ABSTRACT

Incretin hormones, originally identified in the 1930s, were not fully appreciated for their potential role in the treatment of type 2 diabetes mellitus until their insulinotropic properties were recognized in the 1960s. Incretins are hormones produced by the gastrointestinal tract and released upon nutrient entry into the gut. Once released, incretins stimulate insulin secretion. The concept of this incretin action was based upon studies noting that the insulin response to oral glucose exceeded that for equivalent amounts of intravenous glucose. The predominant incretin hormone is glucagon-like peptide-1 (GLP-1). In addition to stimulating insulin secretion, GLP-1 suppresses glucagon release, slows gastric emptying, improves insulin sensitivity, and reduces food intake. In rodent and cell model systems, GLP-1 has been shown to promote β-cell regeneration and mass in addition to stimulating reduced apoptosis. Targeting GLP-1 receptor stimulation and action is central to investigational therapeutic strategies for the treatment of type 2 diabetes mellitus and involves chronic infusion of GLP-1, oral dipeptidyl peptidase-IV inhibitors, and incretin mimetics, including the recently approved natural GLP-1–like peptide, exendin-4. (Adv Stud Med. 2006;6(7A):S581-S585)

MECHANISM OF ACTION

The concept of incretin was initially hypothesized from studies reporting a greater insulin response to oral glucose versus an equivalent concentration of intravenous glucose. It was postulated that gut-derived substances, released upon oral nutrient intake, were potential insulin secretagogues that augmented insulin release. In 1986, Nauck et al studied this incretin effect (insulin response to oral vs intravenous glucose) by administering 25, 50, and 100 g of glucose either orally or intravenously to study subjects and measuring connecting peptide (C-peptide) levels, which are used as a marker of endogenous insulin production. They found that the degree of incretin secretion was dependent upon the amount of glucose ingested, and that incretins were responsible for approximately 75% of the insulin response after ingestion of 50 g of glucose.

The 2 major incretin hormones are gastric inhibitory polypeptide (GIP), also known as glucose-dependent insulinotropic polypeptide, and glucagon-like peptide-1 (GLP-1). Knowledge of their secretion and actions has led to the development of incretin-based therapies for type 2 diabetes.
and the proximal jejunum. GLP-1 is secreted by the L cells, found mainly in the ileum and colon. Although both incretins are released following oral ingestion of nutrients, carbohydrate- and lipid-rich meals, in particular, seem to be the main stimulants for GIP secretion. These peptides bind to their specific GIP and GLP-1 receptors and are rapidly metabolized by the ubiquitous enzyme dipeptidyl peptidase-IV (DPP-IV).

Both incretins stimulate insulin secretion and, in cell culture models, they have been shown to stimulate β-cell proliferation. Although their effects on insulin sensitivity are not well defined, a 6-week study of patients with type 2 diabetes reported that GLP-1 treatment was associated with a significant increase in insulin sensitivity. In type 2 diabetes, the finding that GIP secretion is preserved while GLP-1 secretion is impaired is central to the rationale behind GLP-1 replacement therapy. Moreover, patients with type 2 diabetes have an impaired insulinoceptive response to exogenous administration of GIP, but a preserved response to exogenous GLP-1. The finding that people with type 2 diabetes have low levels of GLP-1 but a preserved insulin secretory response underlies the therapeutic potential of GLP-1 therapies.

Other effects of incretin hormones differ, with evidence suggesting that GIP accelerates gastric emptying; in contrast, GLP-1 slows gastric emptying, suppresses glucagon secretion, and reduces food intake. GIP has not been reported to affect glucagon secretion or food intake in human studies.

Before further examining the effects of GLP-1, it is useful to recap its overarching properties. GLP-1 is cleaved from intestinal proglucagon and secreted from L cells of the ileum and colon following nutrient intake. Active GLP-1 is rapidly cleaved into an inactivated form by DPP-IV. By virtue of its effects on stimulating insulin secretion, suppressing glucagon secretion, slowing gastric emptying, improving insulin sensitivity, and reducing food intake, GLP-1 ultimately results in a reduction of circulating glucose levels (Figure 2).

**GLP-1 Effects on the Central Regulation of Feeding**

The effect of GLP-1 on central nervous system control of satiety was examined in 1996 by Turton et al. In this study, fasted rats received intracerebroventricular injections of GLP-1 or saline control, with food intake measured at serial 2-hour intervals and a

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**Figure 1. GLP-1 and GIP: Sequence Homology**


**Figure 2. Biological Actions of GLP-1**

minimum of 72 hours between injections. As the concentration of injected GLP-1 increased, food intake progressively decreased. In addition, they demonstrated a blockade of GLP-1 effects on food intake with the GLP-1 receptor antagonist exendin. These observations suggest that GLP-1 had significant central effects on reducing food intake. Further supporting central nervous system activity, researchers localized GLP-1 and its receptors to the amygdala and hypothalamus. A meta-analysis of studies of human subjects has also shown that GLP-1 is associated with a dose-dependent decrease in food intake.10

GLP-1 EFFECTS ON THE PANCREAS

Effects of GLP-1 on the pancreatic islet cells include increased insulin secretion from β cells in a glucose-dependent fashion, increased somatostatin secretion from δ cells, and decreased glucagon secretion from α cells. These actions contribute to decreased hepatic glucose output (Figure 3).11,12 An important clinical implication of the dependence on blood glucose concentrations at or above normal fasting plasma glucose levels is that GLP-1 does not cause hypoglycemia. However, it should be noted that GLP-1 receptor signaling is not essential for glucose responsiveness in β cells.13

EFFECTS OF GLP-1 ON β CELLS

In animal studies, GLP-1 treatment has been shown to increase β-cell mass and maintain β-cell function. The effects of GLP-1 on β cells generally include acute, subacute, and chronic effects.14 Acutely, GLP-1 enhances glucose-dependent insulin secretion, whereas subacute effects include stimulation of proinsulin transcription and insulin biosynthesis. Chronic effects include stimulation of β-cell proliferation and neogenesis from precursor ductal cells, in addition to increased expression of GLUT-2 transporters and glucokinase, which regulate pancreatic glucose uptake and metabolism.

In 2002, Zander et al studied the effects of GLP-1 on the first- and second-phase insulin response in patients with type 2 diabetes.9 Subjects received a continuous subcutaneous infusion of GLP-1 or saline for 6 weeks, with a battery of tests performed at weeks 0 (prior to infusion), 1, and 6. A hyperglycemic clamp at 30 mM glucose for 90 minutes, with L-arginine stimulation of insulin secretion for 45 minutes, was used to measure β-cell function. Results from this study showed that the first-phase (0–10 minutes) and second-phase (10–45 minutes) insulin responses improved with continuous GLP-1 infusion. The peak insulin response, as measured with C-peptide levels, increased a mean of 3.3-fold from baseline values ($P<.0001$) after 6 weeks of continuous GLP-1 infusion. Significant improvements in β-cell function, insulin sensitivity, and other measured parameters were shown in response to continuous GLP-1 infusion.

Several model systems have shown that GLP-1 treatment stimulates β-cell regeneration and mass (Figure 4). Studies have shown GLP-1 treatment is associated with increased β-cell neogenesis, proliferation, and hypertrophy, in addition to reduced β-cell apoptosis.16

Figure 3. GLP-1: Pancreatic Effects

GLP-1 = glucagon-like peptide-1.
Data from Drucker et al11; Orskov et al.12

Figure 4. GLP-1 Stimulates β-Cell Regeneration and Mass

GLP-1 = glucagon-like peptide-1.
Data from Farilla et al15; Farilla et al.16
apoptosis. Using the Zucker fatty rat model, Farilla et al showed that after GLP-1 treatment, β-cell proliferation significantly increased while β-cell apoptosis decreased. These effects in combination contributed to an increase in β-cell mass. The effects of GLP-1 on β-cell apoptosis have also been demonstrated in isolated human islet cells. Cells cultured in the absence and presence of GLP-1 for up to 5 days showed that GLP-1 treatment significantly reduced the percentage of apoptotic cells ($P<.01$ vs control).

Impairment of pancreatic islet function in type 2 diabetes has been long established. Muller et al reported deficits in β- and α-cell secretion as early as 1970. In that study, subjects with type 2 diabetes showed a dramatic initial and sustained reduction in insulin secretion following an oral 200-g carbohydrate meal compared with a brisk and sharp rise of insulin in nondiabetic subjects. Moreover, an oral glucose load resulted in sustained levels of glucagon secretion from the pancreatic α cells in subjects with type 2 diabetes compared with suppressed levels in nondiabetic subjects. These results demonstrate the dual defects in pancreatic islet cells of subjects with type 2 diabetes.

**GLP-1 IMPAIRMENT IN TYPE 2 DIABETES**

The impaired incretin effect associated with type 2 diabetes was demonstrated by Nauck et al in 1986. In this study, oral and intravenous glucose ingestion elicited identical changes in plasma glucose over a 3-hour period for subjects with normal glucose tolerance. Similarly, oral and intravenous glucose ingestion caused identical changes in plasma glucose for subjects with type 2 diabetes. C-peptide levels, an index of endogenous insulin secretion, were also measured during both routes of glucose administration. Figure 5 shows the results of this study, with nondiabetic subjects having reduced C-peptide levels in response to intravenous versus oral glucose, despite having similar plasma glucose levels. However, in the type 2 diabetes group studied at equivalent hyperglycemia, C-peptide levels were similar regardless of route of glucose administration. Thus, subjects with type 2 diabetes were missing the incretin effect resulting from orally administered glucose. The incretin defect in type 2 diabetes seems to have 2 causes: a decreased secretion of GLP-1 and a profoundly impaired insulinotropic effect of GIP.

**Figure 5. The Incretin Effect Is Impaired in Type 2 Diabetes Compared with NGT**

**Figure 6. Release of GLP-1 Is Impaired in Patients with Type 2 Diabetes**

GLP-1 = glucagon-like peptide-1.

Adapted with permission from Toft-Nielson et al. J Clin Endocrinol Metab. 2001;86:3717-3723.
In addition to an impaired incretin effect, type 2 diabetes has also been associated with impaired GLP-1 release. Toft-Nielsen et al studied the secretion of incretins over a 4-hour period following breakfast in subjects with type 2 diabetes compared with those having normal glucose tolerance. They demonstrated a significant reduction in GLP-1 response in patients with type 2 diabetes (Figure 6). In a study of a small group of identical twins discordant for type 2 diabetes, the GLP-1 response was lower in the diabetic twin. Also, in first-degree nondiabetic relatives of patients with diabetes, 24-hour GLP-1 profiles were normal. These observations suggest that the GLP-1-impaired secretion is more likely a consequence rather than a cause of diabetes.

**METHODS TO ENHANCE GLP-1 RECEPTOR STIMULATION AND ACTION**

A greater understanding of the role of incretins in type 2 diabetes has led to the development of therapeutic approaches aimed at enhancing GLP-1 receptor stimulation and action. The utility of GLP-1 administration is limited by difficulties of chronic infusions and the transient nature of the effects upon infusion cessation. Oral DPP-IV inhibitors are currently under clinical investigation, with several (eg, NVP-LAF237, BMS-477118, and MK-0431) in phase III development. Incretin mimetics are the furthest along in development, with the natural GLP-1–like peptide exendin-4 (exenatide) approved by the US Food and Drug Administration in 2005 for use in type 2 diabetes in combination with metformin and sulfonylureas. Of the remaining analogs of GLP-1, NN2211 (liraglutide) is in phase III studies, whereas other incretin mimetics are in earlier stages of development. The therapeutic potential of incretin approaches in the treatment of type 2 diabetes is the focus of subsequent articles in this monograph.

**REFERENCES**