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EDITORIAL

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.[1] Indeed, hyperinsulinemia occurs before weight gain in leptin-deficient *ob/ob* mice,[2] and there are significant improvements in hyperglycemia and hyperinsulinemia before weight loss in leptin-treated *ob/ob* mice.[3]

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 Janus kinase (JAK)-signal transducer and activator of transcription 3 (STAT3) and phosphatidylinositol 3-kinase (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 and He et al[4] 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.[5] They showed that MKP-3 dephosphorylates forkhead box protein O1 (FoxO1) to promote its nuclear translocation, subsequently inducing the transcription of gluconeogenic genes.[5] 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).

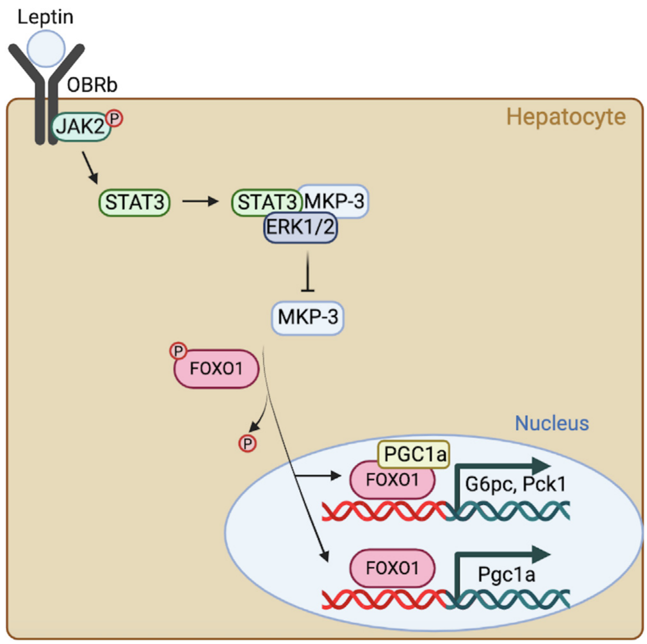

Figure 1. Model of hepatic leptin suppression of gluconeogenesis. Leptin binds to its receptor OBRb at the plasma membrane, which activates STAT3 via JAK2 (Janus kinase 2) signaling. STAT3, possibly by complexing directly with ERK1/2 (extracellular signal-regulated protein kinase 1/2) and MKP-3, leads to MKP-3 protein degradation. Decreased MKP-3 levels lead to increased phosphorylation of FOXO1 (forkhead box protein O1), thereby excluding FOXO1 from the nucleus and decreasing expression of key gluconeogenic genes, *G6pc* and *Pck1*, and their regulatory gene *Pgc1a*. Created with BioRender.com

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 *Obr* 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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References

1. D'souza AM, Neumann UH, Glavas MM, Kieffer TJ. The glucoregulatory actions of leptin. Mol Metab 2017;6:1052–1065.
2. Genuth SM, Przybylski RJ, Rosenberg DM. Insulin resistance in genetically obese, hyperglycemic mice. Endocrinology 1971;88:1230–1238.
3. Harris RBS, Zhou J, Redmann SM, Smagin GN, Smith SR, Rodgers E, Zachwieja JJ. A leptin dose-response study in obese (ob/ob) and lean (+/?) mice. Endocrinology 1998;139:8–19.
4. Huang X, He Q, Zhu H, et al. Hepatic Leptin Signaling Improves Hyperglycemia by Stimulating MAPK Phosphatase-3 Protein Degradation via STAT3. Cell Mol Gastroenterol Hepatal 2022;14:983–1001.
5. Wu Z, Jiao P, Huang X, Feng B, Feng Y, Yang S, Hwang P, Du J, Nie Y, Xiao G, Xu H. MAPK phosphatase-3 promotes hepatic gluconeogenesis through dephosphorylation of forkhead box O1 in mice. J Clin Invest 2010;120:3901–3911.

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The authors disclose no conflicts.

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