GLP-1 receptor signaling: effects on pancreatic β-cell proliferation and survival

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Abstract

Type 2 diabetes is a metabolic disorder characterized by insulin resistance as well as a progressive deterioration of pancreatic β-cell mass and function. Glucagon-like peptide 1 (GLP-1), an incretin hormone secreted by intestinal L cells, is a promising therapeutic agent in the treatment of diabetes. GLP-1 analogs and enhancers constitute a novel class of anti-diabetes medications which address both the insulin secretion defect as well as the decline in β-cell mass. GLP-1 improves glucose-stimulated insulin secretion, restores glucose competence in glucose-resistant β-cells, and stimulates insulin gene expression and biosynthesis. Furthermore, GLP-1 acts as a growth factor by promoting β-cell proliferation, survival and neogenesis. This review focuses on the molecular mechanisms by which GLP-1 signaling induces β-cell mass expansion.

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1. Introduction

Diabetes mellitus, a metabolic disorder often associated with obesity, is characterized by insulin resistance as well as β-cell dysfunction. The global figure of people with diabetes is set to rise from the current estimate of 190 millions to 330 millions in the next 20 years [1]. The striking increase in the prevalence of diabetes suggests that it is now taking epidemic proportions and constitutes a significant socioeconomic problem [2]. The insulin-secreting pancreatic β-cell is central to the etiology of diabetes. It is generally accepted that diabetes results when there is an inadequate functional mass of β-cells (reviewed in [3]). In type 1 diabetes, immune-mediated destruction of β-cells greatly reduces β-cell mass [4]. In type 2 diabetes, β-cells initially compensate for the increased metabolic demand in the face of insulin resistance.

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resistance by expanding its mass and enhancing insulin secretion [5]. The disease appears at a later stage and results from the progressive deterioration of β-cell mass and function [5]. Thus, the reduction in β-cell mass is a common feature of both type 1 and type 2 diabetes [6]. Consequently, new approaches for diabetes treatment should aim at the preservation and the expansion of pancreatic β-cell mass.

Traditional medications for type 2 diabetes include insulin, sulfonylureas, metformin and thiazolidinediones [7]. However, their usage is associated with risks of hypoglycaemia, weight gain or gastrointestinal intolerance. Moreover, these therapeutic agents lose their efficacy over time, resulting in a loss of glycaemic control [7]. This can be explained by the fact that traditional medications fail to address the progressive loss of β-cell mass and function. For these reasons, there is a need for new therapeutic approaches for the treatment of diabetes.

2. GLP-1 mimetics and enhancers: a promising new class of medications in the treatment of type 2 diabetes

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by intestinal L cells in response to nutrient ingestion [8]. Upon secretion, GLP-1 acts on a small selection of tissues to regulate glucose homeostasis. Several clinical studies have shown the potential therapeutic value of GLP-1 in treating type 2 diabetes [9, 10]. When administered to type 2 diabetic subjects, GLP-1 normalizes blood glucose levels, increases circulating insulin, and diminishes glucagon secretion [11]. The stimulation of β-cell insulin secretion is a prominent action of GLP-1 [12, 13]. GLP-1 exerts its insulinotropic action at elevated glucose levels (> 5 mm), thereby preventing hypoglycaemia.

The short half-life (< 2 min) of GLP-1 in circulation represents a major obstacle to its use as an anti-diabetes medication. Therefore, long-lasting GLP-1 analogs such as Exendin4 (traded under the commercial name Byetta™) were developed and characterized. Another promising approach is to enhance and prolong the physiological actions of endogenous GLP-1 by inhibiting dipeptidyl peptidase 4 (DPP4), the enzyme responsible for its rapid degradation [14]. Thus, GLP-1 mimetics and enhancers constitute a novel class of anti-diabetes medications that will have a major impact in the treatment of type 2 diabetes mellitus.

3. GLP-1 receptor signaling in β-cells (Fig. 1)

The GLP-1 receptor (GLP-1R) was initially cloned from rat pancreatic islet cells [15] and subsequently from a human pancreatic islet library [16]. GLP-1R belongs to the B-class (also termed “secretin-like”) of the G-protein-coupled receptor (GPCR) superfamily [17]. This subclass of receptors couples with Gs and activates adenylate cyclase (AC) to stimulate cAMP production. Downstream effectors of cAMP include protein kinase A (PKA) and cAMP-regulated guanine nucleotide exchange factors of the Epac family. In β-cells, GLP-1 triggers Ca2+ signaling and insulin secretion via both PKA and Epac [18-20].

A growing body of evidences indicates that GLP-1 improves β-cell function and mass through other signaling pathways as well. Thus, GLP-1R signaling induces proteolytic maturation of betacellulin by membrane-bound metalloproteinases to transactivate the epidermal growth factor receptor (EGFR) [21]. In turn, EGFR sequentially activates PI3K and its downstream targets Akt, PKCζ, and p38 Mapk. Activation of Akt causes FoxO1 nuclear exclusion, relieving the constraint on Pdx1 and Foxa2 expression. The β-cell specific transcription factor Pdx1 regulates the expression of genes important for β-cell function such as Insulin, Glucokinase (Gk) and Glut2. GLP-1 induced activation of NF-κB promotes β-cell survival via up-regulation of the anti-apoptotic genes lap2 and Bcl2.

4. Biologic actions of GLP-1 in the β-cell

The biologic actions of GLP-1 in the β-cell include 1) stimulation of insulin gene expression and insulin biosynthesis [28], presumably via increased expression and activity of the β-cell specific transcription factor pancreatic and duodenal homeobox gene-1 (Pdx1) [22, 29]; 2) enhancement of glucose-stimulated insulin secretion [11]; 3) restoration of glucose competence in glucose-resistant β-cells
[30]; and, finally, 4) stimulation of \(\beta\)-cell mass expansion. Indeed, GLP-1 acts as a growth factor for the \(\beta\)-cell both in experimental animal models and cultured \(\beta\)-cells by stimulating proliferation, survival and differentiation. Therefore, GLP-1 addresses both the defect in insulin secretion and the decline in \(\beta\)-cell mass that contribute to the deterioration of \(\beta\)-cell function in the etiology of type 2 diabetes.

5. GLP-1R signaling, DPP4 inhibition and \(\beta\)-cell mass expansion

5.1. \(\beta\)-cell replication

GLP-1 has been initially shown to promote \(\beta\)-cell replication in vitro [21-23] as well as in vivo in a partial pancreatectomy rat model of type 2 diabetes [29]. As mentioned above, genetic and pharmacological analyses of GLP-1R signaling have demonstrated that the growth promoting action of GLP-1 requires the transactivation of the EGFR, and the subsequent activation of PI3K and its downstream effectors Akt, PKC\(\gamma\), and p38 Mapk [21-25, 27]. Whereas this constitutes the proximal steps of GLP-1R signaling, the long-term effects upon \(\beta\)-cell growth and survival could implicate the up-regulation of Irs2 gene expression [31], presumably via an increase in cAMP production [32].

GLP-1 has been recently shown to inhibit the forkhead transcription factor FoxO1 through Akt-mediated nuclear exclusion [33]. In addition, Exendin4 fails to stimulate \(\beta\)-cell expansion in transgenic mice expressing a constitutively nuclear FoxO1 in \(\beta\)-cells [33]. These results indicate that FoxO1 mediates the effects of the incretin hormone on \(\beta\)-cell proliferation and survival. Moreover, GLP-1 up-regulates Pdx1 and Foxa2, two transcriptional targets of FoxO1 that participate to the pleiotropic actions of the incretin hormone [33, 34]. The action of GLP-1 on Pdx1 and Foxa2 expression is also inhibited by the constitutively active FoxO1 mutant. Not only is FoxO1 a negative regulator of Pdx1, but FoxO1 and Pdx1 show mutually exclusive nuclear localization [35]. Thus, the modulation of FoxO1 sub-cellular localization by GLP-1 provides a molecular mechanism by which the incretin hormone increases both the expression and the activity of the \(\beta\)-cell specific transcription factor Pdx1 [22]. Noteworthy, Exendin4 fails to stimulate \(\beta\)-cell mass expansion in mice with \(\beta\)-cell specific ablation of Pdx1 expression [36], indicating that the actions of GLP-1 on \(\beta\)-cell growth and survival are dependent on the expression of Pdx1.

5.2. \(\beta\)-cell survival

The action of GLP-1 on cell proliferation is complemented by its effect on cell survival. Indeed, GLP-1 and its analogs exhibited anti-apoptotic properties in several rodent models. Exendin4 has been shown to delay the onset of diabetes in \(db/db\) mice via attenuation of \(\beta\)-cell apoptosis and, consequently, preservation of \(\beta\)-cell mass [37]. Infusion of native GLP-1 in Zucker diabetic rats promotes cell growth and inhibits apoptosis, concomittantly with a reduction in caspase-3 expression [38]. Mice with disruption of the Glp1r gene exhibit enhanced \(\beta\)-cell death and more severe hyperglycaemia following administration of the \(\beta\)-cell toxin, streptozotocin [39].

In vitro studies have demonstrated the ability of GLP-1 to prevent \(\beta\)-cell apoptosis induced by a variety of cytotoxic stimuli. GLP-1 prevents peroxide – mediated oxidative stress in a CAMP- and PI3k- dependent fashion [26]. The action of GLP-1 on \(\beta\)-cell survival was accompanied by increased expression of the anti-apoptotic genes Bcl2 and Bclxl. In addition, GLP-1 prevents glucose- as well as fatty acid-mediated toxicity in freshly isolated human islets [24]. This observation has important clinical implications since it suggests that GLP-1 could protect \(\beta\)-cells from hyperglycaemia and dyslipidemia, two abnormalities that accompany type 2 diabetes. The proposed mechanism implicates NF-kB-dependent transcription of the anti-apoptotic genes lap2 and Bcl2. GLP-1 has also been shown to protect \(\beta\)-cells from cytokine-induced cell death [36]. Since cytokines are important mediators of \(\beta\)-cell destruction in type 1 diabetes, this result hints towards a potential therapeutic value of GLP-1 for the treatment of type 1 diabetes. Very recently, it has been demonstrated that GLP-1 attenuates endoplasmic reticulum (ER) stress in \(\beta\)-cells [40, 41]. Conditions interfering with the function of ER (notably, overproduction of misfolded protein aggregates) are collectively called ER stress. The molecular mechanisms underlying ER stress remain elusive and have gathered much interest since ER stress impairs \(\beta\)-cell function and survival. Yusta et al. [40] have demonstrated that diabetes is associated with the development of ER stress in \(\beta\)-cells and that GLP-1/R signaling reduces ER stress via activation of PKA and induction of ATF4 translation in \(db/db\) diabetic mice.

6. GLP-1’s effects on \(\beta\)-cell mass reiterated by DPP4 inhibitors

Since DPP4 inhibitors acutely increases the circulating levels of bioactive incretins, the prediction is that DPP4 inhibition would recapitulate the effects of GLP-1 and promote \(\beta\)-cell mass expansion. Indeed, DPP4 inhibition has been shown to improve glucose-tolerance and to preserve islet function in mice made insulin-resistant by a high-fat diet [42]. Consistently, islets isolated from DPP4 inhibitor-treated animals showed enhanced GLUT2 expression and glucose-stimulated insulin secretion after 8 weeks of treatment. This result dovetails with DPP4 inhibitors’ ability to stimulate insulin biosynthesis and \(\beta\)-cell survival in streptozotocin-induced diabetic rats [43]. In this study, DPP4 inhibitor treatment decreased postprandial blood glucose as a result of enhanced insulin secretion capacity and to cause an eightfold increase in insulin content after 7 weeks of...
treatment. Concomitantly, histological analyses of the pancreas revealed increases in the number of small islets and β-cells. Taken together, these results suggest that DPP4 inhibition improves β-cell function, promotes β-cell mass expansion and stimulates insulin biosynthesis.

7. Conclusion

Traditional medications fail to address the progressive nature of type 2 diabetes. GLP-1 analogs and enhancers, through their complementary ability to restore and preserve functional β-cell mass, have great therapeutic value in treating type 2 diabetes. Further studies are required to ascertain the full potential of this novel class of antidiabetic medications. Notably, to evaluate whether their action on β-cell mass and function is durable. The potential value of GLP-1 for the treatment of type 1 diabetes, by enhancing residual endogenous β-cell mass and function, remains to be tested.

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References


