Incretin Therapy and Heart Failure

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Type 2 diabetes mellitus (T2DM) is widely prevalent and a critical risk factor for cardiovascular disease that increases both morbidity and mortality. Recently, new therapies based on the actions of the incretin hormones have become widely used, offering advantages over conventional treatments by limiting hypoglycemia and achieving glycemic control. Moreover, many experimental studies have suggested that GLP-1 and related drugs exert cardioprotective effects on atherosclerosis and cardiac dysfunction both in vitro and in vivo. However, there is thus far little clinical evidence supporting the efficacy of incretin therapy in patients with cardiovascular disease. This review focuses on the effects of GLP-1-related therapy on cardiac function from the bench to the bed, with a discussion of possible underlying mechanisms. (Circ J 2014; 78: 819–824)

Key Words: DPP-4 inhibitor; GLP-1; Heart failure; Incretin; Type 2 diabetes mellitus (T2DM)

Type 2 diabetes (T2DM) is one of the most important risk factors for the development of cardiovascular disease, as it promotes both systemic atherosclerosis and lifestyle-associated diseases. Incretin-based therapies, including treatment with glucagon-like peptide-1 (GLP-1) receptor (GLP-1R) agonists and dipeptidyl peptidase (DPP)-4 inhibitors, have become widely used as a new class of antidiabetic drugs that exhibit different mechanisms of action from those of conventional antidiabetic agents. Incretin hormones depend on blood glucose to stimulate insulin. Because the use of DPP-4 inhibitors is associated with a lower incidence of hypoglycemia than is observed with conventional hypoglycemic drugs, they potentially improve the mortality rate of patients with T2DM by achieving strict glycemic control without causing fatal hypoglycemia. The GLP-1R has been detected in coronary endothelial cells, coronary smooth muscle cells, cardiomyocytes and human umbilical vein endothelial cells, as well as monocytes and macrophages.1–4 Interestingly, GLP-1 acts on multiple organs, not simply the pancreas, including the heart and vasculature (Figure 1). Therefore, GLP-1-related therapy exerts effects on the cardiovascular system, and recent evidence suggests that GLP-1-related treatment has potent pleiotropic beneficial effects on cardiovascular risk factors, beyond its effects on glycemic control. This review focuses on the theoretical and practical effects of incretin-related therapy on cardiac function, with a description of possible mechanism(s) of action.

Biology of Incretins

Incretin hormones are secreted from the gastrointestinal tract in response to food intake and have several systemic effects, including glucose-dependent stimulation of insulin secretion by pancreatic beta cells. Two incretins have been identified: GLP-1, which is derived from the L cells of the distal small intestine and large bowel, and glucose-dependent insulinotropic polypeptide (GIP), which is derived from the K cells of the proximal small intestine. GLP-1 and GIP are glucose-lowering agents that can interfere with postprandial hyperglycemia, which has been demonstrated as associated with cardiovascular complications. The biologically active forms of GLP-1 include GLP-1(7-37) and GLP-1(7-36)amide. These peptides arise from the selective cleavage of the proglucagon molecule. GLP-1(7-36)amide is abundant in the circulation after meals and stimulates insulin secretion by interacting with the GLP-1 receptors on pancreatic beta cells. DPP-4 degrades GLP-1(7-36)amide to inactive GLP-1(9-36)amide, and DPP-4 inhibitors bind to DPP-4 to prevent the breakdown of GLP-1 and GIP, thereby increasing the half-life and bioavailability of active incretins, ultimately enhancing their physiological effects. GLP-1(7-36)amide has been widely studied for its role as an active incretin and is referred to as GLP-1, unless otherwise specified. GLP-1(9-36)amide is thought to be an inactive metabolite because of its 1,000-fold lower affinity for GLP-1R and action as a weak competitive antagonist without incretin activity at pharmacological doses. However, GLP-1(9-36)amide may have potent effects on the cardiovascular system, similar to GLP-1(7-36)amide. Although it remains controversial, GLP-1 may undergo multiple cycles of enzymatic degradation by DPP-4 and nephrilysin. Therefore, the precise biological pathways of GLP-1 and related enzymes and the roles of metabolites in each step of the process in vivo need to be elucidated in the near future.

Effects of Incretins on Cardiac Function

Cardiomyocytes in Vitro

GLP-1 rapidly increases the 3′-5′-cyclic adenosine monophosphate (cAMP) levels in adult rat ventricular cardiac myocytes, consistent with its effect on pancreatic beta cells, in a manner...
that is not coupled with an increase in the intracellular Ca\(^{2+}\) concentration or subsequent cardiomyocyte contractility, as would be expected for cAMP-generating agents in the heart.\(^6\) Liraglutide increases cAMP formation and reduces caspase-3 activation in murine cardiomyocytes in a GLP-1R-dependent manner in vitro.\(^6\) Therefore, GLP-1R activation in primary cultures of cardiomyocytes increases the cAMP content in association with anti-apoptotic properties.

In Vivo and ex Vivo Experimental Data
GLP-1R knockout mice exhibit a reduced resting heart rate (HR), elevated left ventricular end-diastolic pressure (LVEDP) and increased LV thickness because of impaired LV contractility and diastolic dysfunction, as compared with wild-type mice.\(^8\) Conversely, GLP-1R preserves the HR and LV thickness and normally lowers the LVEDP.

Model of Myocardial Ischemia-Reperfusion (IR) and Infarction (MI)
GLP-1 and its related therapy have been demonstrated to inhibit the activation of cell death mechanisms in several experimental models of myocardial IR and MI.

GLP-1 has also been demonstrated to exert beneficial effects on cardiac function via downregulation of inflammatory cells activated by MI.\(^9,10\) In addition, GLP-1 enhances LV function by myocardial glucose uptake in the postischemic myocardium through an increase in the expression of glucose transporter (GLUT)-1 and -4 in the myocardium in association with increased p38 α MAP kinase activity, eNOS expression and myocardial NO uptake, although GLP-1 changes neither the myocardium adenylyl cyclase activity nor the level of Akt phosphorylation, known insulin-dependent signaling pathways for glucose uptake.\(^7,11,12\)

GLP-1 and the GLP-1(9-36) metabolite also improve myocardial contractility and coronary blood flow following ischemia in a mouse perfused heart model.\(^4\) GLP-1 directly protects the heart against myocardial IR injury and reduces the activation of the pro-apoptotic protein, Bad, as well as the infarct size in isolated perfused rat hearts and animal models of IR; these effects are abolished in the hearts in vitro by GLP-1R antagonists, cAMP inhibitors, phosphoinositide 3-kinase (PI3K) inhibitors and p42/44 mitogen-activated protein kinase inhibitors.\(^13\) DPP-4-resistant GLP-1 analogs fused to non-glycosylated human transferrin possess anti-apoptotic properties accompanied by a reduction in the infarct size and improvements in wall motion abnormalities and the ejection fraction (EF) in a model of myocardial IR in rabbits.\(^14\) The infusion of GLP-1 or the exenatide analog at 2 weeks after coronary ligation significantly increases the LVEF, while also reducing the incidence of adverse LV remodeling and improving survival.\(^15\) Exenatide reduces the infarct size and reactive oxygen species (ROS) production and inhibits caspase-3 expression and DNA fragmentation in a porcine model of myocardial IR injury.\(^16\) Similarly, treatment with liraglutide for 1 week prior to coronary ligation in mice reduces both the frequency of cardiac rupture and the infarct size, and increases the cardiac output (CO) and survival rate via the inhibition of caspase-3 activation in cardiomyocytes.\(^7\) Furthermore, albiglutide therapy preserves myocardial viability and reduces the production of lactate after IR injury in the rat heart.\(^17\)

The genetic deletion or chemical inhibition of DPP-4 in mice improves their cardiac function after MI by activating cell survival signaling, including that of phosphorylated Akt and pGSK3\(^{\beta}\).\(^18\) Combined treatment of mice with granulocyte colony-stimulating factor and a DPP-4 inhibitor preserves cardiac function via enhanced stem cell mobilization and cardiomyocyte regeneration after MI.\(^19\)

In summary, a number of findings suggest that the cardioprotective effects of incretins in IR models are mediated by: (1) reductions in the number of inflammatory cells,\(^8,10\) (2) improvements in myocardial circulation,\(^10\) (3) increases in the level of myocardial glucose uptake in order to stimulate more efficient ATP production,\(^7,11,12,17\) and (4) activation of reperfusion injury signaling kinase (RISK) pathway kinases, such as PI3K, ERK1/2, cAMP, PKA, Akt and P70S6K.\(^7,18,20-26\) as PI3K activation results in myocardial protection in the setting of IR injury.\(^27\)

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**Figure 1.** Schema of the physiological effects of glucagon-like peptide-1 (GLP-1) on various organs.
Cardiomyocyte apoptosis.

In spontaneously hypertensive and HF-prone rats, in addition to reducing the plasma levels of norepinephrine over, GLP-1 decreases the HR and increases LV systolic function. However, the administration of vildagliptin to nondiabetic rats before or after coronary ligation has no beneficial effects on either LV function or cardiac gene expression. Sokos et al demonstrated in a single-center nonrandomized trial that a continuous infusion of GLP-1 for 5 weeks in 12 patients with HF (New York Heart Association (NYHA) class III/IV) with or without T2DM improved the LVEF, oxygen consumption, 6-min walk test scores and quality of life, even in the nondiabetic patients. However, Halbirk et al reported that infusion of GLP-1 for 48 h in 15 nondiabetic patients with stable CHF (LVEF <40% and NYHA class II–III) and HF reduced the blood glucose levels and increased the plasma insulin levels, although it had no significant effect on LV function, with only modest increases in HR and diastolic blood pressure (BP), in a double-blind placebo-controlled crossover design. Trainsdottir et al demonstrated a beneficial trend in cardiac function in patients with T2DM and HF after infusion of recombinant GLP-1. A short duration of infusion of GLP-1 may be insufficient to treat a decompensated failing heart.

Model of HF
Studies using animal models have demonstrated that GLP-1R activation-independent actions via the effects of GLP-1R may have a beneficial effect on the failing heart. In dogs with pacing-induced dilated cardiomyopathy (DCM), the infusion of recombinant GLP-1, GLP-1 (7-36) and GLP-1 (9-36) increases the myocardial glucose uptake and insulin sensitivity, improves LV function, stroke volume (SV) and CO, enhances cardiac insulin sensitivity and the LV dp/dt values and decreases the LVEDP, HR and systemic vascular resistance. Moreover, GLP-1 decreases the HR and increases LV systolic function, in addition to reducing the plasma levels of norepinephrine and glucagon. In spontaneously hypertensive and HF-prone rats, GLP-1 treatment for 3 months improves the survival rate and preserves LV contractility in association with reduced cardiomyocyte apoptosis. The administration of sitagliptin for 3 weeks to nondiabetic pigs with pacing-induced DCM results in a reduced HR, increased SV and preserved renal function. However, the administration of vildagliptin to nondiabetic rats before or after coronary ligation has no beneficial effects on either LV function or cardiac gene expression. Sitagliptin therapy in db/db mice reduces AMPK and acetyl CoA carboxylase phosphorylation, as well as CD36 expression in the sarcomemal membrane of the myocardium, suggesting that DPP-4 inhibition reduces myocardial fatty acid (FA) uptake and subsequent metabolism. However, treatment with sitagliptin does not improve systolic function in db/db mice, although it reduces the degree of myocardial fibrosis and improves the LV relaxation constant in association with improved diastolic function, in addition to reducing myocardial p53 expression and apoptosis of cardiomyocytes.

Clinical Investigation of Human Cardiac Function (Table)
GLP-1 has been cited as improving myocardial function in T2DM patients with MI and/or HF. In patients with a low level of LV dysfunction after MI or PCI, infusion of GLP-1 results in an improvement of both the LVEF and wall motion. A randomized study assessing the effect of continuous GLP-1 infusion in 20 patients undergoing coronary artery bypass grafting documented improved glycemic control, reduced frequency of inotropic and vasoactive infusions, and a lower incidence of arrhythmias in the GLP-1-treated patients. Treatment with sitagliptin was found to improve dobutamine-induced regional wall motion abnormalities in ischemic segments on stress echocardiography and attenuate postischemic stunning in 14 patients with coronary artery disease (CAD) and preserved global LV function. Sokos et al demonstrated in a single-center nonrandomized trial that a continuous infusion of GLP-1 for 5 weeks in 12 patients with HF (New York Heart Association (NYHA) class III/IV) with or without T2DM improved the LVEF, oxygen consumption, 6-min walk test scores and quality of life, even in the nondiabetic patients. However, Halbirk et al reported that infusion of GLP-1 for 48 h in 15 nondiabetic patients with stable CHF (LVEF <40% and NYHA class II–III) and HF reduced the blood glucose levels and increased the plasma insulin levels, although it had no significant effect on LV function, with only modest increases in HR and diastolic blood pressure (BP), in a double-blind placebo-controlled crossover design. Trainsdottir et al demonstrated a beneficial trend in cardiac function in patients with T2DM and HF after infusion of recombinant GLP-1. A short duration of infusion of GLP-1 may be insufficient to treat a decompensated failing heart.

Other Possible Effects of Incretins on Cardiovascular Risk Factors
Lowering BP and Improving Endothelial Function
In recent studies, DPP-4 inhibitors and GLP-1 analogs have been recognized as lowering systemic BP. A possible mechanism underlying this effect is the extraction of Na+, as GLP-1 induces natriuresis in humans. For diabetic vascular and endothelial injury, substantial data exist regarding the beneficial effects of GLP-1 and related drugs on endothelial function and the incidence of atherosclerosis, including (1) increasing the eNOS expression, (2) increasing the number of endothelial progenitor cells (EPCs), (3) decreasing the number of inflammatory cells and ROS production, and (4) reducing the adhesion and activation of macrophages, although these mechanisms cannot be described in detail in this review. Nevertheless, improved myocardial perfusion following the recovery of endothelial function may contribute to myocardial contractility. In addition, the incremental activity of eNOS may reduce BP, as increased BP is recognized by genetic deletion or pharmacological inhibition of NOS in vivo. Indeed,
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Possible effects of incretins on the failing heart. In addition to the effects of GLP-1, DPP-4 cleaves a wide variety of substrates, DPP-4 inhibition keep the biological active forms of substrates and have many possible functions on cardiovascular system (red arrow). BNP, brain natriuretic peptide; DPP, dipeptidyl peptidase; EPC, endothelial progenitor cell; GLP-1, glucagon-like peptide-1; GLUT, glucose transporter; NOS, nitric oxide synthase; ROS, reactive oxygen species; SDF-1, stromal cell-derived factor-1.

Figure 2

**Incretins and Cardiovascular Outcomes**

Do Incretins Really Improve Mortality From Cardiovascular Disease?

Recently, the results of cardiovascular safety trials T2DM drugs (EXAMINE trial with alogliptin and SAVOR-TIMI 53 trial with saxagliptin) were reported. These studies found no effect on the risk of fatal or nonfatal cardiac events and no increases in the risk of pancreatitis or pancreatic cancer. Although this is good news for users of these drugs, the results were disappointing because the studies did not demonstrate any cardiovascular protective benefits of DPP-4 inhibitors. On the other hand, the follow-up period was too short to evaluate the incidence of cardiovascular events, as the effects of drugs in combating proatherosclerotic processes in patients with diabetes mellitus usually requires more than 10 years. In the SAVOR-TIMI 53 trial, more patients were hospitalized for HF in the saxagliptin group than in the placebo group. These results are unexpected and should be considered within the context of multiple testing, which may have produced false-positive findings. The results of further subanalyses and other ongoing trials are waited. The relatively small HbA 1c-lowering effects of saxagliptin and alogliptin in the SAVOR and EXAMINE trials, averaging only 0.3–0.4 percentage points, must be also discussed. However, the effect of adequate glycemic control without severe hypoglycemia is irreplaceable for those with T2DM. How-ever, sitagliptin improves endothelial function and reduces inflammation in patients with T2DM and CAD.51

**Shift of Cardiac Metabolism in the Failing Heart**

Alterations in myocardial substrate preference from FA to glucose are recognized in the failing heart. It may be substitutional. Therefore, insulin resistance with reduced GLUT-4 expression and increased levels of insulin are recognized in patients with HF.52 Although it is controversial whether myocardial glucose uptake is increased or not in the failing heart, DPP-4 inhibition or GLP-1 upregulate GLUT4 expression, and regulation of cardiac metabolism can be a therapeutic target for incretin therapy.53,54

Possible Original Effects of DPP-4 Inhibitors

In contrast to GLP-1 and GLP-1 receptor agonists, DPP-4 inhibitors inhibit DPP-4 throughout the body. As DPP-4 cleaves a wide variety of substrates, including stromal cell-derived factor-1 (SDF-1) alpha, which stimulates the bone marrow mobilization of EPCs and B-type natriuretic peptide (BNP) (1–32), the active form of BNP,55 DPP-4 inhibition repairs Endothelial cells and improves cardiac function, thus resulting in an indirect improvement in endothelial function. Neuropeptide Y (NPY) and peptide YY (PYY) are also targets for cleavage by DPP-4. As both these peptides induce vasoconstriction through Y(1) receptors, inhibition of DPP-4 may result in vasoconstriction.56 Although it remains uncertain, NPY and its substrates appear to influence the cardiovascular system. These findings are promising, and the precise biological role of DPP-4 in the cardiovascular system requires further investigation. Figure 2 summarized the possible mechanisms underlying GLP-1 and DPP-4 inhibition in the failing heart.
ever, new drugs require outrageous costs nowadays and both doctors and patients expect excessive benefits beyond conventional ones. Further studies must be conducted dispassionately as to whether incretin-related drugs have beneficial effects on prognosis, including the incidence of cardiovascular events, in humans.

Conclusions
Atherosclerosis and subsequent cardiovascular disease are often fatal, and providing early preventive care for cardiovascular complications by ensuring strict glucose control is essential for patients with T2DM. Although the final answer remains uncertain, the current findings add to a growing body of evidence suggesting that we may be entering a new era of cardiovascular diabetes with the development of new drugs. Ongoing randomized prospective clinical studies will provide more solid evidence regarding the long-term clinical effects of GLP-1-related therapies in patients with T2DM with a high risk of cardiovascular disease.

Conflict of Interest Statement

References


