

EDITORIAL COMMENT

Modulation of Glucagon Signaling

A Metabolic Approach for Heart Failure?*

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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).

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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

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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.

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