JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 4, NO. 2, 2019

EDITORIAL COMMENT

Modulation of Glucagon Signaling

A Metabolic Approach for Heart Failure?*

Alessandro Pocai, MD

Glucagon is secreted mainly from the α-cells of the pancreas and regulates glucose homeostasis through modulation of hepatic glucose production. As elevated glucagon levels contribute to the pathophysiology of hyperglycemia in patients with type 2 diabetes (T2D) (1), there have been several attempts to develop small-molecule glucagon receptor (GCGR) antagonists. Although promising glucose-lowering effects have been reported, dose-dependent increase in LDL-cholesterol, blood pressure, body weight, and plasma transaminases have been observed (2–4). In recent years, and thanks also to the information obtained from these clinical trials, more under-acknowledged pleiotropic effects of glucagon on lipids and body weight have become clearer (5). Glucagon is also reported to have effects on the cardiovascular system, but a thorough understanding of the impact of modulation of GCGR on the heart is still lacking (6). Several drugs already used in patients with T2D result in increased or decreased circulating glucagon and have been tested in cardiovascular outcome trials. The data obtained so far have not established a clear beneficial or deleterious directionality for glucagon. Dipeptidyl peptidase-4 inhibitors that have a glucagonostatic effect have shown cardiovascular neutrality or higher risk of hospitalization for heart failure (7), whereas glucagon-like peptide-1 receptor (GLP1R) agonists lower glucagon but also have additional effects on body weight and blood pressure and are either neutral or cardioprotective (7). Sodium glucose cotransporter-2 inhibitors (SGLT2i), which have been reported to increase plasma glucagon (8), result in reduction of the rates of hospitalization for heart failure (7).

SEE PAGE 161

In this issue of *JACC: Basic to Translational Science*, Gao et al. (9) report the consequences of antagonizing glucagon receptors with a monoclonal antibody (REMD2.59) in 2 nondiabetic rodent models of heart failure.

Mice with myocardial infarction (MI)-induced by ligation of the left coronary artery were treated with PBS, REMD2.59, or glucagon. Histopathologic and morphological analysis of heart post-MI showed reduced infarct size areas in animals treated with REMD2.59, whereas glucagon-injected animals showed a trend toward larger infarct size areas. REMD2.59 also reduced myocardial fibrosis, heart weight, and myocyte cross-sectional area. Consistent with impact on systolic function, chamber dilation was observed in vehicle- and glucagon-treated groups and was blunted by treatment with REMD2.59. REMD2.59 also improved both systolic and diastolic parameters in the post-MI heart. The authors concluded that REMD2.59 reduces pathological remodeling post-MI by reducing fibrosis and cardiomyocyte hypertrophy, leading to improvement of cardiac function.

Treatment with REMD2.59 (REMD) at the onset of pressure-overload (TAC) partially prevented cardiac hypertrophy and chamber dilation with preservation of systolic and diastolic function. Two weeks after pressure overload, REMD2.59 (REMD therapy) reduced the progression of cardiac pathology but no longer had any effects on left ventricle hypertrophy

*Editorials published in *JACC: Basic to Translational Science* reflect the views of the authors and do not necessarily represent the views of *JACC: Basic to Translational Science* or the American College of Cardiology.

From Cardiovascular and Metabolism, Janssen Research and Development, Spring House, Pennsylvania. Dr. Pocai is an employee of Janssen Pharmaceutical Companies of Johnson and Johnson.

The author attests that he is in compliance with human studies committees and animal welfare regulations of the author's institutions and Food and Drug Administration guidelines including patient consent when appropriate. For more information, visit the *JACC: Basic to Translational Science* author instructions page.

ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2019.03.006

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 4, NO. 2, 2019
APRIL 2019:173–5

while partially preserving residual function of the heart. REMD and REMD-therapy reduced chronic pressure-overload-induced cardiac fibrosis, suggesting reduction in pathological remodeling.

The authors proposed glucagon receptor antagonism as a new therapeutic approach to treat onset and progression of heart failure with different etiologies, independently of any improvements on metabolic status.

The data presented herein are consistent with cardiomyocyte-specific deletion of GCRG (10), demonstrating that heart-specific elimination of GCGR signaling reduces mortality that is induced by experimental ischemia in normal mice.

However, there are some experimental caveats and questions that need to be explored further.

Glucagon was administered as 4 injections a day for the first 6 days to post-MI mice and is expected to increase glucose production with changes in overall metabolic status (5). Also, a placebo group to control for vehicle composition and frequency of administration was not included in this study. Consistent with the above-mentioned metabolic changes in normal mice, the authors reported decreased fasting plasma glucose in mice treated with REMD2.59. Although the animals were nondiabetic, and the injury was localized to the heart, it is unclear if these metabolic changes contributed to the effects observed.

An important consideration is the potential for transability of these findings from mice to humans. Ligation of the left coronary artery is 1 of the preferred methods of inducing local injury and subsequent heart failure. However, contrary to the clinical situation, in which the patient has progressive nonocclusive coronary artery obstruction, MI in this model is due to occlusion of a normal artery. Although the latter is 1 of the strengths of this work—as it allows the evaluation of a potential direct effect on the heart, limiting systemic metabolic changes—it reduces the translational relevance of the model. It would be important to generate mechanistic data supporting a direct effect of REMD2.59 on the heart: for example, by evaluating REMD2.59 in isolated cardiomyocytes. This last experiment would be helpful also because pharmacological blockade may not entirely replicate cardiomyocytes genetic ablation of GCGR (10). As mentioned above, small-molecule GCGR antagonists in patients with T2D have shown increased plasma LDL-cholesterol, blood pressure, weight, and plasma transaminase (2–4). Of note, preliminary assessment of a GCGR antisense did not result in any of these adverse events in patients with T2D, opening the possibility that some actions may not be mediated by GCGR (11). However, there are additional changes observed in humans that need to be evaluated carefully, such as the impact on pancreatic abnormalities including α-cell hyperplasia reported in patients with loss of function of the GCGR (12,13). REMD 2.59 is a surrogate human antibody generated for preclinical studies and is functionally identical to REMD-477 (9). REMD-477 was tested in a short-term study in patients with T1D, and the effects on glucose and circulating hormones were monitored between day 6 and 12 post-treatment (14). Longer-term studies are required to demonstrate that the antibody approach does not have similar liabilities that might offset any direct and indirect benefit on the heart.

In a previous publication, the same authors reported that REMD2.59 activates adenosine monophosphate-activated protein kinase (AMPK) in the heart, leading to improved diabetic cardiomyopathy (15). Activation of heart AMPK has been shown to result in cardiac hypertrophy without apparent functional consequences, reminiscent of cardiac hypertrophy observed in athletes. Whether this effect is tolerable in humans with heart failure of different etiologies has yet to be determined (16).

Recent data suggest a potential beneficial action of ketone bodies in the failing heart (17) and, because glucagon stimulates ketone bodies formation through the liver, it is important to consider that GCGR antagonism may deprive the heart of a key fuel it requires under failing conditions.

Many questions remain regarding the potential beneficial effects of GCGR antagonism on the failing heart. For the reasons highlighted above, these results must be interpreted with caution.

Several combinations with metabolic targets such as GLP-1 and SGLT2i are currently in clinical trials, with the promise of achieving profound weight loss and glucose lowering while leveraging their cardioprotective effects (18–20). These novel approaches are expected to have important bidirectional effects on GCGR. Modulation of metabolic pathways with direct and indirect action on the heart may be critical for the treatment of heart failure with and without concurrent metabolic disorders and support the need for continued mechanistic work to define the pathways involved.

ADDRESS FOR CORRESPONDENCE: Dr. Alessandro Pocai, Janssen Research and Development, Cardiovascular and Metabolism, 1516 Welsh and McKean Roads, Spring House, Pennsylvania 19477. E-mail: apocai1@ITS.JNJ.com.

REFERENCES

1. Ali S, Drucker DJ. Benefits and limitations of reducing glucagon action for the treatment of type 2 diabetes. Am J Physiol Endocrinol Metab 2009;296:e415–21.

2. Engel SS, Xu L, Andryuk PJ, et al. Efficacy and tolerability of MK-0893, a glucagon receptor antagonist (GRA), in patients with type 2 diabetes (T2DM). Diabetes 2011;60 suppl 1:A85.

3. Guzman CB, Zhang XM, Liu R, et al. Treatment with LY2409021, a glucagon receptor antagonist, increases liver fat in patients with type 2 diabetes. Diabetes Obes Metab 2017;19:1521–8.

4. Bergman A, Tan B, Somayaji VR, et al. A 4-week study assessing the pharmacokinetics, pharmacodynamics, safety, and tolerability of the glucagon receptor antagonist PF-06291874 administered as monotherapy in subjects with type 2 diabetes mellitus. Diabetes Res Clin Pract 2017;126:95–104.

5. Müller TD, Finan B, Clemmensen C, et al. The new biology and pharmacology of glucagon. Physiol Rev 2017;97:721–66.

6. Petersen KM, Bøgevig S, Holst JJ, et al. Hemodynamic effects of glucagon: a literature review. J Clin Endocrinol Metab 2018;103:1804–12.

7. Sinha B, Ghosal S. Meta-analyses of the effects of DPP-4 inhibitors, SGLT2 inhibitors and GLP1 receptor analogues on cardiovascular death, myocardial infarction, stroke and hospitalization for heart failure. Diabetes Res Clin Pract 2019;20;150:8–16.

8. Saponaro C, Pattou F, Bonner C. SGLT2 inhibition and glucagon secretion in humans. Diabetes Metab 2018;44:383–5.

9. Gao C, Ren VS, Yu J, et al. Glucagon receptor antagonism ameliorates progression of heart failure. J Am Coll Cardiol Basic Trans Science 2019;4:161–72.

10. Ali S, Ussher JR, Baggio LL, et al. Cardiomyocyte glucagon receptor signaling modulates outcomes in mice with experimental myocardial infarction. Mol Metab 2015;4:132–43.

11. Morgan E, Smith A, Watts L, et al. ISIS-GCGRRX, an antisense glucagon receptor antagonist, caused rapid, robust, and sustained improvements in glycemic control without changes in BW, BP, lipids, or hypoglycemia in T2DM patients on stable metformin therapy. (Abstr109-LB). Diabetes 2014;63 Suppl 1:LB28.

12. Zhou C, Dhall D, Nissen NN, et al. Homozygous P86S mutation of the human glucagon receptor is associated with hyperglucagonemia, alpha cell hyperplasia, and islet cell tumor. Pancreas 2009;38:941–6.

13. Larger E, Wewer Albrechtsen NJ, Hansen LH, et al. Pancreatic alpha cell hyperplasia and hyperglucagonemia due to a glucagon receptor splice mutation. Endocrinol Diabetes Metab Case Rep 2016;2016:16–0081.

14. Pettus J, Reeds D, Cavaiola TS, et al. Effect of a glucagon receptor antibody (REMD-477) in type 1 diabetes: A randomized controlled trial. Diabetes Obes Metab 2018;20:1302–5.

15. Sharma AX, Quittner-Strom EB, Lee Y, et al. Glucagon receptor antagonism improves glucose metabolism and cardiac function by promoting AMP-mediated protein kinase in diabetic mice. Cell Rep 2018;22:1760–73.

16. Myers RW, Guan HP, Ehrhart J, et al. Systemic pan-AMPK activator MK-8722 improves glucose homeostasis but induces cardiac hypertrophy. Science 2017;357:507–11.

17. Horton JL, Davidson MT, Kurishima C, et al. The failing heart utilizes 3-hydroxybutyrate as a metabolic stress defense. JCI Insight 2019;21:4.

18. Gasbjerg LS, Gabe MBN, Hartmann B, et al. Glucose-dependent insulinotropic polypeptide (GIP) receptor antagonists as anti-diabetic agents. Peptides 2018;100:173–81.

19. Clemmensen C, Finan B, Müller TD, DiMarchi RD, Tschöp MH, Hofmann SM. Emerging hormonal-based combination pharmacotherapies for the treatment of metabolic diseases. Nat Rev Endocrinol 2019;15:90–104.

20. Hollander P, Bays HE, Rosenstock J, et al. Coadministration of canagliflozin and phentermine for weight management in overweight and obese individuals without diabetes: a randomized clinical trial. Diabetes Care 2017;40:632–9.

KEY WORDS glucagon, heart failure, metabolism