**THE PHYSIOLOGIC EFFECT OF INCRETIN HORMONES**

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Incretins, hormones produced by the gastrointestinal tract in response to nutrient entry, stimulate insulin secretion. The concept of incretins was first developed from the observation that the insulin response to oral glucose exceeded that following the administration of equivalent amounts of intravenous glucose. Nauck et al matched the plasma glucose attained from oral glucose with plasma glucose attained by giving intravenous glucose.¹ Over a 3-hour period, by looking at the C-peptide levels, which are a marker of endogenous insulin production, these researchers noted that the insulin (C-peptide) response to intravenous glucose was considerably lower than the response to oral glucose. This incretin effect is now known to be a result of stimulation of insulin secretion by the production of gut hormones following oral nutrient intake. The principal incretins are glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1).

There are many incretin hormones, but the 2 major incretin hormones belong to the glucagon peptide superfamily. They are gastric inhibitory polypeptide, also known now as GIP, and GLP-1.

Incretins were first defined in the 1930s, but little work was done in the period between 1930 and 1960 because incretins were not believed to be present or have significant physiologic effects. Since the insulinotropic action of incretins was confirmed in the 1960s, progressive development of knowledge about their secretion and actions has now led to incretin-based therapies for type 2 diabetes.

**MECHANISM OF ACTION**

Glucose-dependent insulinotropic peptide is a 42-amino acid peptide, whereas GLP-1 is a 30- or 31-amino acid peptide.² GIP is secreted from the K cells, located primarily in the duodenum and the proximal jejunum, whereas GLP-1 is secreted by the L cells, found mainly in the ileum and colon. Both incretins are stimulated by oral ingestion of nutrients...
and are metabolized very rapidly by the ubiquitous enzyme, dipeptidyl peptidase-IV (DPP-IV).3

As for insulin secretion, both incretins stimulate insulin secretion, and in cell culture models, they both stimulate β-cell proliferation.4 However, the effects on insulin sensitivity are not well defined for either. GLP-1 may, in fact, have insulin-sensitizing properties, but little is known about GIP in this regard. In addition, the insulinotropic response to the exogenous administration in type 2 diabetes is impaired for GIP, whereas it is preserved for GLP-1.

Finally, other important features of incretin hormones include effects on gastric emptying, glucagon secretion, and food intake. There is some evidence that GIP accelerates, while GLP-1 slows gastric emptying. No effects of GIP are noticed for glucagon secretion or food intake. By contrast, GLP-1 significantly suppresses glucagon secretion and reduces food intake.

To summarize, GLP-1 is secreted from the intestinal L cells of the ileum and colon following food ingestion. When intestinal proglucagon is converted to active GLP-1, secreted GLP-1 is subsequently broken down very rapidly and inactivated by DPP-IV. The major effects of GLP-1 include stimulation of insulin secretion, suppression of glucagon, slowing of gastric emptying, improvement of insulin sensitivity, and reduction of food intake, all of which contribute to reduced circulating glucose levels (Figure 1).2

**Figure 1. Mechanism of Action of GLP-1**

Food ingestion

GLP-1 secretion

• Stimulates glucose-dependent insulin secretion
• Suppresses postprandial glucagon secretion
• Slows gastric emptying
• Inhibits food intake

Reduced circulating glucose levels

GLP-1 = glucagon-like peptide-1.


**ROLE OF GLP-1 IN THE CENTRAL REGULATION OF FEEDING**

To determine whether GLP-1 has central effects on feeding, Turton et al conducted a study approximately a decade ago on fasted rats receiving intracerebral-ventricular GLP-1 injections.5 During serial 2-hour food intake intervals, with GLP-1 infusions being done at 72-hour periods, progressive reductions in food intake were clearly seen as the dose of GLP-1 was progressively increased, suggesting that GLP-1 has significant central effects on reduction of food intake. In further support of a central role for GLP-1, the authors demonstrated GLP-1 receptors in the thalamic and hypothalamic regions.

**Figure 2. GLP-1: Pancreatic Effects**

GLP-1 = glucagon-like peptide-1.

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**EFFECTS OF GLP-1 ON ENDOCRINE HORMONE SECRETION**

Glucagon-like peptide-1 increases insulin secretion from β cells in a glucose-dependent fashion. It also increases somatostatin secretion from δ cells, and decreases glucagon secretion from α cells, which contributes to a reduction in hepatic glucose output (Figure 2).6,7

**EFFECTS OF GLP-1 ON β CELLS**

In long-term studies in animals, GLP-1 increased β-cell mass and maintained β-cell function. The effects of GLP-1 on β cells essentially can be broken down into
the following categories: acute, subacute, and chronic.\textsuperscript{8} The acute effects enhance glucose-dependent insulin secretion. In the subacute phase, GLP-1 stimulates transcription of proinsulin and the biosynthesis of insulin. Finally, for chronic effects, GLP-1 stimulates proliferation of islet cells and neogenesis of $\beta$ cells from precursor ductal cells, and also increases the expressions of GLUT-2 transporters and glucokinase, which regulate pancreatic glucose uptake and metabolism.

Zander et al published a study in The Lancet several years ago that assessed the effects of GLP-1 on first- and second-phase insulin responses in type 2 diabetes patients who underwent a continuous subcutaneous infusion of GLP-1 for 6 weeks.\textsuperscript{9} Before and again after this prolonged GLP-1 infusion, patients had a hyperglycemic clamp study at 30 mM glucose for 90 minutes, with L-arginine stimulation of insulin secretion at 45 minutes.\textsuperscript{9} Following the continuous subcutaneous infusion of GLP-1, the first-phase and the second-phase insulin responses were increased. The peak insulin response was also dramatically increased—approximately 4- or 5-fold—by the continuous GLP-1 administration. Hence, significant improvements occurred in all aspects of insulin secretion in response to the GLP-1 infusion.

Additionally, GLP-1 stimulates $\beta$-cell mitosis and increases islet mass in a number of model systems (Figure 3).\textsuperscript{10,11} Studies have shown increased $\beta$-cell neogenesis, $\beta$-cell proliferation, and $\beta$-cell hypertrophy, in addition to reduced $\beta$-cell apoptosis. Farilla et al looked at $\beta$-cell mass, $\beta$-cell proliferation, and $\beta$-cell apoptosis in the Zucker fatty rat model.\textsuperscript{10,11} Following GLP-1 treatment, significant increases were noted in $\beta$-cell proliferation, whereas major reductions in $\beta$-cell apoptosis were observed—both contributing to an increase in $\beta$-cell mass. Farilla et al conducted a study on the effects of GLP-1 on $\beta$-cell apoptosis in isolated human islets.\textsuperscript{12} Over 5 days of culture, GLP-1, again, significantly reduced the percentage of apoptotic cells compared to controls.\textsuperscript{8}

It has for many years been known that pancreatic islet function is impaired in type 2 diabetes. Abnormalities in $\beta$- and $\alpha$-cell secretion were clearly documented by Muller et al.\textsuperscript{13} Following an oral 200-g carbohydrate meal, in contrast to the brisk and sharp rise of insulin in nondiabetic subjects, patients with type 2 diabetes had a dramatic initial and sustained reduction of insulin secretion. In contrast, glucagon secretion from the pancreatic $\alpha$ cells was sustained and not suppressed in subjects with type 2 diabetes as occurred in nondiabetic subjects following an oral glucose load. Thus, dual defects in pancreatic islet cell function favor the development of hyperglycemia.

**GLP-1 Impairment in Type 2 Diabetes**

Nearly 2 decades ago, Nauck et al demonstrated that
the incretin effect is impaired in patients with type 2 diabetes compared to those with normal glucose tolerance.\(^1\)

To carry out this study, changes in plasma glucose over 3 hours following oral glucose ingestion were mimicked by a variable infusion of intravenous glucose in normal subjects with glucose tolerance and those with type 2 diabetes. In both groups during both routes of glucose administration, C-peptide levels were measured as an index of endogenous insulin secretion. As is shown in Figure 4, nondiabetic subjects had reduced C-peptide responses to intravenous compared to oral glucose administration, despite similar plasma glucose levels.\(^1\) In the subjects with type 2 diabetes who were studied at equivalent levels of hyperglycemia, there was no difference in the C-peptide response regardless of the route of administration. Thus, the normal incretin effect from oral glucose was absent in those patients with type 2 diabetes.

Not only is the incretin effect impaired in type 2 diabetes, so is the release of GLP-1. In data from Toft-Nielsen et al., during a 4-hour period following breakfast, a progressive reduction was observed in GLP-1 response with increasing glucose intolerance (Figure 5).\(^1\)

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

As new therapies are explored for type 2 diabetes, several methods to enhance GLP-1 receptor stimulation and action are currently available or under active investigation. Although GLP-1 could be administered by chronic infusion, this method is difficult and the effects are evanescent when infusion is stopped. The oral DPP-

**REFERENCES**