Commentary

MOLECULAR METABOLISM

Glucagon signaling in the heart: Activation or inhibition?*

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In this issue of Molecular Metabolism, Ali and colleagues [1] report the consequences of modulating glucagon receptor (GCGR) signaling in the non-diabetic ischemic mouse heart. The authors showed that glucagon administration impairs survival following experimental ischemia. Supporting a direct effect of glucagon on cardiomyocytes, the authors demonstrated that glucagon activates PPARα target genes in cardiac myocytes in a p38-dependent manner and that glucagon promotes cardiomyocyte apoptosis. The authors proposed that stimulation of GCGR signaling in the heart leads to enhanced fat oxidation without the proper clearance of accumulated acylcarnitine derivatives. This ultimately results in impaired *ex vivo* recovery of ventricular pressure in ischemic mouse hearts. The direct effect of glucagon on cardiac performance was supported by the cardioprotective phenotype observed in mice with cardiomyocyte-selective lack of GCGR signaling. This was associated with reduced accumulation of incompletely oxidized fatty acid metabolites leading the authors to hypothesize that this reduced accumulation may be related to the protective effect seen in the ischemic mouse heart.

Patients with diabetes are at a two- to three-fold increased risk of developing cardiovascular disease (CVD). Myocardial infarction and stroke are the major causes of death in patients with diabetes [2]. The increasing interest in drugs that reduce or potentiate GCGR signaling for the treatment of diabetes and obesity raises important questions about the cardiovascular actions and safety of such agents. Therapies already available for the treatment of type 2 diabetes (T2D) can provide important information for combinatorial approaches currently in development that leverage activation of the GCGR [3]. Dipeptidyl peptidase-4 inhibitors (DPP-4i) block the degradation of glucagon-like peptide-1 (GLP-1) improving glucose levels primarily via its insulinotropic and glucagonostatic effects [4]. Recently published clinical trials have evaluated the cardiovascular safety of two DPP-4i in T2D subjects. Contrary to study expectations based on a reduction in events from meta-analysis of short-term clinical trials, neither study demonstrated a reduction in events [4]. These controlled clinical trials are considered by many the first assessment of GLP-1 receptor (GLP1R) activation on cardiovascular safety. While these studies evaluated the effect of GLP1R agonism, they also evaluated the simultaneous reduction of GCGR signaling and changes in numerous cardioactive peptides resulting from inhibition of DPP-4. It is possible that different outcomes would be observed with protease-resistant GLP1R agonists that are known to have insulinotropic and glucagonostatic effects and reduce body weight and blood pressure [4].

The initial data obtained in people with T2D treated with GCGR antagonists showed a promising effect on glucose lowering [5,6]. However, this pharmacological approach results in partial attenuation of the glucagon receptor signaling so it cannot be assumed that it will produce a cardiovascular phenotype similar to the non-diabetic mice with heart-specific reduction of Gcgr signaling. Moreover, if the reported increase in cardiovascular risk factors such as lipids and body weight in patients receiving GCGR antagonists are demonstrated to be on target, they may offset any potential direct beneficial effects on the heart [5].

Other important data will come from the ongoing CV outcome trials for sodium-glucose co-transporter-2 inhibitors (SGLT-2i), a promising new class of oral anti-diabetic medications that act by blocking renal glucose reabsorption [4]. SGLT-2i results in blood pressure and body weight lowering. Recently it has been reported that SGLT-2i increases plasma glucagon levels in subjects with T2D [7].

The findings by Ali and collaborators [1] shed new light on glucagon-mediated control of cardiac physiology and ischemic injury, which could be relevant for therapies designed to either promote or inhibit glucagon action. One of the major merits of the paper is that the *in vivo* loss of function was assessed in mice that allowed the deletion of the cardiac Gcgr expression upon injection with tamoxifen, preventing the potential contribution of compensatory factors arising from the congenital loss of function. Many questions remain to be answered. What is the relevance of these findings for humans with diabetes and insulin resistance? Performing analog acute and chronic experiments in the disease state such as experimental models of obesity and diabetes and *ex-vivo* human models may help address this question. What is the net result on cardiovascular safety of drugs with a direct effect on the heart and metabolic changes that indirectly modulate GCGR signaling and other cardiovascular risk factors? It will be important to evaluate therapeutics that increase GCGR signaling in wild type mice and mice with heart-selective inactivation of GCGR. These findings could be

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relevant also in people with type 1 diabetes (T1D) and T2D treated with insulin who present with or without pre-existing coronary artery disease. In these individuals new glucagon-insulin delivery systems and T2D drugs that modulate glucagon action (GLP1R agonists, DPP-4i, SGLT-2i) are being studied [8]. The authors emphasized the potential issues of GCGR activation in combination therapies that are currently in development [3]. Thus far, no pharmacological or epidemiological data in humans suggest that glucagon action in the heart is deleterious. Data from preclinical models showed that glucagon, not GCGR/GLP1R dual agonists, compromised the energetic state of isolated ischemic rat hearts, thereby mitigating the adverse effects of glucagon [9]. Part of the rationale behind these approaches is driven by the synergistic metabolic effects. It is expected, for example, that GLP1R/GCGR dual agonists will require lower receptor activation and, therefore, lower plasma concentrations to elicit its effect on body weight and glucose lowering as demonstrated in rodents and monkeys [10]. It is important to evaluate any future potential findings associated with single receptor activation in the context of clinical relevant doses for these new classes of compounds. Because therapies currently in use for T2D modulate GCGR signaling in the heart [3,4,7], it would be important to integrate the author's findings with the data available on these drugs. As mentioned above, cardiovascular outcome trials with DPP-4i (resulting in reduction of circulating glucagon in patients with T2D) have not shown improvement in CV events [4]. Finally, Ali et al. [1] showed that the adverse effects of exogenous glucagon on cardiac injury are in part-mediated through a PPARα-dependent pathway, which ultimately leads to increased fatty acid oxidation. Fibrates (PPARα agonists) enhance fatty acid oxidation and have a positive influence in experimental models of cardiac injury and heart failure [11] potentially reflecting differences in systemic vs. cardiac-specific effects. These data suggest that the integrated metabolic changes and the translation to humans need to be taken into account to understand the net effect on cardiovascular safety.

In conclusion, the paper by Ali et al. [1] demonstrates that acute glucagon receptor agonism has negative effects on the heart during experimental ischemia, whereas heart-specific elimination of Gcgr signaling reduces mortality induced by experimental ischemia in normal mice. Additional studies are required to address the relevance of these findings in humans with T1D and T2D. Therefore, in the absence of additional data, it is important to avoid the risk of over-interpretation and extending these observations prematurely to human studies.

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