INCRETIN BIOLOGY

How does the GLP-1 receptor pathway achieve these effects? Although the effect on the β cell is clearly mediated through GLP-1 receptors expressed on the β cell, many effects of GLP-1 are indirect and independent of the β cell. These indirect effects are mediated in part through activation of ascending vagal pathways that stimulate centers in the central nervous system.
system, which then feed forward to communicate with the pancreas, liver, and peripheral tissues, such as muscle and fat (Figure 1). This complex physiological pathway is difficult to study in vitro, but it is more elegantly studied with physiological experiments in whole animals or humans.

Rachman et al explored the potential of GLP-1 as a therapy for type 2 diabetes by administering native GLP-1 continuously to human subjects. This study showed it is possible to virtually normalize glycemic excursion throughout the day, not only in the fasting state, but also in the postprandial state. This study and others like it demonstrated that GLP-1 may be an effective therapy for the treatment of type 2 diabetes.

Furthermore, the actions of GLP-1 to lower blood glucose are not independent of the normal control mechanisms used by β cells and α cells to regulate their secretions. GLP-1 is infused and blood glucose is progressively lowered to normal, insulin secretion is increased and glucagon secretion is suppressed. But as the glucose level becomes normal, insulin secretion is terminated, and the glucagon suppression is alleviated. These responses markedly reduce the chance of developing hypoglycemia because when the glucose level comes down to normal, activation of the GLP-1 receptor is no longer coupled to stimulation of insulin secretion or inhibition of glucagon secretion. Such protection against hypoglycemia differs markedly from the actions of secretagogues of the sulfonylurea or glitinide class, which continue to stimulate insulin secretion even as glucose returns to normal or falls to lower levels.

Zander et al carried out the critical study supporting the concept of GLP-1 therapy; it involved a continuous infusion of GLP-1 for 6 weeks to patients with type 2 diabetes. Study subjects had diabetes for several years and a body mass index of 30 kg/m² or greater. Patients wore an infusion pump that delivered GLP-1 continuously (24 hours a day, 7 days a week) for 6 weeks through a needle placed in the subcutaneous tissue. The study showed that after only 1 week, there was a marked improvement in blood glucose, which lasted for many hours—not only in the fasting state but also after meals (Figure 2).
However, GLP-1 infusion did not completely normalize blood glucose levels.

The study by Zander et al yielded several important findings. First, it showed that it is possible to administer GLP-1 continuously for 6 weeks—a finding that has now been extended to 3 months—without significant diminution in the clinical response. To date, there is no evidence for clinical tachyphylaxis or receptor desensitization with this approach. Second, the infusion was extremely well tolerated and was associated with a marked improvement in β-cell function and a resensitization of the β-cell response to glucose. Thus, GLP-1 not only stimulated insulin secretion from the β cell, but it also reprogrammed a defective β cell to reawaken and become more sensitive to glucose. This effect also has been demonstrated with the agents exenatide and liraglutide. Most importantly, the 6-week GLP-1 infusion studies demonstrated that these patients were not as hungry as patients on traditional therapies; they were more easily satiated and lost weight. The weight loss was independent of nausea and vomiting because these side effects were not reflected in the native GLP-1 studies.

NEW CLINICAL APPROACHES

What are the approaches currently being studied to utilize these actions of incretins for the treatment of type 2 diabetes? Several alternative approaches for enhancing incretin action are under clinical development.

EXENATIDE

Exendin-4 (exenatide) is a naturally occurring peptide, originally isolated from the salivary secretions of the gila monster, that shares many of the structured properties and actions of GLP-1. Exenatide is not lizard GLP-1 but is encoded by a distinct gene for exendin-4. Exenatide has a remarkably similar affinity for and ability to activate the mammalian GLP-1 receptor. The ability of exenatide to improve glucose control has been examined in multiple studies. Figure 3 shows the improvement in postprandial glucose seen in 3 combined AMIGO: Diabetes Management for Improving Glucose Outcomes studies.

Before the start of therapy, the type 2 diabetes characteristic of elevation in fasting and postprandial glucose is shown in the graph on the left in Figure 3. After administration of exenatide for 30 weeks, as shown by the graph on the right, the meal-related glucose excursion is potentially reduced.
LIRAGLUTIDE

Liraglutide, an agent currently in late-stage clinical trials, is a human GLP-1 receptor agonist that has a number of structural modifications rendering this peptide resistant to degradation by dipeptidyl peptidase-IV (DPP-IV). Liraglutide also contains a fatty-acid moiety that allows it to bind to albumin noncovalently. This noncovalent association with albumin prolongs the circulating half-life and pharmacokinetic profile of the agent, allowing it to be administered as a once-daily injection.

Liraglutide has demonstrated the glucose-lowering properties expected for a GLP-1 receptor agonist. A study by Chang et al. showed resensitization of the β cell to glucose after liraglutide administration to patients with type 2 diabetes. Enhanced insulin sensitivity and control of blood glucose also have been demonstrated for liraglutide. One example of these effects is from a phase II human clinical study in which liraglutide controlled blood glucose and significantly lowered A1c in patients with type 2 diabetes (Figure 4).

CJC-1131

An alternative approach to overcoming the short half-life of GLP-1 is to form a constant bond of GLP-1 with albumin—as is the case with CJC-1131. This DPP-IV–resistant human GLP-1 analog binds to and activates the GLP-1 receptor. This agent has a 10-day half-life in humans. A study examining the repeat-dose pharmacokinetic profile of CJC-1131 showed that even days after its last administration to human subjects, CJC-1131 was still detectable in the circulation.

ALBUGON

Albugon is yet another approach to developing albumin-based therapies. Albugon is a human recombinant albumin/GLP-1 hybrid protein that contains the sequence of GLP-1 in the same open-reading frame as human serum albumin. Albugon activates the GLP-1 receptor in vitro, but with less potency than exendin-4 (Figure 5). The rationale for developing such a therapy is that the circulating half-life of human albumin ranges from 11 to 14 days, thus prolonged pharmacokinetic profiles may be achieved following administration of a GLP-1/albumin-based compound. In studies in mice, after a single injection, levels of the compound are detected for days. It is important to note that the half-life of albumin in mice and rats is considerably shorter than in humans.

ALTERNATIVE APPROACHES

A critical limitation in the use of native GLP-1 is its rapid inactivation by a ubiquitous specific protease, DPP-IV. Because DPP-IV cleaves GLP-1 and gastric inhibitory polypeptide (GIP) at their N-terminus within seconds of their secretion, the half-life of these native peptides is only minutes. One way to overcome this rapid inactivation is to develop GLP-1 analogs that are resistant to DPP-IV action. An alternative approach is to inhibit the activity of this enzyme itself with chemicals (DPP-IV inhibitors) that can be taken orally, and this approach is currently under active clinical development in phase III trials.

Is DPP-IV (also known as CD26) simply a pharmacological target for the treatment of diabetes? Or is the DPP-IV gene physiologically essential for the control of blood glucose? In an experiment by Marguet et al., reduced glycemic excursion after a glucose challenge, improved glucose-stimulated insulin secretion, and increased levels of GLP-1 were seen in CD26 knockout mice. These findings suggest DPP-IV inhibition is not merely a pharmacological strategy for the treatment of type 2 diabetes, but that the gene is itself absolutely essential for physiological control of blood glucose.

Figure 5. Albugon Exhibits Similar Efficacy but Less Potency Than Exendin-4 at GLP-1 Receptor In Vitro

![Graph showing cAMP levels in cells treated with different GLP-1 analogs](#)
MECHANISM OF ACTION OF DPP-IV INHIBITORS

The way that DPP-IV inhibitors work is a subject of much controversy, particularly in the treatment of patients with type 2 diabetes. One approach to understanding how these inhibitors operate is to study the activity of several DPP-IV inhibitors in different groups of mice—normal mice; mice with an inactivated GIP receptor; mice with no GLP-1 receptors; and mice that have no GLP-1 or GIP receptors, known as dual incretin receptor knockout (DIRKO) mice.\(^{16}\) Hansotia et al administered 4 compounds (Val-Pyr, LAF-237, SYR106124, and TP8211) to these groups of mice.\(^{16}\) Mice with no GLP-1 and no GIP receptors (DIRKO mice) completely failed to respond to the glucose-lowering actions of the DPP-IV inhibitors. Although these types of data are not yet available in humans, many active investigations seek to determine whether GLP-1 and GIP alone are the critical determinants of DPP-IV inhibitor action.

VILDAGLIPTIN

Administration of DPP-IV inhibitors to human subjects with type 2 diabetes (as was done in a phase II study with the agent vildagliptin) improved glucose excursions and, as predicted, was associated with enhanced meal-stimulated GLP-1 levels in the plasma.\(^{17}\) Insulin levels in subjects treated with vildagliptin were identical to those in placebo-treated patients, yet the patients treated with vildagliptin had much lower glucose excursions, demonstrating that the insulin-to-glucose ratio was significantly improved in patients treated with the DPP-IV inhibitor. Furthermore, as may be expected from the inhibition of glucagon secretion by GLP-1, a potent suppression of glucagon levels was seen in these patients treated with the DPP-IV inhibitor.

CONCLUSIONS

Exenatide has been approved by the US Food and Drug Administration for the treatment of type 2 diabetes and is now available to patients. Looking at the landscape of the agents under clinical development, several others hold promising new options for the treatment of type 2 diabetes, based on this enhancement of incretin action.

REFERENCES

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