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Review

Glucagon-Like Peptide 1 Analogs and their Effects on Pancreatic Islets

Eva Tudurí,[1,2,*] Miguel López,[1,2,3] Carlos Diéguez,[1,2,3] Angel Nadal,[4] and Rubén Nogueiras[1,2,3,*]

Glucagon-like peptide 1 (GLP-1) exerts many actions that improve glycemic control. GLP-1 stimulates glucose-stimulated insulin secretion and protects β cells, while its extrapancreatic effects include cardioprotection, reduction of hepatic glucose production, and regulation of satiety. Although an appealing antidiabetic drug candidate, the rapid degradation of GLP-1 by dipeptidyl peptidase 4 (DPP-4) means that its therapeutic use is unfeasible, and this prompted the development of two main GLP-1 therapies: long-acting GLP-1 analogs and DPP-4 inhibitors. In this review, we focus on the pancreatic effects exerted by current GLP-1 derivatives used to treat diabetes. Based on the results from *in vitro* and *in vivo* studies in humans and animal models, we describe the specific actions of GLP-1 analogs on the synthesis, processing, and secretion of insulin, islet morphology, and β cell proliferation and apoptosis.

Trends

Although GLP-1-based drugs have been improved to have long-term effects, there are still issues surrounding their oral administration.

GLP-1 analogs stimulate insulin synthesis and secretion and inhibit β cell apoptosis in rodent models.

Most preclinical studies show increased β cell proliferation and mass after GLP-1 analog treatment; however, whether these effects are also seen in humans remains unclear.

GLP-1 analogs reduce plasma glucagon levels, but this effect might not be exerted by a direct action on α cells.

Targeting the Incretin System to Treat Diabetes

Type 2 diabetes mellitus (T2DM) is characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The incidence of diabetes is increasing worldwide, mainly due to the rise in obesity; approximately 80% of humans with T2DM are either overweight or obese [1]. Although a proportion of those patients control their glycemic levels by following controlled diets and exercise, many others require specific treatments, including exogenous insulin, sulfonylureas, metformin, or thiazolidinediones. Over recent years, new compounds targeting the GLP-1 signal transduction pathway have been used for the treatment of T2DM. Both GLP-1 and gastric inhibitory polypeptide (GIP) are incretin hormones released from intestinal L and K cells, respectively, after nutrient ingestion [2]. These hormones account for 50–70% of the total insulin secreted in response to oral glucose [3], a phenomenon known as the 'incretin effect'. Patients with T2DM show a reduced, or even absent, incretin effect, which may result at least partially from reduced postprandial active GLP-1 levels [4]. The administration of pharmacological doses of GLP-1 to patients with T2DM can restore the insulin secretory function [5], whereas GIP infusion cannot [6]. In addition to its well-known insulinotropic (i.e., insulin-releasing) properties, GLP-1 exerts a variety of actions that improve glycemic control. Insulin secretion in response to nutrients is potentiated by GLP-1, glucagon secretion is reduced, gastric emptying is decreased, and hepatic glucose production (HGP) is inhibited [7]. Importantly, GLP-1 effects on islet hormone secretion are glucose dependent; thus, it is difficult for hypoglycemia to occur under GLP-1-based therapy [8]. Moreover, GLP-1 induces satiety, leading to a reduction in food intake and, eventually, weight loss [9], offering an advantage over other antidiabetic drugs that may cause weight gain. Given that GLP-1 secretion is decreased in diabetes and its aforementioned physiological actions, GLP-1 has been considered an attractive candidate for the treatment of T2DM. However, circulating active

[1]Instituto de Investigaciones Sanitarias (IDIS), CIMUS, University of Santiago de Compostela, Santiago de Compostela 15782, Spain
[2]CIBER Fisiopatología de la Obesidad y Nutrición (CIBERobn), Santiago de Compostela 15706, Spain
[3]Department of Physiology, CIMUS, University of Santiago de Compostela, Santiago de Compostela 15782, Spain
[4]Instituto de Bioingeniería and CIBER de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Universidad Miguel Hernández, Elche, Spain

*Correspondence: eva.tuduri@usc.es (E. Tudurí) and ruben.nogueiras@usc.es (R. Nogueiras).

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GLP-1 has a very short half-life (1–2 min) primarily because of its rapid breakdown by DPP-4 and, to a lesser extent, due to the action of neutral endopeptidase and glomerular filtration [3]. Thus, native GLP-1 cannot be administered as a practical antidiabetic treatment. Two different strategies have been used to overcome this limitation: the synthesis of GLP-1 analogs resistant to DPP-4, and DPP-4 inhibitors. To date, five GLP-1 derivatives have been approved by the US Food and Drug Administration (FDA) and/or the European Medicines Agency (EMA) for their use as drugs for T2DM. In this review, we recapitulate the specific effects of these marketed GLP-1 analogs on the physiology of pancreatic islets.

Current GLP-1 Analogs Used for the Treatment of T2DM

Efficacy and long-lasting effects are the two main properties of GLP-1 analogs. In 2005, the FDA approved the first GLP-1 receptor (GLP-1R) agonist, exenatide (Byetta), for adjunctive glycemic control in patients with T2DM. Exenatide is bio-identical to exendin-4 (Ex-4), a 39-amino acid peptide isolated from the saliva of the Gila monster (*Heloderma suspectum*). Exenatide shares 53% homology with GLP-1 [10] and has proven efficacy when given alone, in combination with metformin and sulfonylureas, or both [11]. The replacement of an alanine with a glycine at the N terminus of exenatide confers increased resistance to DPP-4 activity and longer half-life (2.4 h) compared with GLP-1 [10]. Nonetheless, exenatide is a short-acting compound that requires twice-daily injections [10]. Thus, additional efforts were focused on designing strategies to achieve enhanced incretin action. Liraglutide (Victoza) was synthesized by substituting an arginine for lysine at position 34, and attaching a 16-carbon fatty-acid chain, via a glutamic acid spacer, to the lysine residue at position 26 [12]. Liraglutide shares 97% homology with native human GLP-1 and allows for once-daily administration [12]. The next approved GLP-1 analog was lixisenatide (Lyxumia), a 44-amino acid peptide based on the structure of Ex-4, with deletion of a proline residue and six additional lysine residues added to the C terminus [13]. Lixisenatide does not produce stronger effects than either exenatide or liraglutide on fasting blood glucose, HbA1c, or body weight [14]; however, it has fewer adverse effects and can be administered once daily due to its high binding affinity for GLP-1R [15]. A different approach to achieve a longer action of incretin comprised encapsulating exenatide in poly (D,L-lactic-co-glycolic acid) microspheres, for sustained release. This preparation is known as exenatide long-acting release (exenatide-LAR) or exenatide once-weekly, and has proved to be effective for the treatment of T2DM [16].

Two new prolonged-acting GLP-1 analogs were recently launched to the market; albiglutide (Tanzeum or Eperzam) was synthesized by the fusion of two repeats of a DPP-4-resistant analog of human GLP-1 to recombinant human albumin [17]. The half-life of albiglutide is 6–8 days, making it suitable for once-weekly injection [17]. Compared with liraglutide, albiglutide has some advantages, including fewer gastrointestinal (GI) adverse effects; however, it has been reported to be less effective [18]. Finally, dulaglutide (Trulicity) comprises two identical polypeptide chains linked to each other by a disulfide bond. Each polypeptide chain is a fusion protein that contains a GLP-1 variant linked to the Fc portion of a human IgG4 [19]. The GLP-1 analog 'amino acid' portion of dulaglutide is homologous to native human GLP-1 (7–37). Dulaglutide has shown similar efficacy and safety as other GLP-1 derivatives [20]. Detailed information on these GLP-1 analogs is given in Table 1 and other reviews [20,21].

Effects of GLP-1 Analogs on Insulin Synthesis and Secretion

Insulin is synthesized and released from β cells The synthesis of insulin results from the sequential cleavage of two precursor molecules: first, preproinsulin is translocated across the rough endoplasmic reticulum (ER) membrane into the lumen, where the initial amino-terminal segment of the protein is removed to yield proinsulin. Following transportation to the Golgi, proinsulin enters immature secretory granules where, by the action of carboxypeptidase E and the prohormone convertases PC1/3 and PC2, it is processed to insulin. Glucose is the major stimulus for insulin secretion via the exocytosis of secretory granules.

Glossary

AC: adenylate cyclase
ADA: American Diabetes Association
Akt: serine/threonine protein kinase
AMP: adenosine monophosphate
ATF4: activating transcription factor 4
ATF6: activating transcription factor 6
BAX: BCL2-associated X Protein
BCL-2: B-cell lymphoma 2
CAD: caspase-activated DNase
cAMP: cyclic adenosine monophosphate
CASP3: caspase 3
CASP8: caspase 8
CAT: catalase
CHOP: C/EBP homologous protein
CIDEA: cell death-inducing DNA fragmentation factor A
CYCD: cyclin D
CYLD: cylindromatosis (turban tumor syndrome)
DPP-4: dipeptidyl peptidase 4
EGFR: epidemial growth factor receptor
ER: endoplasmic reticulum
ERK1: extracellular signal-regulated kinase
Ex-4: exendin-4
Exenatide-LAR: exenatide long acting release
FFA: free fatty acid
FOXO1: forkhead box O1 protein
GCK: glucokinase
GIP: glucose-dependent insulinotropic peptide
GK: Goto-Kakizaki
GLP-1: glucagon-like peptide 1
GLP-1R: GLP-1 receptor
GLUT2: glucose transporter 2
GPX: guaiacol peroxidase
GSIS: glucose-stimulated insulin secretion
CSPG2: Chondroitin sulfate proteoglycan 2 (versican)
GAS2: growth arrest-specific 2
HbA1c: hemoglobin A1c
HES1: hairy and enhancer of split-1
HFD: high fat diet
HLXB9: homeobox protein HB9
HOMA: homeostasis model assessment
IRS2: insulin receptor substrate 2
MAFA: v-maf musculoaponeurotic fibrosarcoma oncogene homolog A
mTOR: mechanistic target of rapamycin
NEUROD: neurogenic differentiation
NEP: neutral entopeptidase
PARP: poly-ADP ribose polymerase
PC: protein convertase
PDX1: pancreatic and duodenal homeobox 1
PI3K: phosphatidylinositol 3-kinase
PNUTL2: peanut-like 2