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Glucagon-like peptide-1 receptor mediated control of cardiac energy metabolism

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ABSTRACT

Glucagon-like peptide-1 receptor (GLP-1R) agonists are frequently used to improve glycemia in patients with type 2 diabetes (T2D). Recent data from cardiovascular outcomes trials for the GLP-1R agonists, liraglutide and semaglutide, have also demonstrated significant reductions in death rates from cardiovascular causes in patients with T2D. As cardiovascular death is the number one cause of death in patients with T2D, understanding the mechanisms by which GLP-1R agonists such as liraglutide and semaglutide improve cardiac function is essential. Yet despite strong evidence from preclinical and clinical studies supporting the cardioprotective actions of GLP-1R agonists, the precise mechanism(s) by which this drug-class for T2D may produce these beneficial actions remains enigmatic. Negligible GLP-1R expression in ventricular cardiac myocytes suggests that GLP-1R agonist-induced cardioprotection is likely partially attributed to indirect actions on peripheral tissues other than the heart. Because insulin increases glucose oxidation, whereas glucagon increases fatty acid oxidation in the heart, GLP-1R agonist-induced increases and decreases in insulin and glucagon secretion, respectively, may modify cardiac energy metabolism in T2D patients. This may represent a potential mechanism for GLP-1R agonist-induced cardioprotection in T2D, as increases in fatty acid oxidation and decreases in glucose oxidation are frequently observed in the hearts of animals and human subjects with T2D.

1. Introduction

The prevalence of type 2 diabetes (T2D) continues to increase at an endemic rate, as there are currently over 420 million people living with diabetes worldwide. Of these, ~90% have T2D, with the majority resulting from underlying obesity [14,22]. Fortunately, we have a number of therapies available to prescribe to patients with T2D that improve glycemic control. This includes the first-line therapy metformin, the sulfonylureas, and the thiazolidinediones. Since 2005, we have seen 3 new drug-classes approved for the treatment of T2D, including the glucagon-like peptide-1 (GLP-1) receptor (GLP-1R) agonists, the dipeptidypeptidase-4 (DPP-4) inhibitors, and the sodium-glucose co-transporter 2 inhibitors. Despite the overall control of glycated hemoglobin and glucose homeostasis being for most part consistent among the majority of these approved therapies [52,73], the vast majority of T2D patients will eventually die from cardiovascular causes including myocardial infarction (MI) and heart failure [73]. As a result, pharmaceutical companies developing therapies for T2D now face intense scrutiny and must ensure their therapies are cardiovascular safe versus standard-of-care in large-scale cardiovascular outcomes trials. In 2016, the GLP-1R agonists liraglutide (LEADER – Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results – A Long-Term Evaluation) and semaglutide (SUSTAIN 6–Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with T2D) demonstrated significant reductions in the rates of cardiovascular death in their respective cardiovascular outcomes trials [35,36].

These exciting findings have prompted us to evaluate the mechanisms by which GLP-1R agonists may confer their cardioprotective actions in patients with T2D. As accumulating evidence illustrates that ventricular cardiac myocytes do not express the GLP-1R [66,69], it is highly likely that GLP-1R agonist-induced cardioprotection is mediated via indirect actions on other peripheral tissues that subsequently improve cardiac function in patients with T2D. The primary aim of this review is to address whether GLP-1R agonists may indirectly improve cardiac function in T2D subjects via improving cardiac energy metabolism. We herein will provide a brief overview of incretin hormone action, we will describe the perturbations in cardiac energy metabolism

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elicited by obesity/T2D, and end by describing the various mechanisms of action by which GLP-1R agonists may influence cardiac energy metabolism. For an in-depth analysis of the overarching cardiovascular actions of GLP-1 and GLP-1R agonists, we encourage the reader to read the many excellent reviews already published on this topic [15,68,69].

1.1. The incretin hormones and the incretin effect

The incretin hormones include glucose-dependent insulinotropic polypeptide (GIP) and GLP-1, which are secreted from enteroendocrine cells after meal ingestion in a glucose-dependent manner and potentiate insulin secretion (please refer to [3,10,19] for extensive review of incretin hormone action and regulation). The communication between GIP/GLP-1 and the endocrine pancreas accounts for 50–70% of insulin secretion in response to oral glucose administration, thereby representing the "incretin effect". Both GIP and GLP-1 potentiate insulin secretion via activating related Class B Family G-protein coupled receptors expressed on islet β-cells, while both GIP and GLP-1 are also cleaved with minutes of release and subsequently inactivated via DPP-4. This shortcoming of incretin-hormone action facilitated the development of DPP-4 inhibitors for the treatment of T2D, which primarily mediate their glucose lowering actions by preserving the biological activity of endogenously-released GIP/GLP-1 [39]. While both GIP and GLP-1 improve glucose homeostasis via augmenting insulin secretion, GLP-1 also produces additional glucose-lowering by delaying gastric emptying and inhibiting glucagon secretion in a glucose-dependent manner. Because insulin and glucagon both directly influence cardiac energy metabolism (see Section 4), they may represent key nodes by which GLP-1R agonists regulate cardiac energy metabolism in subjects with T2D.

2. Cardiac energy metabolism

As the most metabolically demanding organ in the body on a per-gram basis, the healthy heart is metabolic omnivore that consumes virtually any substrate provided to it through its coronary circulation, generating the equivalent of nearly 6 kg of ATP/day [30,63]. To meet these high energy demands, the heart is extremely flexible, and its complex regulation ensures it optimally metabolizes the predominant substrates delivered to it throughout constant changes in physiological states (e.g. feeding versus starvation). In this particular section, we will describe cardiac energy metabolism profiles in the healthy heart, as well as the metabolic perturbations that alter normal energy metabolism profiles and contribute to cardiac dysfunction in the setting of obesity and/or diabetes (Fig. 1) [7,30,70,83]. For extensive review on the molecular regulation of cardiac energy metabolism during health and disease, please refer to [30,63,70].

2.1. Cardiac intermediary energy metabolism in the healthy heart

Energy metabolism in the healthy heart is primarily met by oxidative metabolism, which accounts for > 90% of cardiac ATP production, with the remaining ATP production derived primarily from anaerobic glycolysis [30,70]. The vast amounts of oxidative metabolism are primarily accounted for by the oxidation of fatty acids and glucose, though amino acids and ketone bodies can also contribute to cardiac oxidative ATP production depending on the physiological state (e.g. starvation). During fasting/prolonged starvation, circulating free fatty acid and very-low-density lipoprotein-triacylglycerol (VLDL-TAG) levels are markedly elevated, thereby increasing fatty acid delivery to the heart and subsequent cardiac fatty acid oxidation rates [30,63]. Furthermore, increased fatty acid oxidation rates in the heart lead to a corresponding reduction in glucose oxidation, as fatty acids and glucose compete for oxidative acetyl CoA production within the mitochondrial matrix, a phenomenon described by Philip Randle and colleagues and coined the "glucose fatty acid cycle" [53]. Conversely, as the heart is highly insulin sensitive, following nutrient ingestion the heart increases its overall reliance on glucose to meet its oxidative energy demands, with insulin augmenting glucose uptake via stimulating glucose transporter 4 (GLUT4) translocation to the sarcolemmal membrane [8]. Furthermore, insulin may increase cardiac glucose oxidation rates via enhancing the activity of pyruvate dehydrogenase (PDH), the rate-limiting enzyme of glucose oxidation [47,48]. Insulin likely contributes to increased cardiac PDH activity/glucose oxidation via inhibiting forkhead box O1, which represses transcription of PDH kinase 4 and subsequent phosphorylation-induced inactivation of PDH [12,18]. However, the more acute effects of insulin on cardiac glucose oxidation may involve activating PDH phosphatases [33,51], which dephosphorylate and subsequently activate PDH [47,48]. Of importance, fatty acid oxidation-mediated inhibition of glucose metabolism is much more potent at the level of glucose oxidation than it is for glycolysis [30,58]. Even in the presence of increased circulating insulin levels following carbohydrate intake, the fraction of glucose uptake in the healthy heart that is actually oxidized rarely exceeds > 40% [75,76].

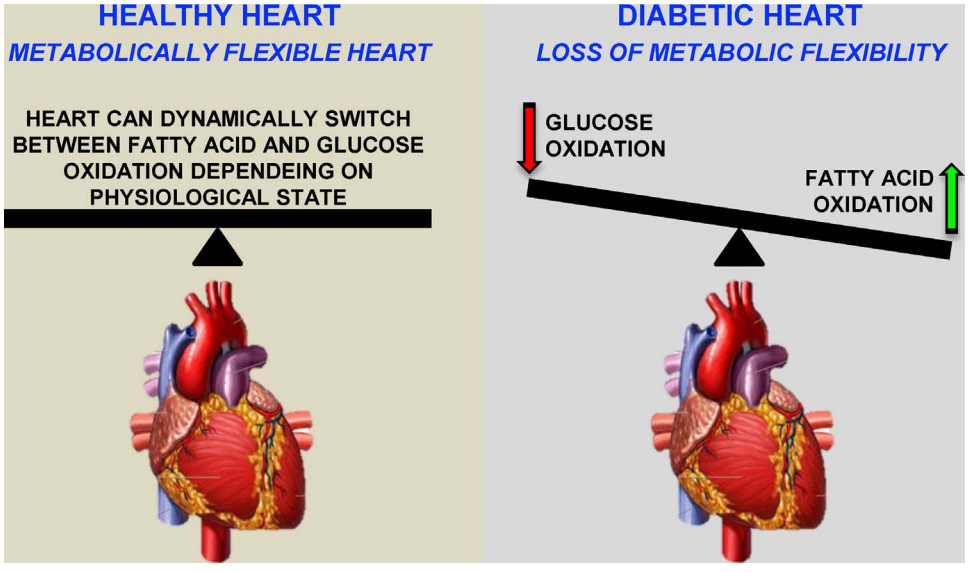

Fig. 1. Cardiac energy metabolism in T2D.
The healthy heart is metabolically flexible and thus able to switch between fatty acids as its primary oxidative fuel source in the fasted state, with carbohydrates becoming its primary oxidative fuel source in the fed state. However, this metabolic flexibility is lost in T2D, as fatty acid oxidation rates are markedly elevated, which comes at the expense of glucose oxidation.