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Reviews

Anti-diabetic actions of glucagon-like peptide-1 on pancreatic beta-cells

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ABSTRACT

Glucagon-like peptide-1 (GLP-1), an incretin hormone, is released from intestinal L-cells in response to nutrients. GLP-1 lowers blood glucose levels by stimulating insulin secretion from pancreatic beta-cells in a glucose-dependent manner. In addition, GLP-1 slows gastric emptying, suppresses appetite, reduces plasma glucagon, and stimulates glucose disposal, which are beneficial for glucose homeostasis. Therefore, incretin-based therapies such as GLP-1 receptor agonists and inhibitors of dipeptidyl peptidase IV, an enzyme which inactivates GLP-1, have been developed for treatment of diabetes. This review outlines our knowledge of the actions of GLP-1 on insulin secretion and biosynthesis, beta-cell proliferation and regeneration, and protection against beta-cell damage, as well as the involvement of recently discovered signaling pathways of GLP-1 action, mainly focusing on pancreatic beta-cells.

1. Introduction

Diabetes mellitus is a global burden, and the prevalence of type 2 diabetes is dramatically increasing worldwide. It is expected that 366 million individuals will be affected by 2030 [1]. Diabetes is characterized by defective control of blood glucose resulting from an absolute or relative deficiency of the pancreatic beta-cell mass. Type 1 diabetes is caused by autoimmune-mediated destruction of pancreatic beta-cells, resulting in an absolute deficiency of insulin, whereas type 2

Abbreviations: AMPK, 5′ AMP-activated protein kinase; Bad, Bcl-xl/Bcl2-associated death promoter homolog; Bcl-2, B-cell lymphoma-2; Bcl-xl, B-cell lymphoma-extra large; BiP, binding immunoglobulin protein; BTG2, B-cell translocation gene 2; C/EBP, CCAAT/enhancer-binding protein; COUP-TFII, chicken ovalbumin upstream promoter transcription factor II; CREB, cAMP response-binding protein; DPP-IV, dipeptidyl peptidase IV; EGFR, epidermal growth factor receptor; Epac, exchange protein activated by cAMP; ER, endoplasmic reticulum; ERK, extracellular signal regulated kinase; Fox, forkhead box; GIP, glucose-dependent insulinotropic peptide; GLP, glucagon-like peptide; GLP-1R, GLP-1 receptor; GLUT, glucose transporter; GPR, G-protein coupled receptor; GRPP, glicentin-related polypeptide; HNF, hepatocyte nuclear factor; IP, intervening peptide; IRS, insulin receptor substrate; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; MPGF, major proglucagon fragment; mTOR, mammalian target of rapamycin; NFAT, nuclear factor of activated T-cells; NOD, nonobese diabetic; p90RSK, p90 ribosomal S6 kinase; PAK, p21-activated kinase; PC, prohormone convertase; PCNA, proliferating cell nuclear antigen; Pdx-1, pancreas duodenum homeobox 1; PK, protein kinase; PI, phosphatidylinositol; SAD, synapses of amphids defective; SOX, Sry-related high mobility group box; SREBP, sterol regulatory element binding protein; TCF7L2, transcription factor 7-like 2 (T-cell specific, HMG-box); TGF, transforming growth factor; TXNIP, thioredoxin-interacting protein.

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diabetes is caused by insulin secretion that is insufficient to compensate for insulin resistance. In the early stages, type 2 diabetes is most commonly managed by drugs that suppress glucose production by the liver (e.g. metformin), increase insulin release from beta-cells (e.g. sulfonylureas), or prevent the digestion of carbohydrates (e.g. alpha-glucosidase inhibitors). However, the beta-cell mass is reduced in later stages of type 2 diabetes, and exogenous insulin therapy is eventually required for control of blood glucose levels. Thus, strategies to restore the functional beta-cell mass by stimulation of beta-cell replication and neogenesis and prevention of beta-cell damage and beta-cell death are under investigation for managing diabetes.

Considerable evidence shows that division of pre-existing beta-cells and neogenesis of beta-cells from ductal cells or pancreatic progenitor cells contribute to the increase in beta-cell mass during normal growth and after injury [2], suggesting the possibility of developing new strategies for stimulating beta-cell regeneration. Such strategies for increasing the number of insulin-producing cells include the expansion of remaining beta-cells, differentiation of beta-cell progenitors, and transdifferentiation of non-beta-cells into insulin-producing cells, both inside and outside the pancreas. Considerable research indicates that such approaches might be accomplished by delivery of growth factors such as GLP-1.

GLP-1 is released from the small intestine and colon in response to food ingestion and stimulates insulin secretion from pancreatic islets in a glucose-dependent manner. GLP-1 also has many other beneficial effects for treatment of diabetes (Table 1). It delays gastric emptying, inhibits food intake, improves insulin sensitivity, inhibits glucagon secretion, and stimulates insulin biosynthesis. GLP-1 also shows beta-cell preservation effects including beta-cell proliferation, beta-cell neogenesis, and prevention of beta-cell apoptosis [3]. Therefore, there is increasing interest in GLP-1 as a therapy for type 2 diabetes. This review will discuss the current understanding of the therapeutic potential of GLP-1 in diabetes, particularly its effect on pancreatic beta-cells.

Table 1 – Anti-diabetic actions of GLP-1.

Tissue		Action
Pancreatic islets	beta-cell	proliferation ↑ differentiation ↑ apoptosis ↓ insulin secretion ↑ insulin biosynthesis ↑
	alpha-cell	glucagon secretion ↓
	delta-cell	somatostatin secretion ↑
Liver		glucose production ↓ lipogenesis ↓ steatosis ↓
Heart		cardioprotection ↑ cardiac function ↑ vasoprotection ↑ inflammation ↓
Brain		appetite ↓ neuroprotection ↑
Stomach		gastric emptying ↓
Intestine		motility ↓ lipoprotein secretion ↓
Muscle		insulin sensitivity ↑ glucose uptake ↑
Adipose tissue		inflammation ↓ lipogenesis ↓ thermogenesis ↑

2. Glucagon-like peptide-1: a brief overview

In 1902, Bayliss and Starling speculated that a hormone, "secretin," stimulates the secretion of some factors from the pancreas after ingestion of nutrients [4]. Later, the name "incretin" was introduced for the factor from the upper gut for this pancreatic stimulating activity. The incretin concept was proved by showing that orally administered glucose induced more insulin secretion than intravenously administered glucose. GIP was the first incretin isolated from the intestinal mucosa [5]. However, incretin activity persisted after inhibiting GIP action with anti-GIP sera, suggesting the presence of additional incretin hormones. GLP-1 (7–36), a gut peptide, was later identified as an insulinotropic incretin hormone [6].

The *proglucagon* (*gcg*) gene is expressed in enteroendocrine L cells in the small and large intestine, pancreatic alpha-cells, taste buds, and some neurons in the caudal brain stem and hypothalamus [7]. A single mRNA transcript encoding the proglucagon peptide is produced in all these tissues. The tissue-specific mRNA expression of the proglucagon is regulated by 5′ flanking regions of the gene, and differential post-translational processing of the proglucagon peptide produces different peptides in different tissues [8]. In pancreatic alpha-cells, processing of proglucagon by PC2 produces glicentin-related pancreatic peptide, glucagon, intervening peptide-1, and major proglucagon fragment. Further processing of major proglucagon fragment by PC1/3 yields GLP-1. In the gut and brain, processing of proglucagon by PC1/3 produces GLP-1(Fig. 1) [8]. In taste buds, both PC1/3 and PC2 are present, and thus they produce GLP-1, GLP-2, and glucagon [9].

GLP-1 secretion is stimulated by mixed meals and nutrients such as carbohydrates, fats, proteins, and dietary fiber. GLP-1 is released in a biphasic pattern with the first phase occurring at 10–15 min after oral ingestion and the second phase occurring at 30–60 min. As majority of L cells are located in the distal region of the small intestine, the first phase of secretion seems to be mediated by neurotransmitters and the vagus nerve rather than by direct stimulation of L cells [10]. However, it is possible that L cells located in the proximal small intestine can trigger the first phase of GLP-1 release after direct contact of nutrients with L cells. The molecular signaling for GLP-1 secretion involves a glucose-sensing signal including glucokinase, ATP-dependent potassium channel, and sodium glucose cotransporter-1 [11]. In addition, the sweet taste receptor is known to be involved in GLP-1 secretion [12]. Many GPRs are expressed in the intestine, and some of these such as GPR119 (ligand: natural lipid amides), GPR40 and GPR120 (ligand: long chain fatty acids), and TGR5 (bile acid receptor) are also involved in GLP-1 secretion [13].