Hepatocentric Leptin Signaling Modulates Gluconeogenesis via MKP-3

Since its discovery in 1994, leptin has been recognized as a satiety hormone required for body weight homeostasis. Leptin is secreted predominantly by white adipose tissue, and its levels in blood are correlated positively with the amount of body fat. Extensive studies of leptin’s actions in the central nervous system (CNS) have shown its ability to control food intake and energy expenditure. However, despite the profound obesity and diabetes resulting from homozygous loss of leptin or its receptor, there has been very limited efficacy of leptin treatment for obesity because most obese individuals already have high circulating leptin levels, rendering them unresponsive to its weight-reducing effects.

Research now has shifted to leptin’s effects in the periphery, particularly in the context of its glucoregulatory actions, where it may have a role independent of body weight regulation. Indeed, hyperinsulinemia occurs before weight gain in leptin-deficient ob/ob mice, and there are significant improvements in hyperglycemia and hyperinsulinemia before weight loss in leptin-treated ob/ob mice.

The leptin receptor (Obr) is present at highest levels in the CNS, but also is expressed throughout the periphery. There are 6 isoforms of Obr that result from alternative splicing and, importantly, only Obrb, the long leptin receptor isoform, is capable of mediating signal transduction. Obrb activates the JAK-STAT3 and PI3K systems, which are critical pathways involved in energy homeostasis and glucose metabolism, respectively.

In this issue of Cellular and Molecular Gastroenterology and Hepatology, Huang et al and He et al reported hepatocyte-specific effects of leptin signaling through Obrb to suppress glucose production. The investigators showed that leptin treatment of primary hepatocytes and hepatoma cells in vitro resulted in STAT3 phosphorylation, suppression of glucose production, and decreased expression of the gluconeogenic genes G6pc, Pepck1, and Pgc1a. These effects were reversed after small interfering RNA-mediated suppression of Obr. These in vitro findings support a cell-autonomous effect of leptin on hepatocyte glucose production (Figure 1). In 2 different mouse models of obesity—leptin-receptor-deficient db/db mice and high-fat diet-fed mice—Obrb overexpression specifically in liver was sufficient to lower blood glucose levels, improve glucose tolerance, and improve insulin tolerance. On the other hand, small interfering RNA-mediated suppression of liver Obr in lean mice had no effect on blood glucose.

Through which signaling pathway does hepatocyte leptin signaling control glucose production? Previously published data from the same research group showed that mitogen-activated protein kinase phosphatase-3 (MKP-3) is increased significantly in the liver of diet-induced obese mice and has regulatory control over gluconeogenesis. They showed that MKP-3 dephosphorylates FoxO1 to promote its nuclear translocation, subsequently inducing the transcription of gluconeogenic genes. The investigators now show that leptin and Obrb overexpression in the presence of leptin significantly decreases MKP-3 protein levels in primary hepatocytes and in mice, whereas Obrb suppression in primary hepatocytes increases MKP-3. Moreover, MKP-3 deficiency blocks the ability of leptin and Obrb overexpression to suppress glucose production and gluconeogenic gene expression, showing that MKP-3 mediates the effects of leptin signaling on hepatic gluconeogenesis (Figure 1).

These data support an effect of leptin signaling through STAT3 and MKP-3 to decrease gluconeogenesis in
hepatocytes. However, critical questions remain. The investigators noted no effect of liver Ob1 suppression in lean mice. Is hepatocyte leptin signaling activated only under certain physiologic or pathologic conditions? Leptin can be thought of as an adipostat, relaying information about body fat status to the brain to control energy balance. Is there a role for leptin’s effects on hepatic glucose production in this context? How do the effects of leptin compare, or synergize, with classic suppression of gluconeogenesis by insulin signaling? Overall, this work highlights the signaling role of leptin outside the CNS and suggests that further research should be performed to understand these pathways.

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