Taking Aim at Islet Hormones With GLP-1: Is Insulin or Glucagon the Better Target?

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The last decade has seen a shift in the therapeutics of type 2 diabetes from insulin-centric to more multifarious approaches. Whereas previously drug treatment was based almost entirely on increasing insulin action—either by giving drugs to raise plasma insulin levels or to increase tissue responsiveness to insulin—it is now clear that addressing other processes controlling glucose metabolism is also fruitful. To wit, drugs that delay gastric emptying or carbohydrate digestion or promote renal glucose elimination have been shown to be effective for treating hyperglycemia. Compounds that affect hepatic glucose production directly or act through the central nervous system to lower blood glucose are in various phases of development. Moreover, glucagon, long known to contribute to abnormal glucose regulation in diabetes (1,2), is now amenable to therapeutic manipulation using drugs based on the naturally occurring hormones islet amyloid polypeptide (IAPP, also known as amylin) and glucagon-like peptide 1 (GLP-1).

GLP-1 is an essential component of the system regulating blood glucose and has been the basis for two new classes of drugs to treat diabetes, GLP-1 receptor (GLP-1r) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors (3,4). GLP-1r activation has a broad reach that affects islet hormone secretion, gastrointestinal motility, food intake, and glucose production, all in a manner that lowers blood glucose (5). While enhanced β-cell function is generally accepted to be central in the glycemic response to GLP-1, it is noteworthy that plasma levels of insulin and C-peptide in patients treated with GLP-1r agonists and DPP-4 inhibitors are not dramatically increased (6–8). This is due in part to the overall effect of GLP-1 signaling to lower blood glucose, reducing the glycemic stimulus to the β-cells. With sophisticated modeling of plasma C-peptide levels, the insulinotropic effects of GLP-1–based drugs are clear (6,7), but the subtlety of the effect has raised questions about other mechanisms for glucose lowering. Thus, there has been a clear reason to focus on other responses to GLP-1r signaling.

Suppression of glucagon secretion by GLP-1 was described soon after the peptide was discovered and was demonstrable in cultured cells, animals, and humans. There remains some question as to whether the effects of GLP-1 to reduce plasma glucagon in vivo is a direct effect mediated through GLP-1r on α-cells, or whether this effect is indirect via neural or paracrine mechanisms (3). However, there is no doubt that some of the most influential observations advancing GLP-1 as a model therapeutic were the demonstrations that intravenous administration to fasting subjects with diabetes lowered blood glucose coincident with reductions in plasma glucagon (9,10). This effect was particularly compelling in a study of type 1 diabetic patients in whom the absence of endogenous insulin secretion supported reduction of glucagon as the primary mechanism by which GLP-1 reduced blood glucose (10). Importantly, these effects have been borne out clinically, since both GLP-1r agonists and DPP-4 inhibitors reduce plasma glucagon as part of their pharmacologic activity (11).

In this issue of *Diabetes*, Hare et al. (12) revisit the glucagonostatic effects of GLP-1 in the context of fasting hyperglycemia. The goal of their study was to quantify the relative contributions of insulin and glucagon to mediate changes in blood glucose induced by GLP-1. To do this, they studied a group of middle-aged men with well-controlled type 2 diabetes who had moderate fasting hyperglycemia after withdrawal from oral agents. Each subject had five separate glucose clamps during which glycemia was maintained at ~10 mmol/l during various combinations of GLP-1, insulin, glucagon, and somatostatin infusion. In the experiment to define the GLP-1 effect (day 1), a supraphysiologic amount of GLP-1 was infused for 2 h while blood glucose concentrations were held steady with a variable glucose infusion. Plasma insulin and glucagon during this treatment reflected the actions of GLP-1 on islet secretion, and the total amount of glucose required to maintain the clamp was used as the sum of GLP-1 action. In subsequent experiments (days 2–5), somatostatin was given to block the secretion of endogenous glucagon and insulin, and these peptides were given intravenously to mimic basal concentrations or levels obtained during GLP-1 treatment. These treatments were arranged in specific combinations to isolate the effects of GLP-1–stimulated insulin or GLP-1–inhibited glucagon on glucose requirements during the clamp. The authors report that during the experiments mimicking GLP-1–induced hyperinsulinemia without glucagon suppression (day 4) and glucagon suppression without elevated plasma insulin (day 3), the glucose requirements were similar and half of what was required on day 1 when GLP-1 was given. When the infusions were adjusted to mimic GLP-1 administration, i.e., stimulated insulin and suppressed glucagon together (day 5), the glucose requirements to maintain stable glycemia were comparable with the GLP-1 infusion alone. The authors conclude from these findings that α-cell inhibition and β-cell stimulation contribute equally to the

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effect of GLP-1 to lower fasting hyperglycemia in type 2 diabetic individuals.

The findings of Hare et al. reiterate the important bihormonal regulation of the islet by GLP-1 and suggest significant benefits from glucagon lowering in the treatment of type 2 diabetes. The general messages of this paper—that the actions of glucagon contribute to fasting hyperglycemia in diabetes and that this can be mitigated by GLP-1—seem beyond question. However, there are reasons to quibble with the relative effects of β-cell stimulation and α-cell inhibition that are estimated from this study. While logically designed and cleanly executed, the investigators had to make several assumptions and compromises in their experiments that potentially affect the outcomes. The regulation of fasting glucose by insulin and glucagon occurs primarily through control of hepatic glucose production and is dependent to a great extent on concentrations of islet hormones in the hepatic portal vein (13–15). Because of the substantial clearance of insulin and glucagon by the liver, steady-state concentrations of endogenously released islet hormones in the portal vein are estimated to be ~1.5- to 3-fold higher than those in the peripheral circulation. Mimicking the effects of hepatic portal insulin and glucagon with exogenous infusions is difficult in humans because portal venous concentrations cannot be directly measured, and because the replacement must be given into a peripheral vein.

Examination of the data presented by Hare et al. suggests that some of the outcomes were biased by difficulties in reproducing portal concentrations of insulin and glucagon to mimic the effects of GLP-1. To recreate the suppressive effects of GLP-1 on portal plasma glucagon, α-cell output was blocked with somatostatin in the absence of glucagon replacement. Although peripheral glucagon levels during these conditions (days 3 and 5) did not appear to be very different from those during the GLP-1 infusion (day 1), portal concentrations of glucagon in these experiments can only be inferred. When GLP-1 was given (day 1), peripheral glucagon levels gradually drifted down from ~20 to ~5 pmol/l, and it is fair to assume that portal glucagon was about twice as high. In contrast, on days 3 and 5, peripheral glucagon levels dropped quickly and approached the limit of detectability, consistent with a near total inhibition of the α-cells. Under these conditions portal levels would also be minimal, magnifying relative differences in the amounts of glucagon seen by the liver with GLP-1 infusion and the experimental reproductions. Mismatch of portal glucagon during the GLP-1 infusion and the matching experiments would overestimate the effects of α-cell suppression to lower blood glucose. The approach to matching plasma insulin during GLP-1 administration (day 1) and the matching studies (days 4 and 5) also needs to be considered. Unlike glucagon, insulin has major effects on peripheral, as well as hepatic, glucose metabolism. The authors admittedly tried to match peripheral insulin levels during their pancreatic clamps so as not to induce major differences in glucose disposal. However, this approach does not account for the two- to threefold greater levels of insulin in portal blood that would be expected during GLP-1 infusion. As a result, it seems likely that any effects of GLP-1 to suppress hepatic glucose production by raising portal levels of insulin would be missed in the matching experiments, reducing the apparent insulinotropic impact of GLP-1. The difficulty in creating appropriately matched hormonal conditions leaves some doubt as to whether the neat 50–50 split between insulin stimulation and glucagon inhibition is an accurate depiction of glucose lowering by GLP-1. Given the considerations discussed above, it seems likely that insulinotropic effects are quantitatively greater than glucagonostatic ones. By how much is a question that requires an experimental paradigm in which portal hormone levels can be measured and reproduced more precisely. Unfortunately, we do now have practical ways to do this in humans.

Do the questions raised about the results in this paper diminish the importance of the results to the clinical application of GLP-1 in diabetes? Probably not. The work of Hare et al. is interesting and informative and, given the current techniques for studying human subjects, it gives as close an approximation of GLP-1 effects on islet secretion as we could ask for. At the least, these results reinforce the potential of glucagon suppression as a useful adjunct to the more conventional insulin–action approaches to treating diabetes. It is probable that the contribution of glucagon to hyperglycemia varies among diabetic patients, and tailored therapy focused on glucagon lowering might be especially effective in some individuals. The ability to target both islet hormones has been one of the novel additions that GLP-1r agonists and DPP-4 inhibitors bring to the therapeutic profile for diabetes. GLP-1 has been an exciting bench-to-bedside success, and taking observations from the clinical application of GLP-1 back to the lab for reexamination seems like a fruitful approach for revising and extending these advances.

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REFERENCES

1. Unger RH, Orci L. The essential role of glucagon in the pathogenesis of diabetes mellitus. Lancet 1975;1:14–16
2. Shah P, Vella A, Basu A, Basu R, Schwenk WF, Rizza RA. Lack of suppression of glucagon contributes to postprandial hyperglycemia in subjects with type 2 diabetes mellitus. J Clin Endocrinol Metab 2000;85:4053–4059
3. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastroenterology 2007;132:2131–2157
4. Lovshin JA, Drucker DJ. Incretin-based therapies for type 2 diabetes mellitus. Nat Rev Endocrinol 2009;5:262–269
5. D'Alessio DA, Vahl TP. Glucagon-like peptide 1: evolution of an incretin into a treatment for diabetes. Am J Physiol Endocrinol Metab 2004;286:E882–E890
6. Mari A, Scherbaum WA, Nilsson PM, Lalanne G, Schweizer A, Dunning BE, Jauffret S, Foley JE. Characterization of the influence of vildagliptin on model-assessed-cell function in patients with type 2 diabetes and mild hyperglycemia. J Clin Endocrinol Metab 2008;93:103–109
7. Mari A, Nielsen LL, Nanayakkara N, DeFronzo RA, Ferrannini E, Halseth A. Mathematical modeling shows exenatide improved beta-cell function in patients with type 2 diabetes treated with metformin or metformin and a sulfonylurea. Horm Metab Res 2006;38:838–844
8. Juhl CB, Hollingdal M, Sturis J, Jakobsen G, Agersø H, Veldhuis J, Pørksen N, Schmitz O. Bedtime administration of NN2211, a long-acting GLP-1 derivative, substantially reduces fasting and postprandial glycemia in type 2 diabetes. Diabetes 2002;51:424–429
9. Nauck MA, Kleine N, Orskov C, Holst JJ, Willms B, Creutzfeldt W. Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7–36 amide) in type 2 (non-insulin-dependent) diabetic patients. Diabetologia 1993;36:741–744
10. Creutzfeldt WO, Kleine N, Willms B, Orskov C, Holst JJ, Nauck MA. Glucagonostatic actions and reduction of fasting hyperglycemia by exogenous glucagon-like peptide I(7–36) amide in type I diabetic patients. Diabetes Care 1996;19:580–586
11. Ahrén B, Schmitz O. GLP-1 receptor agonists and DPP-4 inhibitors in the treatment of type 2 diabetes. Horm Metab Res 2004;36:867–876

12. Hare KJ, Vilsbøll T, Asmar M, Deacon CF, Knop FK, Holst JJ. The glucagonostatic and insulinotropic effects of glucagon-like peptide 1 contribute equally to its glucose-lowering action. Diabetes 2010;59:1765–1770
13. Mittelman SD, Fu YY, Rebrin K, Steil G, Bergman RN. Indirect effect of insulin to suppress endogenous glucose production is dominant, even with hyperglucagonemia. J Clin Invest 1997;100:3121–3130
14. Lewis GF, Vranic M, Giacca A. Glucagon enhances the direct suppressive effect of insulin on hepatic glucose production in humans. Am J Physiol 1997;272:E371–E378
15. Sindelar DK, Chu CA, Venson P, Donahue EP, Neal DW, Cherrington AD. Basal hepatic glucose production is regulated by the portal vein insulin concentration. Diabetes 1998;47:523–529