Commentary

MOLECULAR METABOLISM

FGF19: How gut talks to brain to keep your sugar down*

Sarah Stanley [1], Christoph Buettner [2,*]

The homeostatic systems regulating energy and glucose metabolism perform a complex balancing act of meeting short term requirements for increased energy whilst maintaining long term energy stores. Multiple signals are involved in this process, from the gastrointestinal tract, pancreas and adipose tissue, which in turn also modulate CNS pathways to control appetite and glucose metabolism. The effectiveness of bariatric surgery in treating both obesity and diabetes has highlighted the importance of gut hormones in metabolic control. A long list of signals released from enteroendocrine cells in the gastrointestinal tract act to regulate feeding, induce satiety and control blood glucose, among them cholecystokinin released from I cells, ghrelin from the gastric mucosa, peptide YY, oxyntomodulin and glucagon-like peptide 1 from the L cells.

Recently, fibroblast growth factor 19 (FGF-19) and its rodent homolog, FGF-15, have been added to the catalog of gastrointestinal hormones regulating metabolism. FGF19 levels are reduced in individuals with metabolic syndrome, non-alcoholic fatty liver disease and FGF19 levels are restored to normal values in obese patients who undergo Roux-en-Y gastric bypass bariatric surgery [1,2]. FGF-15 is released from enteroendocrine cells of the ileum in response to post-prandial secretion of bile acids and reduces weight and improves glucose tolerance in obese mice, effects that were believed to be mediated through peripheral effects, mostly on the liver [1]. However, recent papers by Marcelin, in the current edition of Molecular Metabolism [3], Ryan et al. [4] and Morton et al. [5] have shown that the actions of FGF-19 within the CNS play an important role in its ability to regulate appetite and glucose homeostasis. Marcelin et al. demonstrate that central FGF-19 acts to decrease food intake and body weight and improve glucose tolerance in obese mouse models. In addition, all three groups show that the CNS mediated improvements in glucose homeostasis are independent of a reduction in body weight.

Studies performed by Ryan et al. in chow fed rats demonstrate that administration of FGF-19 improved glucose tolerance with no change in insulin release. Morton et al. found similar results in ob/ob mice. A single ICV injection of FGF-19 improved glucose tolerance with no change in insulin secretion. Minimal model analysis of the data from the frequently sampled intravenous glucose tolerance testing suggested this improvement was the result of improved insulin-independent glucose disposal rather than insulin sensitivity. Marcelin et al. assessed the effects of repeated and single ICV administration of FGF-19. Daily ICV injections of FGF-19 over 4 days to mice fed a high fat diet did not alter basal glucose but reduced fasting insulin whilst in ob/ob mice both fasting glucose and insulin were decreased. Glucose administration significantly increased plasma insulin in both FGF-19 treated HFD and ob/ob mice but only to the levels seen in vehicle treated mice. Acute FGF-19 administration (though two injections rather than one) to HFD treated mice similarly improved glucose tolerance without changing plasma insulin. However, in contrast to the findings in Morton et al., Marcelin et al. also demonstrated that FGF-19 enhanced the phosphoAKT response to insulin in liver and skeletal muscle. This suggests that the actions of central FGF-19 to augment peripheral insulin signaling in selected tissues may underlie its ability to improve glucose tolerance. These differences may reflect the differing obesity models (ob/ob versus high fat feeding), but, probably more importantly, they result from the differing methods used to assess glucose homeostasis.

Morton et al. used for the first time the frequently sampled i.v. glucose tolerance test (FSIGT) to study the CNS actions of a hormone and demonstrated that the glucose effectiveness was enhanced by central FGF19 in ob/ob mice while they were unable to find any improvement in insulin sensitivity as assessed by the FSIGT. Insulin sensitivity is commonly assessed with hyperinsulinemic clamp studies. What are the potential limitations of the FSIGT and clamp protocols in the study of glucose fluxes? The FSIGT is potentially inaccurate in the assessment of insulin sensitivity when used in severely insulin resistant animals such as ob/ob mice, analogous to what has been reported in humans with significant insulin resistance [6]. The advantage of the clamp is that it is able to control insulin levels while maintaining euglycemia. This clamp can be used to study insulin action when insulin is raised as is done during a hyperinsulinemic clamp. However, the direct effects of insulin on the liver are potent and often override more subtle regulators such as a modulation of the autonomic nervous system that can also regulate hepatic glucose fluxes. Thus, the direct actions of insulin on the liver during a hyperinsulinemic clamp will in many settings mask the more subtle effects that are exerted via the CNS on the liver and it is therefore often not a good protocol to study the role of the CNS in controlling

[1]Department of Molecular Genetics, The Rockefeller University, 1230 York Avenue, New York, NY 10065, USA [2]Department of Medicine, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, New York, NY 10029-6574, USA

*Corresponding author. Email: christoph.buettner@mssm.edu.(C. Buettner)

Received October 28, 2013 • Accepted October 30, 2013 • Available online 5 November 2013

http://dx.doi.org/10.1016/j.molmet.2013.10.008

hepatic glucose fluxes. For that reason Rossetti et al. studied the effects of centrally infused hormones with the basal insulin clamp protocol where insulin is kept at low levels, an experimental protocol that turned out to be a more sensitive approach to studying the roles of central hormone signaling in regulating glucose fluxes and that has been used by several investigator [7–9]. During a basal clamp the direct effects of insulin on the liver are mostly absent (as insulin is low) and insulin concentrations are maintained constant and not raised [8] and therefore one can make the argument that what is assessed is not insulin action *per se*, but rather insulin independent effects on glucose fluxes, for example due to a change in autonomic input to the liver. Admittedly, most investigators, one of the authors included have described the effects of central infusions of hormones such as leptin and insulin on hepatic glucose fluxes during a basal insulin clamp, as an assessment of hepatic insulin action, which, based on above considerations, is not accurate [7–9]. It is quite possible that the basal clamp and the FSIGT study the same phenomenon of insulin independent regulation of glucose fluxes, with the clamp having the advantage that one avoids unphysiologic hyperglycemia and is able to control circulating insulin levels. What are the advantages of the FSIGT versus a clamp? The FSIGT does not require a somatostatin infusion which is used to control insulin secretion during a clamp. Since somatostatin receptors are expressed at many sites within the CNS it is possible that somatostatin may interfere with the central actions of hormones. A direct comparison of the basal clamp with the FSIGT as a method to characterize the effects of CNS control of glucose fluxes would be useful to test if both methods describe the same insulin independent phenomenon as further validation of these two methods to study CNS control of nutrient partitioning.

Interestingly, many gastrointestinal signals converge on the CNS in the hypothalamic arcuate nucleus and these recent papers show FGF-15 is among them. In a manner similar to $PYY_{3\text{-}36}$ [10], Marcelin et al. show that FGF-19 inhibits fasting-induced increases in c-fos in the arcuate NPY neurons and reduces fasting-induced increases in NPY and Agrp mRNA. These findings suggest reduced NPY/Agrp neuronal activity and so reduced inhibition of, i.e. increased, melanocortin signaling are involved in mediating the effects of FGF-19 on glucose homeostasis. In keeping with this, the improvement in glycemic control with FGF-15 was lost in Agouti mice with constitutive blockade of MC3R and MC4R. In contrast, Morton et al. found that loss of MC4R expression in $MC4R^{-/-}$ mice did not affect the ability of FGF-19 to improve glucose tolerance. Whether these differences are due to MC3R signaling versus different developmental compensation in these two genetic mouse models remains to be determined.

There is still much to learn: which FGF receptor in what neuron is regulated by FGF-19 as well as other members of this class of hormones that includes FGF-21? How does FGF-19 depend on MC3R versus MC4R and interact with ghrelin, oxyntomodulin and Pyy3-36 that also signals in arcuate NPY/Agrp neurons?

And on a more general basis, how is this CNS control of systemic glucose metabolism exerted in peripheral tissues? Is the liver the primary target organ, or are muscle and adipose tissue part of this regulatory pathway that is under the control of central FGF-19; and if so, is this all mediated via the autonomic nervous system or are circulating hormones involved? Lastly, the central aspect of FGF-19 could be particularly important as previous studies demonstrated that hepatic responses to FGF-19 are impaired in obese mice [11] while these studies suggest that FGF-19 still is able to act via the CNS [3,4] which positions FGF-19 as a promising therapeutic target for the treatment of obesity and diabetes. Thus, while these studies identify the CNS actions of the gut hormone FGF-19 as an important regulatory pathway in glucose homeostasis, they also may lead to a reappraisal of the methods used to study CNS control of glucose partitioning.

REFERENCES

[1] Schreuder, T.C., Marsman, H.A., Lenicek, M., van Werven, J.R., Nederveen, A.J., Jansen, P.L., et al., 2010. The hepatic response to FGF19 is impaired in patients with nonalcoholic fatty liver disease and insulin resistance. American Journal of Physiology – Gastrointestinal and Liver Physiology 298 (3):G440–G445.

[2] Pournaras, D.J., Glicksman, C., Vincent, R.P., Kuganolipava, S., Alaghband-Zadeh, J., Mahon, D., et al., 2012. The role of bile after Roux-en-Y gastric bypass in promoting weight loss and improving glycaemic control. Endocrinology 153 (8):3613–3619.

[3] Marcelin, G., Jo, Y.-H., Li, X., Schwartz, G., Zhang, Y., Dun, N.J., et al., 2013. Central action of FGF19 reduces hypothalamic AGRP/NPY neuron activity and improves glucose metabolism. Molecular Metabolism 3, http://dx.doi.org/10.1016/j.molmet.2013.10.002.

[4] Ryan, K.K., Kohli, R., Gutierrez-Aguilar, R., Gaitonde, S.G., Woods, S.C., Seeley, R.J., 2013. Fibroblast growth factor-19 action in the brain reduces food intake and body weight and improves glucose tolerance in male rats. Endocrinology 154 (1):9–15.

[5] Morton, G.J., Matsen, M.E., Bracy, D.P., Meek, T.H., Nguyen, H.T., Stefanovski, D., et al., 2013. FGF19 action in the brain induces insulin-independent glucose lowering. Journal of Clinical Investigation 123 (11):4799–4808.

[6] Lee, S., Muniyappa, R., Yan, X., Chen, H., Yue, L.Q., Hong, E.G., et al., 2008. Comparison between surrogate indexes of insulin sensitivity and resistance and hyperinsulinemic euglycemic clamp estimates in mice. American Journal of Physiology – Endocrinology and Metabolism 294 (2):E261–E270.

[7] Obici, S., Feng, Z., Arduini, A., Conti, R., Rossetti, L., 2003. Inhibition of hypothalamic carnitine palmitoyltransferase-1 decreases food intake and glucose production. Nature Medicine 9 (6):756–761.

[8] Scherer, T., O'Hare, J., Diggs-Andrews, K., Schweiger, M., Cheng, B., Lindtner, C., et al., 2011. Brain insulin controls adipose tissue lipolysis and lipogenesis. Cell Metabolism 13 (2):183–194.

[9] Mighiu, P.I., Yue, J.T., Filippi, B.M., Abraham, M.A., Chari, M., Lam, C.K., et al., 2013. Hypothalamic glucagon signaling inhibits hepatic glucose production. Nature Medicine 19 (6):766–772.

[10] Batterham, R.L., Cowley, M.A., Small, C.J., Herzog, H., Cohen, M.A., Dakin, C.L., et al., 2002. Gut hormone PYY(3-36) physiologically inhibits food intake. Nature 418 (6898):650–654.

[11] Fu, T., Choi, S.E., Kim, D.H., Seok, S., Suino-Powell, K.M., Xu, H.E., et al., 2012. Aberrantly elevated microRNA-34a in obesity attenuates hepatic responses to FGF19 by targeting a membrane coreceptor beta-Klotho. Proceedings of the National Academy of Sciences of the United States of America 109 (40):16137–16142.

