Review Article

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GLUCAGON LIKE PEPTIDE – 1: A NEW ERA IN TREATMENT OF TYPE- 2 DIABETES MELLITUS

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ABSTRACT

Therapies based on the incretin hormone glucagon-like peptide 1 (GLP-1) are novel treatment options for type 2 diabetes that act through a variety of complementary mechanisms. GLP-1 is produced by the proglucagon gene in L-cells of the small intestine in response to nutrients. It stimulates glucose-dependent insulin release from the pancreatic islets. In addition to its insulinotropic effects, it is thought to exert ant hyperglycemic effects by slowing gastric emptying, inhibiting inappropriate glucagon release, stimulating β-cell proliferation and differentiation, and improving satiety. GLP-1 secretion is decreased in type 2 diabetes, thus making it a logical target for novel treatments of type 2 diabetes. In clinical trials, GLP-1 effects are evident regardless of the duration or severity of diabetes. Thus, modulating GLP-1 levels and GLP-1 activity through administration of the native hormone, analogs, and mimetics or by inhibiting its degradation has become a major focus of investigation for treating type 2 diabetes over the past decade.

Keywords: Diabetes Mellitus, GLP-1, Insulin, Incretin, Antihyperglycemic, DPP-IV inhibitor

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INTRODUCTION

Diabetes mellitus is a group of metabolic diseases which is characterized by hyperglycemia, glycosuria, polydypsia, polyphagia that result from defects in insulin secretion, or action, or both. There are many antihyperglycaemic agents which are used for the treatment of diabetes; act on different sites as shown in **figure 1**.

Incretin hormones cause an increase in the amount of insulin released from beta cells in the pancreas following ingestion of food.[1] Incretin hormones act to increase glucose-dependent insulin secretion from beta cells in the pancreas[2]; this action helps to ensure an appropriate insulin response after eating.[1] glucagon-like peptide-1 (GLP-1) is the most well-characterized incretin hormone, which is considered to be the most important incretin released by the gut into the bloodstream in response to meal.[3] In addition to its effects on insulin secretion after eating, GLP-1 also has additional effects that can help in the management of diabetes.[3-5] The primary function of GLP-1 is to enhance insulin secretion only in the presence of elevated blood sugar (glucose) concentrations.[3] GLP-1 also suppresses the release of glucagon from the pancreas.[4] Glucagon stimulates glucose release from the liver[6]; so decreasing the amounts of glucagon helps to improve glucose control.[3,4] It is postulated that GLP-1 acts in the brain to absorbed too quickly into the reduce appetite[4] and in the stomach to slow the rate of gastric emptying so that nutrients are not bloodstream.[5] GLP-1 has been shown to improve acute beta-cell function in humans.[3]

ROLE OF GLP-1 IN GLUCOSE HOMEOSTASIS

GLP-1 exerts multiple effects that contribute to the maintenance of glucose homeostasis as shown in **table 1**.[3-5] GLP-1 enhances glucose-dependent insulin secretion; suppresses inappropriate glucagon secretion; reduces appetite, leading to reduction of food intake; regulates the rate of gastric emptying, so that nutrients are not absorbed as quickly into the bloodstream.

GLP-1 and Type 2 Diabetes

People with type 2 diabetes often have inappropriately elevated levels of glucagon.[7] The elevated glucagon, which is produced in pancreatic alpha cells, causes the liver to release an excessive amount of glucose into the bloodstream, which then contributes to high blood glucose seen in type 2 diabetes.[8] Many people with diabetes may also have an accelerated rate of gastric emptying, which leads to increased nutrient delivery to the intestine resulting in an abnormally rapid rise in glucose following a meal.[9] The levels and actions of GLP-1 appear to be deficient in many people with type 2 diabetes, thus creating an opportunity for antidiabetes medications that act directly on the GLP-1 receptor or inhibit the breakdown of GLP-1 in the bloodstream.[7] Metabolic actions of GLP-1 are summarized in **figure 2**; which shows the importance of GLP-1 in diabetes management.[10]

Administration of GLP-1 by continuous subcutaneous infusion (CSI) for 6 weeks in patients with T2DM caused a significant decrease in hemoglobin A1C (A1C) and reduced hyperglycemia significantly over the course of 8 hours, during which the patients ate breakfast and lunch. The effect of GLP-1 was noted at 1 week of treatment and was maintained over 6 weeks.[11]

GLP-1 concentrations in the picomolar range induce insulin secretion from pancreatic b-cells *in vitro* and *in vivo* when elevated glucose concentrations (> 5 mmol/l) are present. In patients with non-insulin-dependent diabetes mellitus (NIDDM) parenteral (i.v. and s.c.) administration of GLP-1 led to reconstitution of the early phase insulin secretion and reduction of postprandial glucose excursions. Even in insulin-deficient type-1 diabetic patients GLP-1 reduced the insulin requirements, suggesting additional peripheral activities.[12]

DRUGS UNDER DEVELOPMENT

Exendin-4

To compensate for the rapid and robust metabolism of GLP, several peptide analogues with extended action have been developed. The 39 amino acid peptide exendin-4 (exenatide) is homologous to GLP-1 and binds avidly to the GLP-1 receptor,[13] but is resistant to the actions of DPP-IV. Because of this, exendin-4 has a greatly extended duration of insulinotropic activity compared with GLP-1.[14] The effectiveness of repeated dosing with exendin-4 was recently demonstrated in patients with T2DM. Bedtime glucose levels were reduced from 15.5 to 9.2 mmol/L, and A1C decreased from 9.1% to 8.3% over just 1 month[14]. These results were corroborated by another recent placebo-controlled trial of exendin-4 in T2DM.[15] The major side effect of exendin-4 in humans is nausea and vomiting, which seems to occur in a dose-dependent fashion.

Liraglutide

A second long-acting derivative was made by covalently linking GLP-1 to a fatty acid. This fatty acyl-GLP-1 binds to serum albumin, which greatly increases the duration of action of GLP-1 by: (1) limiting metabolism by DPP-IV; (2) delaying/prolonging absorption from the injection site; and (3) reducing renal clearance. The half-life of this compound, previously designated NN2211 and now called liraglutide, is approximately 12 hours in healthy volunteers;[16] therefore, a single daily injection can deliver biologically active amounts of GLP-1 for an entire 24-hour period. In patients with T2DM, a single subcutaneous injection of liraglutide at bedtime reduced glucose levels during the night, greatly reduced the glucose excursions during a standardized lunch, and increased meal-stimulated insulin secretion.[15] Suppression of meal-stimulated glucagon levels and delay of gastric emptying were also observed. However, as with exendin-4 or native GLP-1, nausea and vomiting are dose-limiting side effects.

CJC-1131

An alternative approach to overcome the short half-life of GLP-1is to form a constant bond of GLP-1 with albumin—as in the case with CJC-1131.[17] This DPP-IV-resistant human GLP-1analog binds to and activates the GLP-1 receptor. This agent has a 10-day half-life in humans.[18]

DPP-IV Inhibitors

DPP-IV degrades active glucagonlike peptide (GLP)-1 and abolishes all the effects of GLP-1. An alternative to using exogenously administered GLP-1 receptor agonists is to increase the effect of endogenously secreted GLP-1 by blocking its degradation **(Figure 3)**. There are several inhibitors of DPP-IV currently under investigation. These agents have the advantages of being active in an orally available form and having minimal gastrointestinal side effects. A theoretical problem with blocking DPP-IV is that this enzyme metabolizes a wide range of regulatory peptides and plays a role in the modification of antigens for immune recognition, so other physiologic systems could be affected. Sitagliptin, Vildagliptin, Saxagliptin, LAF237, SRY-322, PHX1149 and GRC-8200 are the agents which inhibit the DPP-IV and prevent degradation of GLP-1.Another potential limitation is that plasma levels of GLP-1 that can be achieved using DPP-IV inhibitors are a function of normal GLP-1 secretion rates and are not likely to reach the levels that can be obtained with GLP-1 analogues.[19.20,21,22,23]

CONCLUSION

GLP-1 has emerged as a key glucoregulatory hormone, exerting several physiologic actions that lower blood glucose levels. In acute and short-term studies, GLP-1 is effective in controlling the hyperglycemia of T2DM. Several promising agents are under development as treatments for diabetes that are based on activation of the GLP-1 signaling system. Encouraging early results with these drugs strengthen the possibility of new treatment option for diabetic patients.

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Table 1: Summary of GLP-1 actions relevant to glucose control and Treatment of Type 2 Diabetes Mellitus

Organ	**Glucagon like peptide-1 actions**
Pancreas	Stimulates glucose-dependent insulin secretion (+) Increases insulin gene transcription, mRNA stability, and biosynthesis (+) Stimulates somatostatin secretion (+) Enhances β cell response to glucose (+) Induces β cell neogenesis and proliferation (+) Inhibits β cell apoptosis (+) Increases expression of key genes important for differentiated β cell function (+)
Gastrointestinal tract	Inhibits gastric emptying (+) Inhibits gastric acid secretion (+)
Central nervous system	Inhibits food and water intake (+) Promotes satiety and weight loss (+) Enhances memory and neuronal survival (+) Activates aversive pathways leading to nausea/vomiting (+)
Cardiovascular system	Improves cardiovascular function after ischemia (+) Reduces the extent of cardiomyocyte death after experimental injury (+)
Adipose tissue	Insulin-like lipogenic actions (-) Lipid storage (-)
"+" denotes that this action occurs; "-" denotes that this action does not occur.	

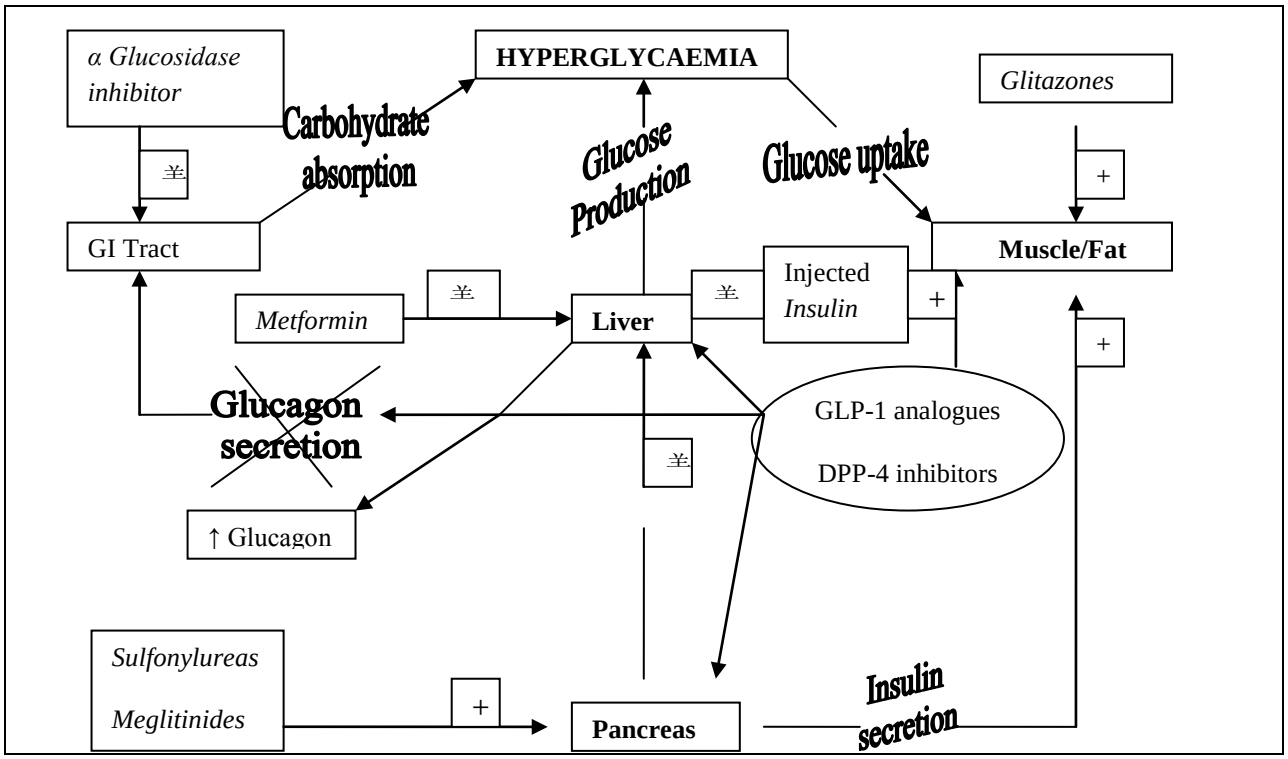
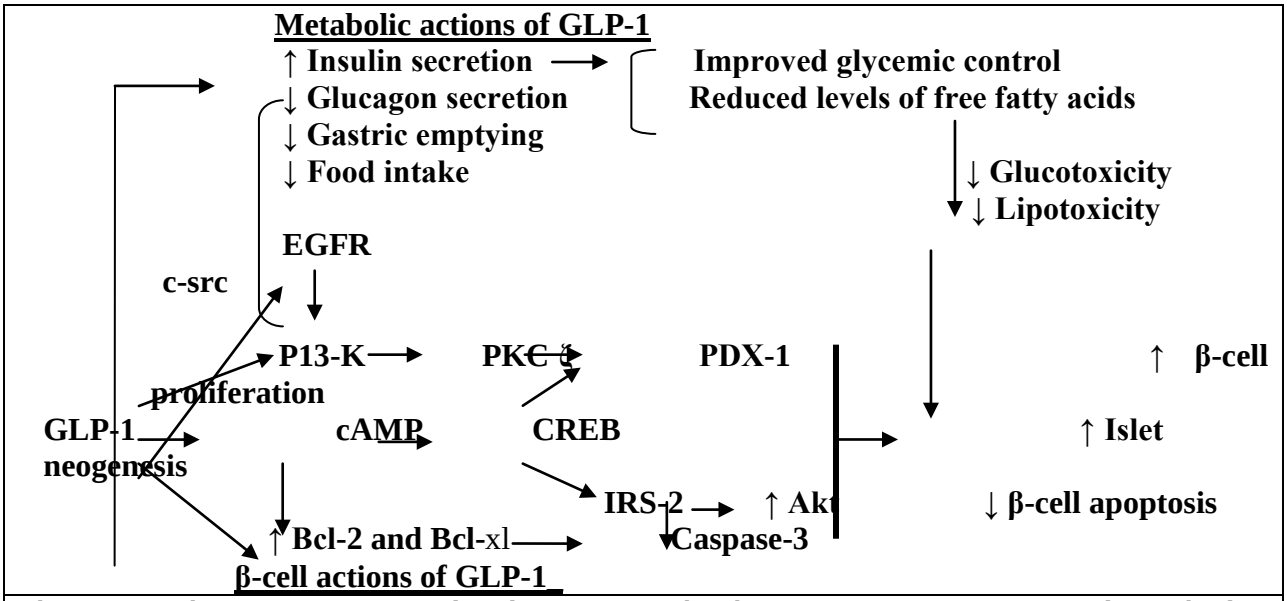


Figure 1: Major sites of action of antihyperglycaemic agents



Akt = proyein kinase B; cAMP = cyclic adenosine monophosphate; CREB = cAMP response element-binding protein; EGFR = epidermal growth factor receptor; GLP-1 = glucagon-like peptide-1; IRS-2 = insulin receptor substrate-2; PDX-1 = pancreatic duodenal homeobox-1; P13-K = phosphatidylinositol 3-kinase; PKC ζ = protein kinase c ζ.

Figure 2: GLP-1 Receptor Signaling Pathway: Protection the Vulnerable β-cell in Type 2 Diabetes

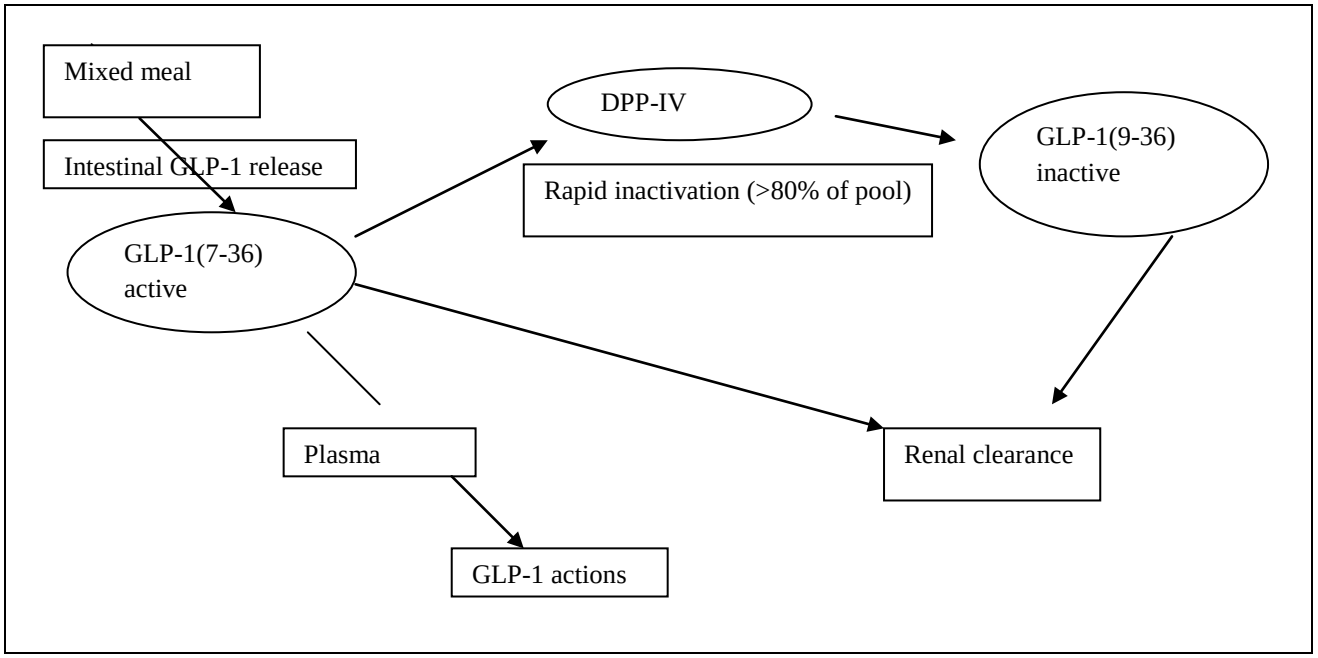


Figure 3: Mechanism of DPP-IV inhibitor

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