

Stimulation of leptin secretion by insulin

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ABSTRACT

Leptin has a crucial role in regulating food intake and maintaining metabolic homeostasis. Although little is known about the process of leptin secretion, insulin, which has an important role in the metabolism of glucose and lipids, is believed to regulate leptin secretion through a posttranscriptional mechanism in the short term, and via glucose metabolism in the long term. The gastric mucosa secretes leptin, but this mechanism has not been completely elucidated. Understanding the mechanism of insulin-regulated leptin secretion could lead to the development of new treatment methods for obesity and its comorbidities, which are serious public health concerns.

Key words: Insulin, leptin, leptin secretion

INTRODUCTION

Leptin, a 167–amino acid hormone, was discovered in 1994^[1] and is secreted mainly by adipocytes. Plasma leptin levels are significantly correlated with body mass index (BMI) and the total amount of body fat.^[2,3] A recent study reported that total fat mass is the strongest predictor of circulating leptin.^[4] The discovery of leptin made it clear that adipose tissue is not only a regulator of body weight but also an endocrine organ with feedback loops between the brain and peripheral tissues. Leptin has a crucial role in regulating food intake and energy expenditure. Leptin is derived from the gastric mucosa and placenta.^[5,6] In particular, the gastric mucosa is the only tissue secreting leptin in an exocrine rather than an endocrine fashion.^[7]

Plasma leptin levels decrease during fasting^[8] or energy restriction^[9] and increase during refeeding,^[10] overfeeding,^[11] and surgical stress.^[12,13] Insulin, glucocorticoids, serotonin, and estrogen have been reported to stimulate leptin secretion.^[14-17] In this paper, we focus on the regulation of leptin secretion by insulin.

RELATIONSHIP BETWEEN LEPTIN AND INSULIN CONCENTRATIONS IN HUMANS AND RODENTS

Plasma leptin was associated with BMI in obese subjects and with fasting plasma insulin levels. In humans, plasma leptin levels exhibited a pulsatile and circadian pattern, peaking at night and reaching its nadir in the morning.^[18-20] Sinha *et al*, reported that the circadian rhythm of leptin levels is not associated with insulin levels or food intake.^[18] In contrast, Schoeller *et al*, suggested that diurnal leptin levels are altered by meal timing.^[20] Many studies on the relationship between postprandial increases in insulin and leptin have been conducted; however, conclusions about the effect of insulin on leptin are controversial.

Dagogo-Jack *et al*, reported that plasma leptin levels did not change post-prandially and concluded that, at least in the short term, insulin does not increase leptin secretion in humans.^[21] Some investigators have reported similar results.^[22-24] The results of studies using the glucose clamp technique support the finding that insulin is not a short-term regulator of leptin secretion. Physiological and supraphysiological euglycemic-hyperinsulinemic clamps did not change plasma leptin levels in response to insulin for up to 120 or 200 min, regardless of the insulin-sensitive or insulin-resistant status of the subjects,^[25,26] and the plasma leptin levels increased only after more than 4hr.^[27-29] Similar findings have been reported in patients with type 2 diabetes mellitus.^[28,30] Vidal *et al*, reported that neither a caloric restriction nor a 3hr euglycemic-hyperinsulinemic

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clamp changed the level of leptin mRNA in abdominal subcutaneous fat tissue, despite changes in metabolic parameters such as decreased insulinemia, glycemia, and resting metabolic rate, and increased plasma ketone bodies. They suggested that leptin gene expression is either not acutely regulated or not regulated by fasting-related metabolic factors.^[31]

On the other hand, Saad *et al.*, have reported a conflicting finding. They observed an acute postprandial increase in plasma leptin levels.^[32] Similar results were reported by Saad *et al.*, who used a glucose clamp in humans. The authors suggested that several previous studies apparently overlooked decreases in leptin levels due to saline infusion and therefore could not detect the acute effect of insulin on leptin.^[33] Carlson *et al.*, reported that postprandial leptin increases correspond with insulin levels at 15 and 30 min.^[34] Postprandial leptin increase has also been reported in rodents.^[35,36] Otukonyong *et al.*, stated that leptin secretion was influenced by consumption of foods high in fat, thereby increasing the insulin for up to 200 min after food intake.^[36] Koopmans *et al.*, reported that pharmacological insulin infusion stimulated leptin increase in 2 h, although 4 h are required to observe a rise in plasma leptin levels after physiological insulin infusion in rodents.^[37] Pagano *et al.*, also reported that insulin had an acute effect on leptin secretion.^[38] Furthermore, insulin is important for inducing an acute increase in plasma leptin levels in rats with streptozotocin-induced diabetes.^[39,40]

In addition to euglycemic-hyperinsulinemic clamps, a hypoglycemic-hyperinsulinemic clamp has been reported.^[41] During hyperinsulinemic euglycemia, serum leptin levels gradually increased after 180 min. However, the leptin profile observed when a hypoglycemic clamp was used differed from the leptin profile in euglycemic conditions: the increase was smaller and it was delayed. Further, Wellhoener *et al.*, showed a smaller increase in serum leptin levels during hypoglycemic conditions than during euglycemic conditions, despite the identical rates of insulin infusion; the total amount of dextrose infused during the clamp was significantly related to the changes in serum leptin levels.^[42] They suggested that leptin secretion is mainly related to glucose metabolism in humans. The reduced leptin secretion during fasting may be, directly or indirectly, due to falling glucose levels. The attenuating effect of prolonged hypoglycemia on hyperinsulinemia-induced leptin secretion may be caused by the response to hypoglycemia rather than the hypoglycemia itself.

LEPTIN SECRETION FROM ADIPOCYTES STIMULATED BY INSULIN

Whether insulin regulation of leptin secretion in humans and rodents is acute, continuing from minutes to several hours is controversial. On the other hand, *in vitro* studies have revealed that insulin does not affect leptin mRNA levels for several hours. Insulin stimulation of leptin secretion is illustrated in Figure 1.

Moreno-Aliaga *et al.*, demonstrated, in 3T3-L1 cells, that leptin mRNA was increased after 48 h of treatment with insulin and was inhibited by 2-deoxy-D-glucose (2-DG), a competitive inhibitor of glucose transport and phosphorylation. They concluded that insulin-stimulated glucose metabolism, and not insulin per se, mediates the effects of insulin to increase leptin mRNA.^[43]

Researchers frequently use 3T3-L1 adipocytes to study adipogenesis, fatty acid metabolism, and insulin-regulated trafficking. When the standard isobutylmethylxanthine/dexamethasone/insulin (Ibmx/Dex/Ins) protocol is applied, 3T3-L1 fibroblasts differentiate into mature adipocytes, but leptin expression is very limited.^[44] Zeigerer *et al.*, modified the standard protocol to better define the molecular mechanisms underlying leptin secretion of adipocytes. They added a peroxisome proliferator-activated receptor (PPAR) gamma agonist to the Ibmx/Dex/Ins differentiation cocktail, which caused a five-fold increase in the leptin mRNA levels. Under these conditions, insulin stimulation for 15 min induced a two-fold increase in leptin secretion without new protein

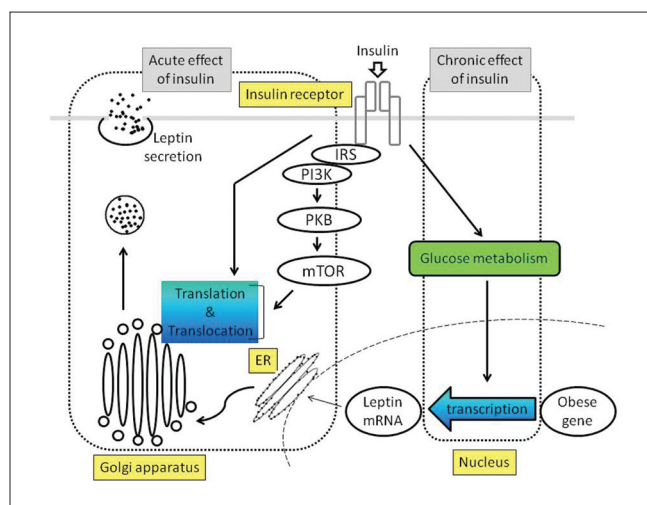


Figure 1: Leptin secretion Insulin stimulates leptin secretion through a posttranscriptional mechanism that is mainly mediated by the PI3K-PKB-mTOR pathway, or other unknown pathways. It has been suggested that the chronic effect of insulin is mediated by glucose metabolism. IRS: Insulin receptor substrate, PI3K: Phosphoinositide 3-kinase, PKB: Protein kinase B, mTOR: mammalian target of rapamycin, ER: Endoplasmic reticulum

synthesis. The increased leptin secretion was not due to the alterations in glucose metabolism. The effect of insulin on leptin exocytosis was blocked by brefeldin A, but not by the phosphoinositide 3-kinase (PI3K) inhibitor wortmannin or the protein synthesis inhibitor cycloheximide. This suggests that leptin is targeted to a regulatory secretory compartment in 3T3-L1 adipocytes, where its release is stimulated by insulin via a PI3K-independent mechanism.^[45]

Leptin mRNA was detectable in mature 3T3-442A cells, but not premature cells.^[46] Furthermore, leptin mRNA levels normalized after transplantation of 3T3-F442A preadipocytes into mice.^[47] These findings suggest that leptin mRNA expression depends on cell culture lines or maturity of cells and some important factors may be missing *ex vivo*.

When rat epididymal fat was incubated with or without insulin for 4hr *in vitro*, leptin secretion increased by about 80% at all-time points studied.^[48] After 10 min of insulin treatment, the amount of tissue-associated leptin had decreased, presumably because of increased secretion. Later, both tissue-associated leptin and total leptin production had increased in insulin-treated fat tissue. Before insulin treatment, leptin was detected in the endoplasmic reticulum by immunostaining. After insulin treatment, leptin staining in many cells became fainter and was restricted to a narrow band near the plasma membrane. These results suggest that insulin increases both secretion and production of leptin and stimulates the transport of leptin from the endoplasmic reticulum.

Mueller *et al.*, reported that the insulin-regulated increase of leptin secretion was more closely related to the amount of glucose taken up by adipocytes than to insulin concentration. Leptin secretion was inhibited by 2-DG and was reversed by high concentrations of glucose. Two inhibitors of glucose transport, phloretin and cytochalasin-B, and 2 inhibitors of glycolysis, iodoacetate and sodium fluoride, inhibited leptin secretion as well.^[49] In addition, they revealed that metformin and vanadium, antidiabetes agents that increase glucose uptake by peripheral tissues, increased glucose uptake and inhibited leptin secretion by cultured adipocytes. The inhibition of leptin secretion by metformin was related to an increase in the metabolism of glucose to lactate, so the effect of increasing leptin by glucose utilization involves the metabolism of glucose to a fate other than anaerobic lactate production.^[50] They concluded that glucose transport and metabolism are important factors in the regulation of leptin expression and secretion.

The precise intracellular compartmentalization and trafficking pathways leading to the secretion of leptin and the molecular components that mediate the transport of

leptin are still poorly understood. Cammisotto *et al.*, found that a portion of leptin was localized in the endoplasmic reticulum and Golgi apparatus, and also in small intracellular vesicles.^[51] Although incubation of isolated adipocytes with insulin did not increase leptin mRNA levels for several hours, insulin did increase leptin concentration. It has been suggested that insulin stimulates leptin release through a posttranscriptional mechanism. Isolated adipocytes without insulin continuously secreted leptin, while their intracellular content remained unchanged. However, the cellular content and secretion of leptin increased in parallel and were significantly different from basal secretion only 45 mins after insulin stimulation. These stimulating effects were abolished by cycloheximide and brefeldin A. In contrast, transcriptional inhibitor actinomycin D did not have any effect before or after insulin stimulation. They concluded that adipocytes continuously synthesize and secrete leptin along a rough endoplasmic reticulum–Golgi secretory vesicle pathway and that short-term leptin secretion does not involve changes in mRNA levels.^[52] Supporting this interpretation, one study found that actinomycin D did not block insulin-stimulated leptin secretion.^[53] In this study, the PI3K inhibitor LY294002, the Map/Erk kinase inhibitor PD98059, and the immunosuppressant rapamycin were utilized to reveal the signaling pathways involved in leptin synthesis/secretion. These agents had no effect on basal levels of leptin secretion; however, all 3 inhibitors markedly decreased both insulin- and dexamethasone-stimulated leptin secretions. These findings suggest a complex set of signaling pathways involved in mediating insulin- and dexamethasone-stimulated leptin synthesis and secretion. Levy *et al.* reported that incubation of isolated rat adipocytes with insulin for 60 mins rapidly increased leptin synthesis, with little or no leptin secretion.^[54] Over 60 mins, leptin was significantly released from the cells into the medium. Cycloheximide prevented the synthesis and the insulin-mediated secretion of leptin. Monensin, an inhibitor of protein translocation, had no effect on leptin synthesis, but it blocked the insulin-mediated secretion of leptin. It has been suggested that insulin promotes leptin secretion by increasing leptin synthesis, rather than by promoting the secretion of a preexisting cytosolic pool of leptin.

ISOLATED ADIPOSE TISSUE FROM RODENTS

Saladin *et al.*, showed that leptin mRNA levels in rats increased with food intake and insulin injection and decreased with fasting; additionally, the insulin increased leptin mRNA expression in adipocytes.^[14] Zheng *et al.*, reported that abdominal fat (epididymal and perirenal fat pads) had higher leptin mRNA levels than subcutaneous fat.^[55] Leptin mRNA levels increased after a 2.5-hr infusion of insulin into fasted

rats in the abdominal fat, however, the level of leptin mRNA did not change in the subcutaneous fat.

Lee *et al.*, showed the mechanisms of increased serum leptin in response to feeding by using metabolic labeling to directly assess leptin biosynthesis, secretion, and turnover.^[56] Starvation decreased serum leptin, adipose tissue leptin content, and leptin secretion during 3 h of incubation. Insulin did not acutely increase leptin biosynthesis *in vitro*, but pulse-chase studies showed that in adipose tissue from fed rats, insulin accelerated the secretion of leptin after 30 and 60 min of chase. The researchers conducting these studies concluded that feeding, rather than starvation, influenced leptin production at multiple posttranscriptional levels: synthesis, tissue storage, turnover, and secretion.

ISOLATED ADIPOSE TISSUE FROM HUMANS

Kolaczynski *et al.*, reported that insulin indirectly regulates leptin production in human adipose tissue.^[30] They investigated whether leptin mRNA changes in response to insulin *in vitro* and *in vivo* under euglycemic and hyperglycemic conditions. Healthy lean, obese, and type 2 diabetes mellitus subjects were infused with insulin for 5hr in a euglycemic clamp and for 64–72 hrs in a hyperglycemic clamp. Isolated abdominal adipocytes were incubated with insulin for 96 hrs. Short-term euglycemic-hyperinsulinemia had no effect on the levels of circulating leptin. During the prolonged hyperglycemic clamp, a rise in leptin was observed at least 40 hrs later. In the presence of insulin *in vitro*, leptin mRNA increased at 72 hrs, followed by an increase in leptin secreted into the medium. They concluded that insulin does not acutely stimulate leptin production; however, a long-term effect of insulin on leptin production could be demonstrated both *in vivo* and *in vitro*.^[30]

It is widely accepted that dexamethasone stimulates leptin secretion. Russell *et al.*, investigated *in vitro* regulation of leptin expression in adipose tissue of severely obese women and men before and after culture with insulin and/or dexamethasone. Leptin mRNA levels and leptin secretion were greater in subcutaneous versus omental adipose tissue before culture. Dexamethasone transiently increased leptin mRNA in both depots after one day of culture, but leptin secretion only increased in omental adipose tissue. Insulin did not increase leptin mRNA in either depot but increased leptin secretion in subcutaneous tissue throughout the seven days of culture. The combination of insulin and dexamethasone increased leptin mRNA and leptin secretion in both depots at day one and maintained leptin expression throughout seven days of culture. Insulin and glucocorticoid had depot-specific effects and

functioned synergistically as long-term regulators of leptin expression in omental and subcutaneous adipose tissue from obese subjects.^[57] Wabitsch *et al.*, also concluded that both insulin and cortisol are physiological regulators of leptin expression in human adipose tissue.^[58]

A partially contradictory study was reported by Casabiell *et al.*,^[59] They reported that insulin has a dual action in leptin regulation: an early (less than 48 hrs) inhibitory action, followed (48–96 hrs later) by stimulation. While the inhibitory phase was observed at every glucose concentration tested (range, 1mM–25mM), the stimulatory phase required the presence of physiological or supraphysiological glucose concentrations. Leptin secretion was eliminated with glucose uptake inhibitors. This dual effect of insulin was not due to modification of leptin mRNA levels, suggesting that it depends entirely on posttranslational mechanisms. They concluded that insulin-related inhibition and stimulation are due to the metabolic changes triggered by the insulin-induced increase in glucose uptake.

INSULIN-REGULATED SECRETION OF LEPTIN BY GASTRIC MUCOSA

Bado reported that gastric mucosa secretes leptin,^[5] and both feeding and administration of cholecystokinin-8 increase plasma leptin. Cammisotto *et al.*, showed that the gastric mucosa largely contributes to levels of circulating leptin, particularly levels measured at the time of food intake.^[7] Nevertheless, very little is known about insulin-regulated secretion of leptin by gastric mucosa. Additional studies are needed to elucidate the relationship between leptin and insulin.

CONCLUSION

Insulin is an important factor in the stimulation of leptin secretion. Whether its *in vivo* activity can be considered acute is controversial. However, insulin regulates the long-term leptin secretion of adipose cells by a transcriptional or posttranscriptional mechanism. The regulation may be mediated by glucose metabolism, but the mechanism is not yet fully understood. Few studies during the last few years have investigated insulin-regulated leptin secretion by adipose cells. This could be because of the very low levels of leptin mRNA expressed by the traditional 3T3-L1 adipocyte cell line or because the cell lines that closely mimic the *in vivo* state are absent or because a cell strain highly sensitive to hormonal signals is not available. Understanding the short-term and long-term insulin-regulated mechanisms of leptin secretion could lead to the development of new

treatments for obesity and its comorbidities, which are serious public health concerns.

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