A Critical Interaction: Leptin and Ghrelin

Continuing research has increased our understanding of regulatory factors involving appetite, food intake, and energy metabolism. There appears to be a complex interaction among insulin, leptin, and ghrelin. A new study explored these interactions and indicates that leptin may regulate ghrelin levels and affect body weight changes.

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Obesity is one of the most common medical problems in the United States. Given the magnitude of the problem, mechanisms of human metabolism and energy regulation have generated much interest. Fat is the principal form of energy storage, and the amount of triglycerides in adipose tissue reflects the difference between energy intake and energy expenditure over a period of time. These systems are highly regulated by signals from adipose tissues, as well as endocrine, gastrointestinal, and neurological systems. The hypothalamus receives afferent neural (vagal and catecholaminergic) and hormonal (insulin, leptin, and glucocorticoids) stimuli regarding appetite and energy status.[1] Within the hypothalamus, these neural and hormonal mediators that are related to metabolic status act on the hypothalamic-pituitary axis and autonomic nervous system to affect energy expenditure and food intake.[2] Many hormones—most notably insulin, leptin, and ghrelin—act as chemical mediators of energy metabolism and operate by regulating energy intake and expenditure.[1] These key interactions are explored in a recent experimental study by Barazzoni et al.[3]

Insulin is an amino acid peptide hormone that is synthesized and secreted by beta cells in the pancreas. It is a major regulator of metabolic function by virtue of its action on metabolically active tissue—liver, muscle, and adipose. Insulin affects glucose metabolism by facilitating and increasing its transport into the cell; glycogen synthesis in liver, muscle, and adipose tissues; and glycolysis in fat and muscle tissues. It also promotes storage of triglycerides in fat cells, decreases lipolysis after meals, and increases protein metabolism. Plasma insulin levels are generally in proportion to adipocyte concentration in the body; in adipocytes, insulin can regulate the expression of leptin to help reduce food intake.[1] Conversely, excess fat stores enhance insulin resistance and contribute to the development of metabolic syndrome X and hyperglycemia.

Leptin is a protein and a cytokine encoded by the *Lep* gene that has important regulatory effects in maintaince of body weight, metabolism, and reproductive function. As a satiety factor, leptin is primarily synthesized in and secreted by adipose tissue. It keeps the hypothalamus perpetually informed about the quantity of fat stores in the body.[4] Central or systemic leptin administration is known to reduce food intake and increase energy expenditure.[5] Leptin-deficient mice (*ob/ob*) display hyperphagia, insulin resistance, hyperinsulinemia, and infertility, all of which are reversible with the administration of leptin.[5] These actions of leptin on energy homeostasis are presumed to be mediated primarily by neuropeptide Y (NPY), a peptide produced in the hypothalamus. NPY reflects the nutritional status of the body based on afferent signals from the gastrointestinal tract, endocrine system, and nervous system. Acting as a central appetite stimulant, NPY influences mediators of energy intake and expenditure, sympathetic and parasympathetic nervous systems, and thyroid hormones.[1] Leptin has potent appetite-suppressant effects in obese mice; however, its role in human obesity is not clear as yet. In rats, administration of leptin normalizes insulin's actions on glucose, decreases hyperphagia, and alleviates infertility.[6] The proposed primary role of leptin in humans is more puzzling; it may signal to the hypothalamus whether somatic fat stores are sufficient for growth and reproduction. A decrease in plasma leptin (inadequate body fat stores) in humans will cause hyperphagia, low energy stores, and infertility.[5] Leptin therefore indicates whether fat stores are adequate for growth, but low levels of leptin (below a certain preset threshold) will result in increased appetite, low energy, and infertility. Leptin levels above this set point have a minimal physiologic effect. This illustrates why obese humans with high leptin concentrations have neither hypophagia nor hypermetabolism.[1]

Ghrelin, a peptide that is a natural ligand for the growth hormone secretagogue receptor, is another cardinal hormonal regulator of energy homeostasis. Ghrelin was identified by Kojima et al. in 1999 as an orexigenic hormone secreted primarily by the stomach and duodenum.[7] It stimulates growth hormone secretion and increases food intake in rodents and humans by influencing mealtime-related appetite and hunger (levels rise before and fall after every meal) and long-term regulation of body weight.[7,8] Ghrelin is secreted in a pulsatile manner and is increased after fasting. Studies have shown that central and peripheral administration of ghrelin increases

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food intake and body weight in rats.[8] Ghrelin is believed to play a key role in the compensatory changes in appetite and energy expenditure associated with weight loss. Ghrelin levels stay consistently above baseline in people who lose weight by restricting calories, but Cummings et al. showed that ghrelin levels are suppressed in patients with weight loss from gastric bypass surgery.[9] This may explain the satietogenic effect of such operations in obese patients.

Although the individual actions of leptin and ghrelin have been described, the effects of their interactions have not been clearly elucidated. Recent literature demonstrates that ghrelin and leptin have inverse amplitude changes during fasting in rodents.[10] Many ghrelin and leptin actions are mediated by NPY, which also modulates the possible counter-regulation of these hormones. Food deprivation decreased the amount of leptin secretion, which allows stimulation of NPY by ghrelin to induce feeding.[10]

In a recent study that further explored the critical interaction between leptin and ghrelin, Barazzoni et al. explored the effect of hyperleptinemia and moderate caloric restriction on plasma ghrelin concentration in lean rats.[3] The study consisted of three comparable groups: the first group received subcutaneous (SC) leptin and a moderate caloric restriction, the second group was given placebo injections and a calorie-matched diet (paired feeding with group one), and the final group was the control (given a placebo injection and allowed ad libitum feeding). All groups were followed for one week.

This study yielded several important findings. As expected, the leptin-treated group lost weight and had higher leptin levels than control animals. During caloric restriction, insulin decreased and ghrelin increased. In the leptin-treated group, however, insulin as well as ghrelin decreased. Investigators found that ghrelin levels increased in calorie-restricted rats (28% fewer calories), but did not increase in the leptin-treated rats (group 1). This in vivo study demonstrated negative regulation of plasma ghrelin concentrations by circulating leptin.

Whereas other studies have examined central leptin administration and evaluated obese rats, the study by Barazzoni et al. examined the action of peripheral leptin injections in lean rats on a calorie-restricted diet. The authors also concluded that a moderate increase in leptin could induce satiety not only by acting at the hypothalamus, but also peripherally by decreasing ghrelin signals directly in the gastrointestinal tract. Although peripheral ghrelin antagonism by leptin is a novel concept, it is unclear whether this will have clinical significance.

Consistent with the findings of Barazzoni et al., Tschop et al. described negative correlations between plasma ghrelin and leptin in lean and obese humans in an observational study.[11] By measuring the body composition (by dual X-ray absorption) and fasting plasma ghrelin concentrations in male and female subjects, they demonstrated high leptin and low ghrelin levels in obese individuals, and the opposite with weight loss secondary to fasting. Fasting plasma ghrelin concentrations were negatively correlated with leptin, insulin, and percent body fat. The authors postulated that human obesity might down-regulate ghrelin owing to elevated plasma leptin or insulin levels, further strengthening the notion that low plasma ghrelin levels in obesity may be a physiologic adaptation in obesity.[11]

A study performed by Toshinai et al. documented weight loss in obese rats with peripheral leptin infusions, but noted increased ghrelin concentrations in doing so.[12] These results were noted in the gastric fundus as well as in venous blood after a standard fast, just as it did following the administration of insulin and leptin. Ghrelin levels returned to normal after refeeding. In this study, mice with leptin resistance secondary to receptor deficiency (*db/db*) were found to have lower ghrelin levels than control mice.[12] These findings apparently contradict Barazzoni's suggestion that peripheral leptin administration will abrogate the expected increase in ghrelin levels during food deprivation.[3] It may be prudent to conclude from these observations that ghrelin is a downstream mediator in the leptin-induced chain of events and not a primary regulator of energy metabolism as proposed by Barazzoni.

Does the mode of leptin administration have any bearing on its systemic effects? Bagnasco et al. injected a leptin-encoding virus into various hypothalamic sites in rats in order to induce hyperleptinemia.[13] These injections resulted in decreased food intake, lowered body weight, and increased serum ghrelin levels. However, the high ghrelin levels were not enough to stimulate food intake in these rats. Central leptin therapy decreased peripheral (serum) leptin levels in these animals, highlighting a difference in the actions of central and peripheral leptin delivery in regulating serum ghrelin.[13]

Dube et al. and Beretta et al. also reported decreased food intake after central leptin therapy, which increased ghrelin secretion in the rat model.[14,15] Ghrelin was not able to stimulate feeding in the face of elevated central leptin levels. A possible mechanism could be that central leptin administration increases restraint on the NPY neurons, which counters the appetite-stimulating effects of peripheral ghrelin.[12] Beretta et al. suggest that that the anorectic effects of leptin blocked the stimulatory effects of ghrelin on appetite in the hypothalamus.[13,15]

Because obesity is rapidly increasing, a greater understanding of the mechanisms involved with energy metabolism is now necessary. Any potential pharmacologic treatments will center on the key hormonal actions of insulin, leptin, and ghrelin. Leptin is understood to be

a satiety factor and a marker of body fat stores, and ghrelin is recognized as a stimulator of feeding (orixigenic) that can be influenced by hormonal mediators like leptin and insulin. Barazzoni et al. concluded that injection of SC leptin in rats suppressed the appetite-stimulating actions of ghrelin and disrupted the feedback ghrelin surge initiated by fasting and weight loss. They proposed that leptin promotes weight loss by direct central and peripheral inhibition of orexigenic actions of ghrelin.[3] There is currently not enough conclusive evidence that these findings apply to the human model. Although an inverse correlation of leptin and ghrelin has been demonstrated, the important question remains: What is more important: the hormonal levels or the final effect (i.e., weight loss)? The exceptional experimental study performed by Barazonni et al. furthers our need for studies to clarify the leptin-ghrelin interaction and to examine the effect of exogenous leptin in the human model given the potential role of pharmacologic hormonal therapy in the treatment of human obesity.

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