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GLP-1 Isoforms for Diabetes-associated Cardiovascular Pathologies

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Type-II diabetes (T2DM) is reaching epidemic proportions in industrialized populations due to the combination of excess calorie consumption and reduced physical activity. Alarmingly, the cardiovascular pathologies associated with diabetes are leading causes of mortality in these patients [1]. The intensive glycemic control induced by classic anti-diabetics has provided only limited success in decreasing cardiovascular complications, and in some cases the use of anti-diabetics has even increased the risk of mortality; indeed, anti-diabetics do not improve β-cell function, and can lead to hypoglycemia and/or weight gain, followed by increased insulin resistance and hyperlipidemia [2]. Thus, there is an urgent need for new therapies that address other associated non-glycemic risk factors while avoiding these drawbacks.

Incretins, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), are enteroendocrine hormones released into the bloodstream in response to ingested nutrients. Mostly GLP-1 increases insulin secretion through its specific transmembrane Gs-protein coupled receptors (GLP-1R) in pancreatic β-cells, by a glucose-dependent manner, and therefore, minimizing the risk of hypoglycemia. However, GLP-1 is rapidly degraded by dipeptidyl peptidase-IV (DPP-IV), which cleaves the N-terminal dipeptides to render a major insulinotropic inactive metabolite known as GLP-1(9-36) [3]. Based on this event, two options for incretin enhancement are DPP-IV inhibitors (DPP-IVi) and GLP-1 mimetics resistant to DPP-IV activity (GLP-1m). DPP-IVi is taken orally and induces beneficial effects in T2DM by moderate increases of β-cell mass and glucose-dependent insulin secretion. DPP-IVi reduce also hepatic glucose production, and both fasting and postprandial hyperglycemia [4-6]. Limited evidence suggests that DPP-IVi could diminish systolic blood pressure (SBP) [5,7], probably because DPP-IV can also cleave vasoconstrictor peptides (i.e., neuropeptide-Y). In addition, DPP-IVi only decrease postprandial, but not fasting lipid levels (i.e., triglycerides, VLDL/LDL lipoproteins, and fatty acids) [7-9]. However, GLP-1m are administered by subcutaneous injection but exhibit higher increases of β-cell mass and insulin secretion, and higher reduction of glucose production and both fasting and postprandial hyperglycemia [10-12]. Also, GLP-1m can slow gastric emptying and gut motility, increase satiety, and reduce food intake, consequently decreasing body weight and insulin resistance [10,13,14]. Additionally, they decrease SBP (even before weight loss) [12,15], and VLDL/LDL lipoproteins, triglycerides and fatty acids [7,16,17]. GLP-1m also improve endothelial function, and produce vasodilatation [18,19]. As a result, both DPP-IVi and GLP-1m have shown cardioprotection in ischemia/reperfusion animal models [18,20-22], and ameliorated cardiovascular events in clinical trials without substantial side effects [23]. Also, infusion of native GLP-1 in humans improved cardiac function and recovery following ischemic conditions [18,24].

The extra-glycemic actions of DPP-IVi and GLP-1m could be justified by the presence of GLP-1R in other tissues such as heart, vessel, kidney, liver, and brain [22]. However, GLP-1m exhibit more cardioprotection than DPP-IVi, which can be explained by the fact that incretin release is also impaired in T2DM [25]. Thus, even after blocking the DPP-IV activity, the secreted GLP-1 may not be satisfactory. More significantly, during GLP-1m administration, the production of GLP-1 (9-36) from endogenous GLP-1 is guaranteed. Importantly, this metabolite may conserve beneficial effects for T2DM patients. GLP-1(9-36) elicits cardioprotection in ischemia/reperfusion models by GLP-1R dependent or independent mechanisms [26]. Also, GLP-1(9-36) induces vasodilatation through nitric oxide formation [26], and protects against oxidation in cardiac and vascular cells [22,27,28]. We also demonstrated anti-apoptotic/necrotic, hypertrophic, and fibrotic actions for GLP-1(9-36) (similarly to GLP-1) in cardiomyocytes exposed to high concentrations of glucose and palmitate [29]. Although we must wait to confirm the long-term cardiovascular safety of DPP-IVi and GLP-1m treatments, we do believe it is crucial to continue studying GLP-1R (or other GLP-1-specific receptors) stimulation in cardiac and vascular cells. Also, the physiological generation of GLP-1 (9-36) may suggest new anti-diabetic therapies based on the enhancement of this metabolite.

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