Deciphering ventricular GLP-1 action: time for a change of heart

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GLUCAGON-LIKE PEPTIDE-1 (GLP-1) is an incretin hormone secreted from gut enteroendocrine L cells in response to nutrient ingestion that potentiates glucose-stimulated insulin secretion via direct actions on the islet β-cell GLP-1 receptor (GLP-1R) (4). Because of these properties, manipulation of GLP-1 action, either through inhibition of dipeptidyl peptidase-4 (DPP4), the enzyme responsible for degradation of GLP-1 (11), or creation of DPP-4 resistant GLP-1R analogs, has been pursued for the treatment of type 2 diabetes mellitus (T2DM). Although incretin-based therapies and other therapies for T2DM are quite effective at controlling glycemia, the majority of patients with T2DM will eventually die from cardiovascular causes (6, 21). Thus there has been a growing interest in the field to understand the cardiovascular risks/benefits associated with therapies for T2DM.

Indeed, incretin-based therapies have shown a number of cardioprotective actions in both preclinical and clinical studies (19, 20), and these cardioprotective actions are further highlighted by Balteau et al. (1), who demonstrated that GLP-1 may protect cardiac myocytes against hyperglycemia-induced oxidative stress in a recent issue of the American Journal of Physiology-Heart and Circulatory Physiology. Using a number of sophisticated techniques, Balteau et al. showed that treatment with native full-length GLP-1 (herein referred to as GLP-17-36) decreased hyperglycemia-induced reactive oxygen species (ROS) production in primary cultures of adult cardiac myocytes. The GLP-17-36-mediated reduction in ROS production was associated with an activation of 5'-AMP-activated protein kinase (AMPK), which prevented p47phox translocation to membrane caveolae and subsequent activation of NADPH oxidase. Illustrating the importance of AMPK activation in their findings, Balteau et al. failed to observe any effect of GLP-17-36 to reduce hyperglycemia-induced p47phox translocation to membrane caveolae in adult cardiac myocytes isolated from mice deficient for the AMPK α2-subunit. Furthermore, treatment of adult cardiac myocytes with additional AMPK activators, A769662 and phenformin, also prevented hyperglycemia-induced ROS production and p47phox translocation to membrane caveolae. Based on their observations, Balteau et al. concluded that GLP-17-36 attenuates early signaling events responsible for glucotoxicity in cardiac myocytes, which has clear beneficial implications with relation to cardiac function in patients with T2DM.

These findings add to the growing body of evidence demonstrating cardioprotective actions of GLP-1R agonists, as treatment of adult mouse cardiac myocytes with the GLP-1R agonist, liraglutide, prevented tumor necrosis factor α-induced apoptosis (14), whereas treatment with GLP-17-36 prevented hydrogen peroxide-induced apoptosis (2). Moreover, a 1-wk pretreatment with liraglutide improved left ventricular (LV) function and reduced adverse LV remodeling in both nondiabetic and diabetic mice (14), whereas a 3-mo infusion of GLP-17-36 improved LV function and improved survival in the spontaneously hypertensive and heart failure-prone rat (15). These findings have been recapitulated in humans, as a 72-h infusion of GLP-17-36, commenced 3.5 h following successful coronary angioplasty in patients undergoing acute myocardial infarction, significantly improved both LV ejection fraction and regional myocardial wall motion (13). Treatment with the GLP-1R agonist exenatide also demonstrated beneficial effects in humans with ischemic heart disease, as a 6-h exenatide infusion initiated 15 min before reperfusion onset in patients undergoing coronary angioplasty decreased infarct size relative to the ischemic area at risk and increased the myocardial salvage index (9). Interestingly, the cardioprotective effects of exenatide in humans with ischemic heart disease are independent of glycemia, as similar effects were observed in both nondiabetic and diabetic patients (10).

While such findings have generally been attributed to direct actions of GLP-17-36/GLP-1R agonists on the cardiac GLP-1R, the recent observation that the GLP-1R is localized to atrial cardiac myocytes and not expressed in ventricular cardiac myocytes (8, 16) prompts a reevaluation of GLP-1R action in the heart. As the majority of ischemic heart disease is due to ischemia of the coronary vessels supplying the LV, how does systemic treatment with GLP-1R agonists improve LV function in humans undergoing coronary angioplasty if there is no GLP-1R present in the ventricular myocardium? Such observations are likely to be explained in part by indirect actions of GLP-17-39/GLP-1R agonists on peripheral tissues that feedback and improve cardiac function, as systemic GLP-1R activation may influence a number of factors associated with cardiovascular risk. This includes reductions in dyslipidemia, hyperglycemia, and adiposity, while also increasing circulating insulin levels (19, 20). Supporting the hypothesis that indirect effects are responsible for GLP-1R-mediated cardioprotection, mice with a cardiac/atrial-specific elimination of the GLP-1R (Glp1r cardiac/−/−) were shown to exhibit similar susceptibility to myocardial infarction-induced mortality and adverse LV remodeling as their αMHCcre-expressing littermates (18). Moreover, treatment with tiraglutide for 1 wk induced robust cardioprotection (improved mortality and reduced adverse LV remodeling) in Glp1r cardiac/−/− mice that was equivalent to the cardioprotection observed in their αMHCcre-expressing littermates (18).

If the cardiac/atrial GLP-1R is not required for GLP-1R agonist-induced cardioprotection and if the GLP-1R is not expressed in ventricular cardiac myocytes, how does direct treatment with GLP-17-36 induce such clear effects in adult mouse ventricular cardiac myocytes observed by Balteau et al.? One possible explanation may be the presence of a second, unidentified, and yet to be characterized GLP-1R or nonreceptor-dependent mechanisms that mediate the effects of GLP-17-36. Indeed, treatment of isolated Langendorff-perfused hearts from whole body GLP-1R-deficient (Glp1r−/−) mice with...
GLP-17-36 and GLP-19-36 can be further cleaved by neutral endopeptidase 24.11, producing multiple smaller carboxy-terminal peptides (7), such as GLP-128-36, and GLP-128-36 may activate mitochondrial signaling pathways through poorly defined mechanisms (17). The cardioprotective actions observed following systemic treatment with GLP-1R agonists may also be due to activation of the GLP-1R in vascular smooth muscle cells and subsequent increases in blood flow and nutrient delivery (5, 16, 19), though that would not explain findings in isolated cardiac myocytes.

Taken together, the observation that GLP-17-36 reduces hyperglycemia-induced oxidative stress in cardiac myocytes by Balteau et al. is consistent with previous literature demonstrating direct actions of GLP-17-36 on isolated cardiac myocytes. However, their findings are unlikely to be due to direct actions of GLP-17-36 on the canonical GLP-1R, as ventricular cardiac myocytes do not express the canonical GLP-1R. Rather, their findings may be explained by GLP-17-36 potentially activating an unidentified GLP-1R or GLP-19-36/GLP-128-36-mediated signal transduction (see Fig. 1). Without a doubt, the cardiovascular biology of GLP-1 is complex and in need of further attention with the growing importance of understanding how therapies for T2DM affect these patients’ cardiovascular function. Future studies should be aimed at understanding the mechanism(s) by which GLP-19-36 and GLP-128-36 mediate their effects in cardiac myocytes, how they may act on mitochondria, whether they may involve an unidentified and yet to be characterized receptor, and whether GLP-17-36 may also bind this unidentified receptor. Furthermore, the fact that structurally distinct GLP-1R agonists, which may not be degraded to GLP-19-36, remain cardioprotective in mice and humans that express an atrial but not a ventricular GLP-1R should reorient the field to understand how the indirect actions of GLP-1R agonists affect ventricular function. Regardless of what the forthcoming answers to these questions may be, therapies employing GLP-1R agonists do appear to show promise for not only improving glycemia in patients with T2DM but also reducing cardiovascular risk.

Fig. 1. Potential glucagon-like peptide-1 (GLP-1)-mediated actions in atrial and ventricular cardiac myocytes. GLP-17-36 has direct actions on atrial cardiac myocytes that express the canonical GLP-1R receptor (GLP-1R), which may be linked to GLP-1-mediated increases in heart rate (18, 19). However, as the canonical GLP-1R is not expressed in ventricular cardiac myocytes, findings of reduced apoptosis and oxidative stress in response to various stimuli are likely the result of dipeptidyl peptidase 4 (DPP-4)-mediated degradation of GLP-17-36 into GLP-19-36, which may act through an unidentified receptor that is sensitive to exendin-9-39 or some other mechanism(s) that remains to be identified. Furthermore, both GLP-17-36 and GLP-19-36 may be cleaved via neutral endopeptidase 24.11 (NEP24.11) into GLP-128-36, which can be taken up internally by cardiac myocytes and has potential direct actions on mitochondria.
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DISCLOSURES

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AUTHOR CONTRIBUTIONS

J.R.U. prepared figure and drafted, edited and revised, and approved final version of manuscript.

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