Fibroblast growth factor 21 (FGF21) is an endocrine hormone that is critical for regulation of intermediary metabolism, and it is also a potential drug target for treating diabetes and other metabolic diseases. Interest in FGF21 exploded with the discovery that pharmacological administration of FGF21 to diabetic rodents and primates increased insulin sensitivity, energy expenditure, and weight loss (1). Administration of the FGF21 analog, LY2405319, to obese humans also significantly reduced body weight and improved plasma metabolic profiles (2). These studies have spurred a number of drug development programs designed to enhance FGF21 activity as a therapeutic approach to increase insulin sensitivity and treat diabetes.

FGF21 is expressed in and secreted by several tissues including liver, white adipose tissue, brown adipose tissue, striated muscle, heart, and pancreas. However, recent work has demonstrated that plasma FGF21 levels are derived primarily, if not completely, from the liver (3). FGF21 signals to specific tissues that express both the traditional FGF receptor, FGFR1, and a coreceptor called βKlotho. The physiological importance of FGF21 in regulating adaptive metabolic responses was demonstrated when complimentary articles showed that FGF21 was highly induced in liver by fasting through activation of the peroxisome proliferator–activated receptor α (4,5).

Using multiple gain-of-function models, Inagaki et al. (4) showed that FGF21 produced by the liver acts as an endocrine hormone to coordinate adipose tissue lipolysis and stimulate ketogenesis, both critical responses to prolonged food deprivation.

FGF21 also plays an important role in regulating hepatic gluconeogenesis, which is another important aspect of the fasting response. FGF21 knockout mice are hypoglycemic under fasting conditions with reduced hepatic glucose production from gluconeogenesis (6). Liver-specific FGF21 knockout mice also are mildly hypoglycemic following a prolonged fast (3), and overexpression of FGF21 is sufficient to stimulate gluconeogenesis in lean, chow-fed mice (6). Although FGF21 increases gluconeogenesis under conditions of low circulating insulin, when insulin levels become elevated—such as during refeeding and overfeeding—FGF21 enhances insulin action (3) and suppresses hepatic glucose production (7,8). Notably, although administration of recombinant FGF21 to mice is sufficient to induce hepatic gluconeogenic enzyme gene expression, recombinant FGF21 treatment of isolated primary hepatocytes or isolated perfused livers does not affect expression of these genes (6). Although one study reported that FGF21 signals directly to the liver (9), a growing body of literature suggests that FGF21 enhances hepatic gluconeogenesis secondarily via effects on distal tissues (6,10,11). These results suggest that the effects of FGF21 on hepatic gluconeogenesis are not mediated by direct effects on hepatocytes.

In this issue of *Diabetes*, Liang et al. (11) provide evidence that FGF21 elicits its hepatic gluconeogenic effects via actions in the hypothalamus and activation of the hypothalamic-pituitary-adrenal (HPA) axis. Consistent with previous work, FGF21 knockout mice were hypoglycemic and exhibited lower circulating corticosterone concentrations during a prolonged fast. Interestingly, fasting hypoglycemia in these mice could be reversed by supplementation with the glucocorticoid, dexamethasone. FGF21, which can cross the blood–brain barrier (12), was hypothesized to act in the hypothalamus to control HPA axis activity. Indeed, administration of a low dose of FGF21 to the paraventricular nucleus (PNV) region of the hypothalamus stimulated glucocorticoid production and corrected the gluconeogenic defects of the FGF21 knockout mice. These central effects of FGF21 could be abrogated by blockade of FGFR1 by administration of a neutralizing antibody to
the PVN, treating mice with the glucocorticoid antagonist RU486, or by surgical adrenalectomy (11). Increased phosphorylation of hypothalamic extracellular signal–related kinase 1/2 (ERK1/2), which is known to be activated by FGFR1 signaling, was observed in the hypothalamus after fasting in wild-type, but not FGF21 knockout, mice and with administration of recombinant FGF21. Finally, central administration of an ERK1/2 inhibitor blocked the effects of recombinant FGF21 on plasma corticosterone and glucose concentrations, as well as hepatic expression of gluconeogenic enzymes. Collectively, these findings suggest a model wherein liver-derived FGF21 acts in the hypothalamus via ERK1/2 signaling to stimulate HPA axis activity and increase the production of corticosterone by the adrenals, thereby enhancing hepatic gluconeogenesis (Fig. 1).

The central mechanism for FGF21 action fits well with another recent report showing that the effects of FGF21 on glucocorticoid secretion, behavior, and peripheral metabolism were mediated in the hypothalamus (10). Using conditional βKlotho knockout mice, Bookout et al. (10) showed that βKlotho in the brain is required for the effects of FGF21 on glucocorticoid secretion. While the work of Liang et al. (11) is consistent with this previous study and provides new mechanistic insight into how FGF21 controls peripheral metabolism via effects in the central nervous system, several questions remain regarding the central actions of FGF21. For example, although the gluconeogenic effects of FGF21 are attributable to hypothalamic mechanisms, glucocorticoid antagonism or ablation did not affect hepatic ketogenesis or fatty acid metabolism in response to FGF21 in the current study. In contrast, Bookout et al. (10) found that loss of βKlotho in the brain attenuated the elevated ketogenesis in the FGF21 transgenic mice in their study. The specific brain nuclei that FGF21 acts upon to elicit the peripheral metabolic effects also will need to be clarified as Bookout et al. reported no expression of mRNA for βKlotho in the PVN and attributed the central effects of FGF21 to the suprachiasmatic nucleus of the hypothalamus and the hindbrain. Both studies also raise questions concerning whether the effects of FGF21 on lipolysis are direct or mediated by increased systemic glucocorticoid levels. Although no effect of FGF21 on hepatic catecholamine levels was observed in the study by Liang et al. (11), it is unclear whether the increased adrenocorticotropic hormone production by FGF21 administration also alters plasma catecholamine levels. Several studies have recently reported an increase in plasma FGF21 during various stresses (13) and in response to a low-protein diet (14,15). Future studies are needed to determine whether induction of FGF21 under these conditions functions to induce a hypothalamic-initiated stress response. Finally, could FGF21 therapeutics that do not engage FGFR1/βKlotho in the central nervous system provide a better pharmacology for treating diabetes by avoiding an undesirable activation of the HPA axis? The new report by Liang et al. (11) highlights these important questions and provides a firm rationale for future studies in this area.

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References

1. Potthoff MJ, Kliewer SA, Mangelsdorf DJ. Endocrine fibroblast growth factors 15/19 and 21: from feast to famine. Genes Dev 2012;26:312–324
2. Gaich G, Chien JY, Fu H, et al. The effects of LY2405319, an FGF21 analog, in obese human subjects with type 2 diabetes. Cell Metab 2013;18:333–340
3. Markan KR, Naber MC, Ameka MK, et al. Circulating FGF21 is liver derived and enhances glucose uptake during refeeding and overfeeding. Diabetes 2014;63:4057–4063
4. Inagaki T, Dutchak P, Zhao G, et al. Endocrine regulation of the fasting response by PPARalpha-mediated induction of fibroblast growth factor 21. Cell Metab 2007;5:415–425
5. Badman MK, Pissios P, Kennedy AR, Koukos G, Flier JS, Maratos-Flier E. Hepatic fibroblast growth factor 21 is regulated by PPARalpha and is a key mediator of hepatic lipid metabolism in ketogenic states. Cell Metab 2007;5:426–437
6. Potthoff MJ, Inagaki T, Satapati S, et al. FGF21 induces PGC-1alpha and regulates carbohydrate and fatty acid metabolism during the adaptive starvation response. Proc Natl Acad Sci U S A 2009;106:10853–10858
7. Xu J, Lloyd DJ, Hale C, et al. Fibroblast growth factor 21 reverses hepatic steatosis, increases energy expenditure, and improves insulin sensitivity in diet-induced obese mice. Diabetes 2009;58:250–259
8. Ding X, Boney-Montoya J, Owen BM, et al. βKlotho is required for fibroblast growth factor 21 effects on growth and metabolism. Cell Metab 2012;16:387–393
9. Fisher FM, Estall JL, Adams AC, et al. Integrated regulation of hepatic metabolism by fibroblast growth factor 21 (FGF21) in vivo. Endocrinology 2011;152:2996–3004
10. Bockout AL, de Groot MH, Owen BM, et al. FGF21 regulates metabolism and circadian behavior by acting on the nervous system. Nat Med 2013;19:1147–1152
11. Liang Q, Zhong L, Zhang J, et al. FGF21 maintains glucose homeostasis by mediating the cross talk between liver and brain during prolonged fasting. Diabetes 2014;63:4064–4075
12. Hsuchou H, Pan W, Kastin AJ. The fasting polypeptide FGF21 can enter brain from blood. Peptides 2007;28:2382–2386
13. Luo Y, McKeohan WL. Stressed liver and muscle call on adipocytes with FGF21. Front Endocrinol (Lausanne) 2013;4:194
14. Lees EK, Kröl E, Grant L, et al. Methionine restriction restores a younger metabolic phenotype in adult mice with alterations in fibroblast growth factor 21. Aging Cell 17 June 2014
15. Stone KP, Wanders D, Orgeron M, Cortez CC, Gettys TW. Mechanisms of increased in vivo insulin sensitivity by dietary methionine restriction in mice. Diabetes 2014;63:3721–3733