

Role of Fibroblast Growth Factor 21 in Biology of Glucagon

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A new report in this issue of *Diabetes* provides evidence that at least some metabolic actions of glucagon may be mediated by fibroblast growth factor 21 (FGF21). Habegger et al. (1) report that native glucagon raises plasma FGF21 levels in human subjects, confirming the report by Arafat et al. (2). They also find that a synthetic glucagon receptor agonist (IUB288) upregulates FGF21 expression in isolated primary hepatocytes from wild-type, but not glucagon receptor-null, mice. Moreover, the new report shows that IUB288-induced effects to curb diet-induced obesity are absent in mice lacking FGF21. The authors conclude that glucagon controls glucose levels, energy, and lipid metabolism, at least in part, via FGF21-dependent pathways. This may constitute an important step forward in our understanding of both glucagon and FGF21 biology.

As the authors recognize, many unanswered questions remain. First and foremost is whether the long-acting glucagon analog IUB288, which is used in most of the experiments, faithfully reproduces the physiologic actions of native glucagon. Based on the greater magnitude of enhancement of hepatocyte cAMP by IUB288 in vitro and its extended half-life, its hyperglycemic effect in vivo is surprisingly weak and short-lived. In contrast, its effect on body weight and cholesterol appears to be more potent than native glucagon. Furthermore, whereas native glucagon is a potent insulinogenic stimulus (3), the analog does not appear to mimic this action. Finally, it is unclear if the analog suppresses native glucagon secretion into the portal circulation. Such an effect could alter the insulin-to-glucagon ratio reaching the liver and profoundly impact metabolic regulation. An extension of this question is whether a loss of biological activity of native glucagon secreted directly into the portal vein is replaced by the biological activity of the peripherally injected analog.

Although discovered in 1923, glucagon was not recognized as a hormone for almost five decades. The development of a radioimmunoassay in 1959 made possible elucidation of glucagon's role in normal physiology and in disorders such as diabetes and stress hyperglycemia (4). By 1975, it was proposed that glucagon plays a crucial role

in the pathogenesis of diabetes (4). Plasma glucagon concentration is now known to be elevated in every known form of diabetes, including total pancreatectomy, and all agents that suppress glucagon also lower hyperglycemia (4). More recently, it was reported that the metabolic abnormalities of diabetes cannot occur in glucagon receptor-null mice in which virtually all insulin-producing pancreatic β -cells are destroyed (5).

In summary, the study by Habegger et al. (1) builds upon evidence that FGF21 is a player in glucagon biology, but fails to identify precisely those glucagon actions that it mediates. Given the sine qua non status of glucagon in diabetes, it is vital to determine if FGF21 is a diabetogenic mediator of glucagon-induced overproduction of glucose and ketones that occurs in untreated insulin deficiency. Alternatively, prior work shows that FGF21 suppresses plasma glucagon (6,7) and is antidiabetic agent (6,7). The report by Habegger et al. (1) should stimulate continued effort to resolve the seemingly conflicting roles of this intriguing regulatory axis.

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REFERENCES

1. Habegger KM, Stemmer K, Cheng C, et al. Fibroblast growth factor 21 mediates specific glucagon actions. *Diabetes* 2013;62:1453–1463
2. Arafat AM, Kaczmarek P, Skrzypski M, et al. Glucagon increases circulating fibroblast growth factor 21 independently of endogenous insulin levels: a novel mechanism of glucagon-stimulated lipolysis? *Diabetologia* 2013;56:588–597
3. Marks V, Samols E. Glucagon test for insulinoma: a chemical study in 25 cases. *J Clin Pathol* 1968;21:346–352
4. Unger RH. The Banting Memorial Lecture 1975. *Diabetes and the alpha cell*. *Diabetes* 1976;25:136–151
5. Lee Y, Wang MY, Du XQ, Charron MJ, Unger RH. Glucagon receptor knockout prevents insulin-deficient type 1 diabetes in mice. *Diabetes* 2011;60:391–397
6. Berglund ED, Li CY, Bina HA, et al. Fibroblast growth factor 21 controls glycemia via regulation of hepatic glucose flux and insulin sensitivity. *Endocrinology* 2009;150:4084–4093
7. Kharitonov A, Shiyanova TL, Koester A, et al. FGF-21 as a novel metabolic regulator. *J Clin Invest* 2005;115:1627–1635

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