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Review

Harnessing the incretin system beyond glucose control: Potential cardiovascular benefits of GLP-1 receptor agonists in type 2 diabetes

B. Cariou [a,b,*]

[a] *Université de Nantes, CHU de Nantes, Hôpital Guillaume et René-Laennec, boulevard Jacques-Monod, Saint-Herblain, 44093 Nantes cedex 1, France*
[b] *L'Institut du Thorax, Clinique d'Endocrinologie, Maladies Métaboliques et Nutrition Hôpital Guillaume et René-Laennec, boulevard Jacques-Monod, Saint-Herblain, 44093 Nantes cedex 1, France*

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Abstract

The management of type 2 diabetes continues to evolve as new data emerge. Although glycaemic control is still important, other risk factors – such as hypertension, dyslipidaemia and obesity – must also be addressed in order to reduce the long-term risks of cardiovascular complications and mortality. In this context, targeting the incretin system, and glucagon-like peptide-1 (GLP-1) in particular, has generated much interest. GLP-1 is released from the gut in response to food ingestion and plays a crucial role in glucose homeostasis. GLP-1 receptors are expressed in the heart and vasculature, prompting evaluation of their physiological role and pharmacological stimulation, both in healthy and disease states. These studies indicate that GLP-1 and GLP-1-based therapies appear to have direct, beneficial effects on the cardiovascular system, in addition to their glucose-lowering properties, such as modulation of blood pressure, endothelial function, and myocardial contractility. Intriguingly, some of these effects appear to be independent of GLP-1 receptor signalling. Data from clinical studies of the GLP-1 receptor agonists, exenatide and liraglutide on cardiovascular risk factors, in patients with type 2 diabetes are also promising and the results from prospective studies to assess cardiovascular outcomes are eagerly awaited.

Keywords: Cardiovascular disease; Incretin therapy; Type 2 diabetes; GLP-1; Endothelial function; Hypertension; Myocardial function; Review

Résumé

Bénéfices cardiovasculaires potentiels des analogues du GLP-1 dans le diabète de type 2 : une action au-delà du contrôle glycémique.

La prise en charge du diabète de type 2 (DT2) a évolué avec l'arrivée des nouvelles classes d'antidiabétiques. Bien que le contrôle glycémique demeure important, les autres facteurs de risque cardiovasculaires tels que l'hypertension artérielle, la dyslipidémie et l'obésité doivent être également pris en compte. Le système incrétine et notamment le *glucagon-like* peptide-1 (GLP-1) a émergé ces dernières années comme une nouvelle cible pour le traitement du DT2. Le GLP-1 est sécrété par l'intestin en réponse aux repas et stimule la sécrétion d'insuline de manière glucose-dépendante. Outre les îlots de Langerhans, les récepteurs du GLP-1 sont aussi exprimés dans la paroi vasculaire et le cœur, ce qui suggère la possibilité de l'existence d'une action cardiovasculaire directe du GLP-1. Des études ont démontré que le GLP-1 endogène ou les agonistes du récepteur du GLP-1 (exenatide ou liraglutide) exerçaient plusieurs effets bénéfiques directement au niveau cardiovasculaire, comme une diminution de la pression artérielle, une amélioration de la fonction endothéliale et de la contractilité du myocarde dans des situations d'ischémie. De façon surprenante, une partie de ces effets est indépendante de la voie de signalisation du récepteur du GLP-1 et semble impliquer la forme clivée inactive du GLP-1 (GLP-1 [9–36]). Les premières données cliniques qui concernent le contrôle des facteurs de risque cardiovasculaire dans le DT2 avec l'exenatide ou le liraglutide sont prometteuses et semblent valider l'hypothèse d'un bénéfice cardiovasculaire de cette nouvelle classe thérapeutique. Néanmoins, il faut encore attendre les résultats des études de morbi-mortalité cardiovasculaire actuellement en cours pour en avoir la confirmation définitive.

Mots clés : Diabète de type 2 ; Incrétines ; GLP-1 ; Hypertension artérielle ; Fonction myocardique ; Insuffisance cardiaque ; Revue générale

* Tel.: +33 2 53 48 27 07; fax: +33 2 53 48 27 08.
E-mail address: bertrand.cariou@univ-nantes.fr

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1. Introduction

It is well established that patients with diabetes have a higher risk of cardiovascular (CV) morbidity and mortality than patients without diabetes. For example, in the Framingham Heart study, diabetes was associated with a 2 to 4-fold risk of myocardial infarction, congestive heart failure and stroke, as well as an increased risk of mortality [1,2]. In addition, in the Multiple Risk Factors Intervention Trial, the absolute risk of CV-disease was much higher for diabetic than non diabetic men, independently of the presence of other CV risk factors [3]. At the end, absolute excess CV risk for diabetic men is progressively greater than for non diabetic men with higher risk factor levels [3]. This increased diabetes-associated risk of CV-disease reflects the negative effects of chronic hyperglycaemia on the vasculature [4]. In addition, patients with diabetes often suffer from other comorbid conditions, such as hypertension, combined dyslipidaemia (high LDL-C and low HDL-C levels) and visceral obesity, which also predispose them to CV complications [5].

Glycaemic control remains fundamental to the management of diabetes, especially for preventing microvascular complications [6]. However, the benefits of tight glycaemic control for preventing CV complications are being questioned since recent prospective intervention studies failed to demonstrate a clear benefit in patients with T2DM at very high CV risk [7–9]. A more holistic approach, designed to address all diabetes-associated risk factors, is now advocated based on data from studies showing significant benefits when multiple risk factors are addressed [10–12]. This approach is exemplified in the most recent guidelines on medical care for diabetes from the American Diabetes Association [13]; i.e., that the ideal antidiabetic drug would improve glycaemic control and CV risk factors simultaneously. However, many standard antidiabetic agents are either risk factor neutral or have a detrimental effect on CV risk factors [14], and it has been suggested that this may explain, in part, the lack of effect on CV outcomes when diabetes is treated using these agents [15].

The incretin system has been the focus of intense research as a potential target for drugs with which to treat T2DM, given its key role in stimulating postprandial insulin secretion and concomitantly reducing glucagon secretion [16]. Therapies in this class include glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors. More recently, attention has turned to its effects on the CV system [17]; this review provides an overview of the current knowledge on the CV effects of native GLP-1 and assesses the potential benefits of incretin-based therapies for T2D, with a primary focus on GLP-1 receptor agonists, to improve indicators of CV-disease, both in animal models and in humans.

2. The incretin effect

The incretin system comprises two major gut hormones: glucose-dependent insulinotropic polypeptide (GIP) and GLP-1, both of which are released into the circulation in response to food ingestion [18,19]. These hormones, which are known to play a crucial role in the normal insulin response, account for 50 to 70% of insulin secretion after food intake [16]. The incretin effect is impaired in patients with T2DM [20]. In the case of GIP, this is characterised by a marked impairment in insulinotropic activity, with relatively unchanged circulating levels of the peptide [21]. The situation with GLP-1 is more complex. Some studies have reported a decrease in GLP-1 secretion in T2DM, but the balance of evidence now suggests that GLP-1 levels are relatively unchanged, and that there is a modest impairment in insulinotropic activity [21]. However, unlike GIP, high concentrations of GLP-1 can restore the insulin response to glucose and normalise insulin secretion in T2DM [22]. In view of this, GLP-1 has become the focus of research and drug development in this area. GLP-1 has additional properties, namely inhibition of glucagon secretion and gastric emptying, which are also attractive in the context of diabetes treatment [18]. Its effects on insulin and glucagon release occur in a glucose-dependent manner, thus minimizing the risk of hypoglycaemia [16,20,22,23]. Based on these properties, GLP-1-based therapies have emerged as pivotal therapies in the pharmacological management of T2DM [24].

In addition to its roles in glycaemic control and satiety, GLP-1 appears to exert several additional effects on many tissues via the GLP-1 receptor, which is expressed not only in the pancreatic islets, but also in the lung, kidney, intestine and several regions of the central nervous system [16]. This widespread expression of the GLP-1 receptor may help to explain the range of extra-pancreatic effects of GLP-1, including a potentially protective effect on the CV system as GLP-1 receptors are also found in endothelial cells, vascular smooth muscle cells, monocytes – macrophages of the vascular wall [25], and in the heart [26].

3. The physiology of native GLP-1 in the cardiovascular system

The pharmacological effects of GLP-1 on CV function (Fig. 1) have been evaluated using infusion of native GLP-1, and knockout mice lacking the GLP-1 receptor. GLP-1 is sometimes specifically referred to as GLP-1(7–36) amide and GLP-1(7–37) amide, the bioactive forms of GLP-1 [27,28], which are derived from the 37-amino acid precursor, GLP(1–37), which in turn is derived from the large proglucagon precursor (Fig. 2) [18]. GLP-1(7–36) amide constitutes 80% of circulating GLP-1 [18],

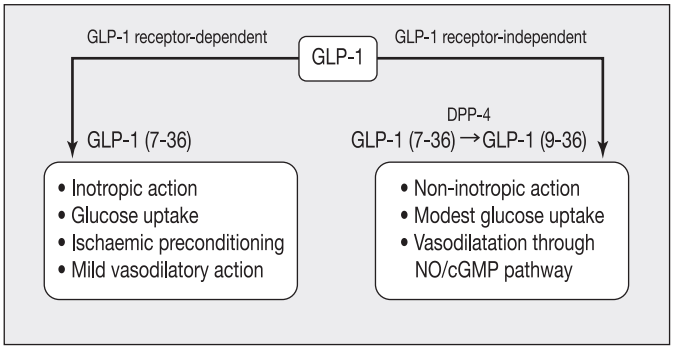

Fig. 1. Summary of receptor-dependent and receptor-independent GLP-1 effects on the heart. GLP-1, glucagon-like peptide-1; DPP-4, dipeptidyl peptidase-4; NO/cGMP, nitric oxide/cyclic guanosine monophosphate.