholamine synthesis by leptin. *Annals of the New York Academy of Sciences*. 2002; 971:522–7. [PubMed: 12438173]
73. Luan B, Goodarzi MO, Phillips NG, Guo X, Chen YD, Yao J, Allison M, Rotter JI, Shaw R, Montminy M. Leptin-mediated increases in catecholamine signaling reduce adipose tissue inflammation via activation of macrophage HDAC4. *Cell metabolism*. 2014; 19(6):1058–65. DOI: 10.1016/j.cmet.2014.03.024 [PubMed: 24768298]
74. Harris RB, Zhou J, Redmann SM Jr, Smagin GN, Smith SR, Rodgers E, Zachwieja JJ. A leptin dose-response study in obese (ob/ob) and lean (+/?) mice. *Endocrinology*. 1998; 139(1):8–19. DOI: 10.1210/endo.139.1.5675 [PubMed: 9421392]
75. Harris RB, Mitchell TD, Yan X, Simpson JS, Redmann SM Jr. Metabolic responses to leptin in obese db/db mice are strain dependent. *American journal of physiology Regulatory, integrative and comparative physiology*. 2001; 281(1):R115–32.
76. Pellemounter MA, Cullen MJ, Baker MB, Hecht R, Winters D, Boone T, Collins F. Effects of the obese gene product on body weight regulation in ob/ob mice. *Science*. 1995; 269(5223):540–3. [PubMed: 7624776]
77. Rosenbaum M, Goldsmith R, Bloomfield D, Magnano A, Weimer L, Heymsfield S, Gallagher D, Mayer L, Murphy E, Leibel RL. Low-dose leptin reverses skeletal muscle, autonomic, and neuroendocrine adaptations to maintenance of reduced weight. *The Journal of clinical investigation*. 2005; 115(12):3579–86. DOI: 10.1172/JCI25977 [PubMed: 16322796]
78. Rosenbaum M, Murphy EM, Heymsfield SB, Matthews DE, Leibel RL. Low dose leptin administration reverses effects of sustained weight-reduction on energy expenditure and circulating concentrations of thyroid hormones. *The Journal of clinical endocrinology and metabolism*. 2002; 87(5):2391–4. DOI: 10.1210/jcem.87.5.8628 [PubMed: 11994393]
79. Chan JL, Mietus JE, Raciti PM, Goldberger AL, Mantzoros CS. Short-term fasting-induced autonomic activation and changes in catecholamine levels are not mediated by changes in leptin levels in healthy humans. *Clinical endocrinology*. 2007; 66(1):49–57. DOI: 10.1111/j.1365-2265.2006.02684.x [PubMed: 17201801]
80. Wahlen K, Sjolín E, Lofgren P. Role of fat cell size for plasma leptin in a large population based sample. *Exp Clin Endocrinol Diabetes*. 2011; 119(5):291–4. DOI: 10.1055/s-0031-1273738 [PubMed: 21560103]
81. Maffei M, Halaas J, Ravussin E, Pratley RE, Lee GH, Zhang Y, Fei H, Kim S, Lallone R, Ranganathan S, et al. Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. *Nature medicine*. 1995; 1(11):1155–61.
82. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, Ohannesian JP, Marco CC, McKee LJ, Bauer TL, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *The New England journal of medicine*. 1996; 334(5):292–5. DOI: 10.1056/NEJM199602013340503 [PubMed: 8532024]
83. Holm JC, Gamborg M, Ward L, Ibsen KK, Gammeltuft S, Sorensen TI, Heitmann BL. Longitudinal analysis of leptin variation during weight regain after weight loss in obese children. *Obes Facts*. 2009; 2(4):243–8. DOI: 10.1159/000226619 [PubMed: 20054230]
84. Frederich RC, Hamann A, Anderson S, Lollmann B, Lowell BB, Flier JS. Leptin levels reflect body lipid content in mice: evidence for diet-induced resistance to leptin action. *Nature medicine*. 1995; 1(12):1311–4.
85. Frederich RC, Lollmann B, Hamann A, Napolitano-Rosen A, Kahn BB, Lowell BB, Flier JS. Expression of ob mRNA and its encoded protein in rodents. Impact of nutrition and obesity. *The Journal of clinical investigation*. 1995; 96(3):1658–63. DOI: 10.1172/JCI118206 [PubMed: 7657836]
86. Boden G, Chen X, Mozzoli M, Ryan I. Effect of fasting on serum leptin in normal human subjects. *The Journal of clinical endocrinology and metabolism*. 1996; 81(9):3419–23. DOI: 10.1210/jcem.81.9.8784108 [PubMed: 8784108]
87. Chan JL, Matarese G, Shetty GK, Raciti P, Kelesidis I, Aufiero D, De Rosa V, Perna F, Fontana S, Mantzoros CS. Differential regulation of metabolic, neuroendocrine, and immune function by leptin in humans. *Proceedings of the National Academy of Sciences of the United States of America*. 2006; 103(22):8481–6. DOI: 10.1073/pnas.0505429103 [PubMed: 16714386]

88. Nuttall FQ, Almokayyad RM, Gannon MC. The ghrelin and leptin responses to short-term starvation vs a carbohydrate-free diet in men with type 2 diabetes; a controlled, cross-over design study. *Nutr Metab (Lond)*. 2016; 13:47.doi: 10.1186/s12986-016-0106-x [PubMed: 27453716]
89. Levy JR, Lesko J, Krieg RJ Jr, Adler RA, Stevens W. Leptin responses to glucose infusions in obesity-prone rats. *American journal of physiology Endocrinology and metabolism*. 2000; 279(5):E1088–96. DOI: 10.1152/ajpendo.2000.279.5.E1088 [PubMed: 11052964]
90. Faraj M, Beauregard G, Tardif A, Loizon E, Godbout A, Cianflone K, Vidal H, Rabasa-Lhoret R. Regulation of leptin, adiponectin and acylation-stimulating protein by hyperinsulinaemia and hyperglycaemia in vivo in healthy lean young men. *Diabetes Metab*. 2008; 34(4 Pt 1):334–42. DOI: 10.1016/j.diabet.2008.01.014 [PubMed: 18562232]
91. Romon M, Lebel P, Velly C, Marecaux N, Fruchart JC, Dallongeville J. Leptin response to carbohydrate or fat meal and association with subsequent satiety and energy intake. *The American journal of physiology*. 1999; 277(5 Pt 1):E855–61. [PubMed: 10567012]
92. Shalev A, Vosmeer S, Keller U. Absence of short-term effects of glucagon-like peptide-1 and of hyperglycemia on plasma leptin levels in man. *Metabolism: clinical and experimental*. 1997; 46(7):723–5. [PubMed: 9225821]
93. Korbonits M, Trainer PJ, Little JA, Edwards R, Kopelman PG, Besser GM, Svec F, Grossman AB. Leptin levels do not change acutely with food administration in normal or obese subjects, but are negatively correlated with pituitary-adrenal activity. *Clinical endocrinology*. 1997; 46(6):751–7. [PubMed: 9274707]
94. Dagogo-Jack S, Fanelli C, Paramore D, Brothers J, Landt M. Plasma leptin and insulin relationships in obese and nonobese humans. *Diabetes*. 1996; 45(5):695–8. [PubMed: 8621026]
95. Drewes C, Nauck MA, Horn R, Holst J, Schmiegel W, Brabant G. A liquid mixed meal or exogenous glucagon-like peptide 1 (GLP-1) do not alter plasma leptin concentrations in healthy volunteers. *Acta diabetologica*. 1997; 34(3):230–4. [PubMed: 9401646]
96. Schultes B, Peters A, Hallschmid M, Benedict C, Merl V, Oltmanns KM, Born J, Fehm HL, Kern W. Modulation of food intake by glucose in patients with type 2 diabetes. *Diabetes care*. 2005; 28(12):2884–9. [PubMed: 16306549]
97. Saad MF, Khan A, Sharma A, Michael R, Riad-Gabriel MG, Boyadjian R, Jinagouda SD, Steil GM, Kamdar V. Physiological insulinemia acutely modulates plasma leptin. *Diabetes*. 1998; 47(4):544–9. [PubMed: 9568685]
98. Malmstrom R, Taskinen MR, Karonen SL, Yki-Jarvinen H. Insulin increases plasma leptin concentrations in normal subjects and patients with NIDDM. *Diabetologia*. 1996; 39(8):993–6. [PubMed: 8858224]
99. Utriainen T, Malmstrom R, Makimattila S, Yki-Jarvinen H. Supraphysiological hyperinsulinemia increases plasma leptin concentrations after 4 h in normal subjects. *Diabetes*. 1996; 45(10):1364–6. [PubMed: 8826972]
100. Kolaczynski JW, Nyce MR, Considine RV, Boden G, Nolan JJ, Henry R, Mudaliar SR, Olefsky J, Caro JF. Acute and chronic effects of insulin on leptin production in humans: Studies in vivo and in vitro. *Diabetes*. 1996; 45(5):699–701. [PubMed: 8621027]
101. Schmitz O, Fisker S, Orskov L, Hove KY, Nyholm B, Moller N. Effects of hyperinsulinaemia and hypoglycaemia on circulating leptin levels in healthy lean males. *Diabetes Metab*. 1997; 23(1):80–3. [PubMed: 9059771]
102. Pagano C, Englaro P, Granzotto M, Blum WF, Sagrillo E, Ferretti E, Federspil G, Vettor R. Insulin induces rapid changes of plasma leptin in lean but not in genetically obese (fa/fa) rats. *International journal of obesity and related metabolic disorders: journal of the International Association for the Study of Obesity*. 1997; 21(7):614–8.
103. Andersen PH, Kristensen K, Pedersen SB, Højlund E, Schmitz O, Richelsen B. Effects of long-term total fasting and insulin on ob gene expression in obese patients. *European journal of endocrinology/European Federation of Endocrine Societies*. 1997; 137(3):229–33.
104. Koopmans SJ, Frolich M, Gribnau EH, Westendorp RG, DeFronzo RA. Effect of hyperinsulinemia on plasma leptin concentrations and food intake in rats. *The American journal of physiology*. 1998; 274(6 Pt 1):E998–E1001. [PubMed: 9611148]

105. Pratley RE, Ren K, Milner MR, Sell SM. Insulin increases leptin mRNA expression in abdominal subcutaneous adipose tissue in humans. *Mol Genet Metab*. 2000; 70(1):19–26. DOI: 10.1006/mgme.2000.2995 [PubMed: 10833328]
106. Boden G, Chen X, Kolaczynski JW, Polansky M. Effects of prolonged hyperinsulinemia on serum leptin in normal human subjects. *The Journal of clinical investigation*. 1997; 100(5):1107–13. DOI: 10.1172/JCI119621 [PubMed: 9276727]
107. Ludwig AK, Weiss JM, Tauchert S, Dietze T, Rudolf S, Diedrich K, Peters A, Oltmanns KM. Influence of hypo- and hyperglycaemia on plasma leptin concentrations in healthy women and in women with polycystic ovary syndrome. *Hum Reprod*. 2007; 22(6):1555–61. DOI: 10.1093/humrep/dem041 [PubMed: 17395684]
108. Aas AM, Hanssen KF, Berg JP, Thorsby PM, Birkeland KI. Insulin-stimulated increase in serum leptin levels precedes and correlates with weight gain during insulin therapy in type 2 diabetes. *The Journal of clinical endocrinology and metabolism*. 2009; 94(8):2900–6. DOI: 10.1210/jc.2008-1005 [PubMed: 19509109]
109. Vidal H, Auboeuf D, De Vos P, Staels B, Riou JP, Auwerx J, Laville M. The expression of ob gene is not acutely regulated by insulin and fasting in human abdominal subcutaneous adipose tissue. *The Journal of clinical investigation*. 1996; 98(2):251–5. DOI: 10.1172/JCI118786 [PubMed: 8755631]
110. Muscelli E, Camastra S, Masoni A, Baldi S, Sironi AM, Natali A, Ferrannini E. Acute insulin administration does not affect plasma leptin levels in lean or obese subjects. *Eur J Clin Invest*. 1996; 26(10):940–3. [PubMed: 8911870]
111. Pratley RE, Nicolson M, Bogardus C, Ravussin E. Effects of acute hyperinsulinemia on plasma leptin concentrations in insulin-sensitive and insulin-resistant Pima Indians. *The Journal of clinical endocrinology and metabolism*. 1996; 81(12):4418–21. DOI: 10.1210/jcem.81.12.8954052 [PubMed: 8954052]
112. Hotta K, Gustafson TA, Ortmeyer HK, Bodkin NL, Nicolson MA, Hansen BC. Regulation of obese (ob) mRNA and plasma leptin levels in rhesus monkeys. Effects of insulin, body weight, and non-insulin-dependent diabetes mellitus. *The Journal of biological chemistry*. 1996; 271(41):25327–31. [PubMed: 8810296]
113. Fisher JS, Hickner RC, Racette SB, Binder EF, Landt M, Kohrt WM. Leptin response to insulin in humans is related to the lipolytic state of abdominal subcutaneous fat. *The Journal of clinical endocrinology and metabolism*. 1999; 84(10):3726–31. DOI: 10.1210/jcem.84.10.6049 [PubMed: 10523021]
114. Gibson W, Liu J, Gaylinn B, Thorner MO, Meneilly GS, Babich SL, Thompson D, Chanoine JP. Effects of glucose and insulin on acyl ghrelin and desacyl ghrelin, leptin, and adiponectin in pregnant women with diabetes. *Metabolism: clinical and experimental*. 2010; 59(6):841–7. DOI: 10.1016/j.metabol.2009.09.033 [PubMed: 20005544]
115. Wellhoener P, Fruehwald-Schultes B, Kern W, Dantz D, Kerner W, Born J, Fehm HL, Peters A. Glucose metabolism rather than insulin is a main determinant of leptin secretion in humans. *The Journal of clinical endocrinology and metabolism*. 2000; 85(3):1267–71. DOI: 10.1210/jcem.85.3.6483 [PubMed: 10720074]
116. Rothman DL, Magnusson I, Katz LD, Shulman RG, Shulman GI. Quantitation of hepatic glycogenolysis and gluconeogenesis in fasting humans with ¹³C NMR. *Science*. 1991; 254(5031):573–6. [PubMed: 1948033]
117. Perry RJ, Peng L, Cline GW, Butrico GM, Wang Y, Zhang XM, Rothman DL, Petersen KF, Shulman GI. Non-invasive assessment of hepatic mitochondrial metabolism by positional isotopomer NMR tracer analysis (PINTA). *Nature communications*. 2017; 8(1):798.doi: 10.1038/s41467-017-01143-w
118. Felig P, Marliss E, Owen OE, Cahill GF Jr. Blood glucose and gluconeogenesis in fasting man. *Arch Intern Med*. 1969; 123(3):293–8. [PubMed: 4885676]
119. Felig P, Marliss E, Owen OE, Cahill GF Jr. Role of substrate in the regulation of hepatic gluconeogenesis in fasting man. *Advances in enzyme regulation*. 1969; 7:41–6. [PubMed: 5367812]

120. Felig P, Owen OE, Wahren J, Cahill GF Jr. Amino acid metabolism during prolonged starvation. *The Journal of clinical investigation*. 1969; 48(3):584–94. DOI: 10.1172/JCI106017 [PubMed: 5773094]
121. Cahill GF Jr. Starvation in man. *The New England journal of medicine*. 1970; 282(12):668–75. DOI: 10.1056/NEJM197003192821209 [PubMed: 4915800]
122. Pozefsky T, Tancredi RG, Moxley RT, Dupre J, Tobin JD. Effects of brief starvation on muscle amino acid metabolism in nonobese man. *The Journal of clinical investigation*. 1976; 57(2):444–9. DOI: 10.1172/JCI108295 [PubMed: 1254728]
123. Freminet A, Leclerc L. Effect of fasting on liver and muscle glycogen in rats and guinea pigs. *J Physiol (Paris)*. 1980; 76(8):877–80. [PubMed: 7241398]
124. Umpleby AM, Scobie IN, Boroujerdi MA, Sonksen PH. The effect of starvation on leucine, alanine and glucose metabolism in obese subjects. *Eur J Clin Invest*. 1995; 25(8):619–26. [PubMed: 7589020]
125. Vagenakis AG, Portnay GI, O'Brian JT, Rudolph M, Arky RA, Ingbar SH, Braverman LE. Effect of starvation on the production and metabolism of thyroxine and triiodothyronine in euthyroid obese patients. *The Journal of clinical endocrinology and metabolism*. 1977; 45(6):1305–9. DOI: 10.1210/jcem-45-6-1305 [PubMed: 591624]
126. Carlson HE, Drenick EJ, Chopra IJ, Hershman JM. Alterations in basal and TRH-stimulated serum levels of thyrotropin, prolactin, and thyroid hormones in starved obese men. *The Journal of clinical endocrinology and metabolism*. 1977; 45(4):707–13. DOI: 10.1210/jcem-45-4-707 [PubMed: 410822]
127. Palmblad J, Levi L, Burger A, Melander A, Westgren U, von Schenck H, Skude G. Effects of total energy withdrawal (fasting) on the levels of growth hormone, thyrotropin, cortisol, adrenaline, noradrenaline, T4, T3, and rT3 in healthy males. *Acta medica Scandinavica*. 1977; 201(1–2):15–22. [PubMed: 835366]
128. Merimee TJ, Fineberg ES. Starvation-induced alterations of circulating thyroid hormone concentrations in man. *Metabolism: clinical and experimental*. 1976; 25(1):79–83. [PubMed: 1246209]
129. Carter WJ, Shakir KM, Hodges S, Faas FH, Wynn JO. Effect of thyroid hormone on metabolic adaptation to fasting. *Metabolism: clinical and experimental*. 1975; 24(10):1177–83. [PubMed: 1165732]
130. Harris AR, Fang SL, Azizi F, Lipworth L, Vagenakis AG, Braverman LE. Effect of starvation on hypothalamic-pituitary-thyroid function in the rat. *Metabolism: clinical and experimental*. 1978; 27(9):1074–83. [PubMed: 98684]
131. Harris AR, Fang SL, Vagenakis AG, Braverman LE. Effect of starvation, nutrient replacement, and hypothyroidism on in vitro hepatic T4 to T3 conversion in the rat. *Metabolism: clinical and experimental*. 1978; 27(11):1680–90. [PubMed: 30020]
132. Gardner DF, Kaplan MM, Stanley CA, Utiger RD. Effect of tri-iodothyronine replacement on the metabolic and pituitary responses to starvation. *The New England journal of medicine*. 1979; 300(11):579–84. DOI: 10.1056/NEJM197903153001102 [PubMed: 105290]
133. Jung RT, Shetty PS, James WP. The effect of refeeding after semistarvation on catecholamine and thyroid metabolism. *Int J Obes*. 1980; 4(2):95–100. [PubMed: 7399806]
134. Burger AG, Berger M, Wimpfheimer K, Danforth E. Interrelationships between energy metabolism and thyroid hormone metabolism during starvation in the rat. *Acta endocrinologica*. 1980; 93(3):322–31. [PubMed: 6445670]
135. Cahill GF Jr. Role of T3 in fasted man. *Life sciences*. 1981; 28(15–16):1721–6. [PubMed: 7242257]
136. Goodman MN, Larsen PR, Kaplan MM, Aoki TT, Young VR, Ruderman NB. Starvation in the rat. II. Effect of age and obesity on protein sparing and fuel metabolism. *The American journal of physiology*. 1980; 239(4):E277–E86. DOI: 10.1152/ajpendo.1980.239.4.E277 [PubMed: 7425120]
137. Hugues JN, Burger AG, Pekary AE, Hershman JM. Rapid adaptations of serum thyrotrophin, triiodothyronine and reverse triiodothyronine levels to short-term starvation and refeeding. *Acta endocrinologica*. 1984; 105(2):194–9. [PubMed: 6695550]

138. Kinlaw WB, Schwartz HL, Oppenheimer JH. Decreased serum triiodothyronine in starving rats is due primarily to diminished thyroidal secretion of thyroxine. *The Journal of clinical investigation*. 1985; 75(4):1238–41. DOI: 10.1172/JCI111821 [PubMed: 3988938]
139. Komaki G, Tamai H, Kiyohara K, Fukino O, Nakagawa T, Mori S, Kumagai LF, Nagataki S. Changes in the hypothalamic-pituitary-thyroid axis during acute starvation in non-obese patients. *Endocrinologia japonica*. 1986; 33(3):303–8. [PubMed: 3757921]
140. Schebendach JE, Golden NH, Jacobson MS, Hertz S, Shenker IR. The metabolic responses to starvation and refeeding in adolescents with anorexia nervosa. *Annals of the New York Academy of Sciences*. 1997; 817:110–9. [PubMed: 9239182]
141. Douyon L, Schteingart DE. Effect of obesity and starvation on thyroid hormone, growth hormone, and cortisol secretion. *Endocrinol Metab Clin North Am*. 2002; 31(1):173–89. [PubMed: 12055988]
142. Rimbach R, Pillay N, Schradin C. Both thyroid hormone levels and resting metabolic rate decrease in African striped mice when food availability decreases. *J Exp Biol*. 2017; 220(Pt 5): 837–43. DOI: 10.1242/jeb.151449 [PubMed: 27994044]
143. Ma SW, Foster DO. Starvation-induced changes in metabolic rate, blood flow, and regional energy expenditure in rats. *Can J Physiol Pharmacol*. 1986; 64(9):1252–8. [PubMed: 3779521]
144. Benthem L, van der Leest J, Steffens AB, Zijlstra WG. Metabolic and hormonal responses to adrenoceptor antagonists in 48-hour-starved exercising rats. *Metabolism: clinical and experimental*. 1995; 44(10):1332–9. [PubMed: 7476294]
145. Even PC, Nicolaidis S. Adaptive changes in energy expenditure during mild and severe feed restriction in the rat. *The British journal of nutrition*. 1993; 70(2):421–31. [PubMed: 8260469]
146. Weyer C, Vozarova B, Ravussin E, Tataranni PA. Changes in energy metabolism in response to 48 h of overfeeding and fasting in Caucasians and Pima Indians. *International journal of obesity and related metabolic disorders: journal of the International Association for the Study of Obesity*. 2001; 25(5):593–600. DOI: 10.1038/sj.ijo.0801610
147. Hukshorn CJ, Westerterp-Plantenga MS, Saris WH. Pegylated human recombinant leptin (PEG-OB) causes additional weight loss in severely energy-restricted, overweight men. *The American journal of clinical nutrition*. 2003; 77(4):771–6. [PubMed: 12663271]
148. Harris RB, Kelso EW, Flatt WP, Bartness TJ, Grill HJ. Energy expenditure and body composition of chronically maintained decerebrate rats in the fed and fasted condition. *Endocrinology*. 2006; 147(3):1365–76. DOI: 10.1210/en.2005-1156 [PubMed: 16357041]
149. McCue MD, Pollock ED. Measurements of substrate oxidation using (13)CO 2-breath testing reveals shifts in fuel mix during starvation. *Journal of comparative physiology B, Biochemical, systemic, and environmental physiology*. 2013; 183(8):1039–52. DOI: 10.1007/s00360-013-0774-z
150. Kosmiski L, Schmiede SJ, Mascolo M, Gaudiani J, Mehler PS. Chronic starvation secondary to anorexia nervosa is associated with an adaptive suppression of resting energy expenditure. *The Journal of clinical endocrinology and metabolism*. 2014; 99(3):908–14. DOI: 10.1210/jc.2013-1694 [PubMed: 24302748]
151. Muller MJ, Enderle J, Pourhassan M, Braun W, Eggeling B, Lagerpusch M, Gluer CC, Kehayias JJ, Kiosz D, Bosy-Westphal A. Metabolic adaptation to caloric restriction and subsequent refeeding: the Minnesota Starvation Experiment revisited. *The American journal of clinical nutrition*. 2015; 102(4):807–19. DOI: 10.3945/ajcn.115.109173 [PubMed: 26399868]
152. Vinales KL, Schlögl M, Piaggi P, Hohenadel M, Graham A, Bonfiglio S, Krakoff J, Thearle MS. The Consistency in Macronutrient Oxidation and the Role for Epinephrine in the Response to Fasting and Overfeeding. *The Journal of clinical endocrinology and metabolism*. 2017; 102(1): 279–89. DOI: 10.1210/jc.2016-3006 [PubMed: 27820654]
153. Nakamura Y, Walker BR, Ikuta T. Systematic review and meta-analysis reveals acutely elevated plasma cortisol following fasting but not less severe calorie restriction. *Stress*. 2016; 19(2):151–7. DOI: 10.3109/10253890.2015.1121984 [PubMed: 26586092]
154. Karl JP, Smith TJ, Wilson MA, Bukhari AS, Pasiakos SM, McClung HL, McClung JP, Lieberman HR. Altered metabolic homeostasis is associated with appetite regulation during and following

- 48-h of severe energy deprivation in adults. *Metabolism: clinical and experimental*. 2016; 65(4): 416–27. DOI: 10.1016/j.metabol.2015.11.001 [PubMed: 26975533]
155. Bergendahl M, Vance ML, Iranmanesh A, Thorner MO, Veldhuis JD. Fasting as a metabolic stress paradigm selectively amplifies cortisol secretory burst mass and delays the time of maximal nyctohemeral cortisol concentrations in healthy men. *The Journal of clinical endocrinology and metabolism*. 1996; 81(2):692–9. DOI: 10.1210/jcem.81.2.8636290 [PubMed: 8636290]
 156. Koutkia P, Schurgin S, Berry J, Breu J, Lee BS, Klibanski A, Grinspoon S. Reciprocal changes in endogenous ghrelin and growth hormone during fasting in healthy women. *American journal of physiology Endocrinology and metabolism*. 2005; 289(5):E814–22. DOI: 10.1152/ajpendo.00093.2005 [PubMed: 15972272]
 157. Schurgin S, Canavan B, Koutkia P, Depaoli AM, Grinspoon S. Endocrine and metabolic effects of physiologic r-metHuLeptin administration during acute caloric deprivation in normal-weight women. *The Journal of clinical endocrinology and metabolism*. 2004; 89(11):5402–9. DOI: 10.1210/jc.2004-1102 [PubMed: 15531489]
 158. Michalsen A, Schneider S, Rodenbeck A, Ludtke R, Huether G, Dobos GJ. The short-term effects of fasting on the neuroendocrine system in patients with chronic pain syndromes. *Nutr Neurosci*. 2003; 6(1):11–8. DOI: 10.1080/1028415021000042811 [PubMed: 12608732]
 159. Bergendahl M, Evans WS, Pastor C, Patel A, Iranmanesh A, Veldhuis JD. Short-term fasting suppresses leptin and (conversely) activates disorderly growth hormone secretion in midluteal phase women—a clinical research center study. *The Journal of clinical endocrinology and metabolism*. 1999; 84(3):883–94. DOI: 10.1210/jcem.84.3.5536 [PubMed: 10084566]
 160. Bergendahl M, Aloï JA, Iranmanesh A, Mulligan TM, Veldhuis JD. Fasting suppresses pulsatile luteinizing hormone (LH) secretion and enhances orderliness of LH release in young but not older men. *The Journal of clinical endocrinology and metabolism*. 1998; 83(6):1967–75. DOI: 10.1210/jcem.83.6.4856 [PubMed: 9626127]
 161. Samuels MH, McDaniel PA. Thyrotropin levels during hydrocortisone infusions that mimic fasting-induced cortisol elevations: a clinical research center study. *The Journal of clinical endocrinology and metabolism*. 1997; 82(11):3700–4. DOI: 10.1210/jcem.82.11.4376 [PubMed: 9360528]
 162. Beitins IZ, Barkan A, Klibanski A, Kyung N, Reppert SM, Badger TM, Veldhuis J, McArthur JW. Hormonal responses to short term fasting in postmenopausal women. *The Journal of clinical endocrinology and metabolism*. 1985; 60(6):1120–6. DOI: 10.1210/jcem-60-6-1120 [PubMed: 3923018]
 163. Misra M, Klibanski A. Endocrine consequences of anorexia nervosa. *The lancet Diabetes & endocrinology*. 2014; 2(7):581–92. DOI: 10.1016/S2213-8587(13)70180-3 [PubMed: 24731664]
 164. Andrisani A, Sabbadin C, Minardi S, Favaro A, Dona G, Bordin L, Ambrosini G, Armanini D. Persistent amenorrhea and decreased DHEAS to cortisol ratio after recovery from anorexia nervosa. *Gynecol Endocrinol*. 2017; 33(4):311–4. DOI: 10.1080/09513590.2016.1255881 [PubMed: 27910716]
 165. Misra M, Klibanski A. Neuroendocrine consequences of anorexia nervosa in adolescents. *Endocr Dev*. 2010; 17:197–214. DOI: 10.1159/000262540 [PubMed: 19955768]
 166. Misra M, Miller KK, Bjornson J, Hackman A, Aggarwal A, Chung J, Ott M, Herzog DB, Johnson ML, Klibanski A. Alterations in growth hormone secretory dynamics in adolescent girls with anorexia nervosa and effects on bone metabolism. *The Journal of clinical endocrinology and metabolism*. 2003; 88(12):5615–23. DOI: 10.1210/jc.2003-030532 [PubMed: 14671143]
 167. Modan-Moses D, Stein D, Pariente C, Yaroslavsky A, Ram A, Faigin M, Loewenthal R, Yissachar E, Hemi R, Kanety H. Modulation of adiponectin and leptin during refeeding of female anorexia nervosa patients. *The Journal of clinical endocrinology and metabolism*. 2007; 92(5): 1843–7. DOI: 10.1210/jc.2006-1683 [PubMed: 17327386]
 168. Misra M, Miller KK, Kuo K, Griffin K, Stewart V, Hunter E, Herzog DB, Klibanski A. Secretory dynamics of leptin in adolescent girls with anorexia nervosa and healthy adolescents. *American journal of physiology Endocrinology and metabolism*. 2005; 289(3):E373–81. DOI: 10.1152/ajpendo.00041.2005 [PubMed: 15811876]

169. Shimizu T, Satoh Y, Kaneko N, Suzuki M, Lee T, Tanaka K, Iijima M, Yamashiro Y. Factors involved in the regulation of plasma leptin levels in children and adolescents with anorexia nervosa. *Pediatr Int*. 2005; 47(2):154–8. DOI: 10.1111/j.1442-200x.2005.02036.x [PubMed: 15771692]
170. Misra M, Miller KK, Almazan C, Ramaswamy K, Lapcharoensap W, Worley M, Neubauer G, Herzog DB, Klibanski A. Alterations in cortisol secretory dynamics in adolescent girls with anorexia nervosa and effects on bone metabolism. *The Journal of clinical endocrinology and metabolism*. 2004; 89(10):4972–80. DOI: 10.1210/jc.2004-0723 [PubMed: 15472193]
171. Misra M, Miller KK, Almazan C, Ramaswamy K, Aggarwal A, Herzog DB, Neubauer G, Breu J, Klibanski A. Hormonal and body composition predictors of soluble leptin receptor, leptin, and free leptin index in adolescent girls with anorexia nervosa and controls and relation to insulin sensitivity. *The Journal of clinical endocrinology and metabolism*. 2004; 89(7):3486–95. DOI: 10.1210/jc.2003-032251 [PubMed: 15240636]
172. Tolle V, Kadem M, Bluet-Pajot MT, Frere D, Foulon C, Bossu C, Dardennes R, Mounier C, Zizzari P, Lang F, Epelbaum J, Estour B. Balance in ghrelin and leptin plasma levels in anorexia nervosa patients and constitutionally thin women. *The Journal of clinical endocrinology and metabolism*. 2003; 88(1):109–16. DOI: 10.1210/jc.2002-020645 [PubMed: 12519838]
173. Herpertz S, Albers N, Wagner R, Pelz B, Kopp W, Mann K, Blum WF, Senf W, Hebebrand J. Longitudinal changes of circadian leptin, insulin and cortisol plasma levels and their correlation during refeeding in patients with anorexia nervosa. *European journal of endocrinology/European Federation of Endocrine Societies*. 2000; 142(4):373–9.
174. Nakai Y, Hamagaki S, Takagi R, Taniguchi A, Kurimoto F. Plasma concentrations of tumor necrosis factor-alpha (TNF-alpha) and soluble TNF receptors in patients with anorexia nervosa. *The Journal of clinical endocrinology and metabolism*. 1999; 84(4):1226–8. DOI: 10.1210/jcem.84.4.5589 [PubMed: 10199758]
175. Herpertz S, Wagner R, Albers N, Blum WF, Pelz B, Langkafel M, Kopp W, Henning A, Oberste-Berghaus C, Mann K, Senf W, Hebebrand J. Circadian plasma leptin levels in patients with anorexia nervosa: relation to insulin and cortisol. *Horm Res*. 1998; 50(4):197–204. [PubMed: 9838240]
176. Balligand JL, Brichard SM, Brichard V, Desager JP, Lambert M. Hypoleptinemia in patients with anorexia nervosa: loss of circadian rhythm and unresponsiveness to short-term refeeding. *European journal of endocrinology/European Federation of Endocrine Societies*. 1998; 138(4): 415–20.
177. Becskei C, Lutz TA, Riediger T. Blunted fasting-induced hypothalamic activation and refeeding hyperphagia in late-onset obesity. *Neuroendocrinology*. 2009; 90(4):371–82. DOI: 10.1159/000251723 [PubMed: 19844081]
178. Grottoli S, Gauna C, Tassone F, Aimaretti G, Corneli G, Wu Z, Strasburger CJ, Dieguez C, Casanueva FF, Ghigo E, Maccario M. Both fasting-induced leptin reduction and GH increase are blunted in Cushing's syndrome and in simple obesity. *Clinical endocrinology*. 2003; 58(2):220–8. [PubMed: 12580939]
179. Johnstone AM, Faber P, Andrew R, Gibney ER, Elia M, Lobley G, Stubbs RJ, Walker BR. Influence of short-term dietary weight loss on cortisol secretion and metabolism in obese men. *European journal of endocrinology/European Federation of Endocrine Societies*. 2004; 150(2): 185–94.
180. Balon-Perin S, Kolanowski J, Berbinschi A, Franchimont P, Ketelslegers JM. The effects of glucose ingestion and fasting on plasma immunoreactive beta-endorphin, adrenocorticotrophic hormone and cortisol in obese subjects. *J Endocrinol Invest*. 1991; 14(11):919–25. DOI: 10.1007/BF03347116 [PubMed: 1666898]
181. Engin A. Diet-Induced Obesity and the Mechanism of Leptin Resistance. *Advances in experimental medicine and biology*. 2017; 960:381–97. Epub 2017/06/07. DOI: 10.1007/978-3-319-48382-5_16 [PubMed: 28585208]
182. Friedman J. The long road to leptin. *The Journal of clinical investigation*. 2016; 126(12):4727–34. Epub 2016/12/03. leptin, the author is named as an inventor on the patent for leptin and, as per University policy, receives a portion of the milestone and royalty payments made to Rockefeller

University by Astra Zeneca, the company that owns the license to the patents. DOI: 10.1172/JCI91578 [PubMed: 27906690]

183. Xu B, Xie X. Neurotrophic factor control of satiety and body weight. *Nat Rev Neurosci.* 2016; 17(5):282–92. Epub 2016/04/08. DOI: 10.1038/nrn.2016.24 [PubMed: 27052383]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript