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Commentary

Does GLP-1 suppress hepatocyte glucose production directly, *via* fibroblast growth factor 21?

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Glucagon-like peptide-1 (GLP-1)-based therapies, including GLP-1 analogs and dipeptidyl peptidase 4 inhibitors, are important options in treating patients with type 2 diabetes (T2D). GLP-1, an incretin hormone released predominantly from intestinal L-cells in response to nutrient ingestion, has clear benefits against postprandial hyperglycemia. GLP-1 potentiates glucose-dependent insulin secretion, suppresses glucagon secretion, reduces food intake and delays gastric emptying [1]. Interestingly, GLP-1 analogs have also been shown to significantly reduce fasting blood glucose in patients with T2D [2,3]. This reduction might be achieved by several actions such as suppression of glucagon secretion, weight loss, enhancement of insulin sensitivity, an increase in insulin-independent glucose disposal, or direct inhibition of hepatic glucose output [1,4]. The latter has been uncertain. In this issue of *EBioMedicine*, Liu et al. [5] presented evidence that direct inhibition of hepatic glucose output by GLP-1 analogs was mediated *via* Fibroblast growth factor 21 (FGF21).

A cytokine array screening approach was used in order to identify new mediators of hepatic glucose metabolism regulated by GLP-1. They found that hepatic FGF21 production was upregulated by GLP-1 analogs in two mouse models of T2D and in cultured mouse and human primary hepatocytes. GLP-1 analogs inhibited hepatic glucose output *in vivo* and *in vitro*, while blockage of FGF21 with neutralizing antibody, small interfering RNA, or gene knockout attenuated the effects. Consistently, upregulation of the serum FGF21 level by treatment with the GLP-1 analog exenatide was more evident in those T2D patients with better glycemic control. These results, while provocative, provide a novel mechanism by which GLP-1 regulates glucose homeostasis and controls T2D.

FGF21, an endocrine factor produced mainly by liver and adipose tissues, plays important roles in glucose and lipid homeostasis [6]. Since its discovery, significant progress has been made in understanding its metabolic functions, pharmacological benefits and potential pathological roles in metabolic disorders, including T2D, obesity and dyslipidemia [7]. Considering the short half-life of native FGF21, the development of long-acting analogs or mimetics have been initiated, and their beneficial metabolic effects have started to be revealed in clinical trials [8].

The circulating FGF21 level is elevated in metabolic disorders associated with insulin resistance, including T2D and hepatic steatosis, which was thought to be a compensatory response to chronic lipotoxicity and/or glucotoxicity. Limited reports showed that blood FGF21 level was either elevated or decreased in patients with T2D after treatment with exenatide [5,9]. The sample size of these studies, including Liu's study, was relatively small. It would be worthwhile increasing the number of samples for a more definitive conclusion in future studies. Because of the complexity of metabolic regulation, it has been difficult to conclude that GLP-1 has a direct effect in stimulating liver FGF21 secretion, even based on the data from large-scale clinical trials. This is where the study published here differs: They not only verified the direct stimulation *in vitro*, but also identified that *in vivo* and *in vitro* function of GLP-1 in hepatic glucose output is affected by liver-derived FGF21 [5]. Nevertheless, a definite role of FGF21 should be further testified in liver-specific *Fgf21* knockout mice if available.

Using cytokine array screening, Liu, et al. identified FGF21 induction in db/db mice and primary mouse hepatocytes, and further demonstrated a direct stimulation of FGF21 production by GLP-1 analogs *in vitro*. A preliminary but consistent result was also obtained in human subjects of T2D. Through FGF21 blockage, they established that hepatic action of GLP-1 in glucose production is mediated at least in part *via* the liver hormone FGF21. The original contributions are the demonstration of a direct stimulation on FGF21 *in vitro*, and that FGF21 mediates GLP-1 effect on glucose production.

Some questions do remain. The gene expression profiles of mouse hepatocytes after an *in vivo* or *in vitro*, direct, GLP-1 treatment is quite different. It suggests the existence of both direct effects on hepatocytes and indirect ones through other systems of the body (such as pancreas, on insulin and glucagon secretions). Nevertheless, elevated FGF21 stood out from both screens. The changes in insulin and glucose tolerance tests of Fig. 4A-D are only minor, if at all. It's still controversial whether GLP-1 has direct effects on muscle, adipose tissue and hepatocytes. Many studies have shown that the effects of GLP-1 on hepatic glucose production were caused by its effects on insulin and glucagon secretion. Is there GLP-1 receptor expressed in hepatocytes? Finally, what causes elevated FGF21 level in diabetes and is it produced from liver, and/or fat?

Author disclosure

The authors declare no conflicts of interest.

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