Glucagon-like peptide 1: evolution of an incretin into a treatment for diabetes

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D’Alessio, David A., and Torsten P. Vahl. Glucagon-like peptide 1: evolution of an incretin into a treatment for diabetes. Am J Physiol Endocrinol Metab 286: E882–E890, 2004; 10.1152/ajpendo.00014.2004.—Glucagon-like peptide 1 (GLP-1) is a product of proglucagon that is secreted by specialized intestinal endocrine cells after meals. GLP-1 is insulinotropic and plays a role in the incretin effect, the augmented insulin response observed when glucose is absorbed through the gut. GLP-1 also appears to regulate a number of processes that reduce fluctuations in blood glucose, such as gastric emptying, glucagon secretion, food intake, and possibly glucose production and glucose uptake. These effects, in addition to the stimulation of insulin secretion, suggest a broad role for GLP-1 as a mediator of postprandial glucose homeostasis. Consistent with this role, the most prominent effect of experimental blockade of GLP-1 signaling is an increase in blood glucose. Recent data also suggest that GLP-1 is involved in the regulation of β-cell mass. Whereas other insulinotropic gastrointestinal hormones are relatively ineffective in stimulating insulin secretion in persons with type 2 diabetes, GLP-1 retains this action and is very effective in lowering blood glucose levels in these patients. There are currently a number of products in development that utilize the GLP-1-signaling system as a mechanism for the treatment of diabetes. These compounds, GLP-1 receptor agonists and agents that retard the metabolism of native GLP-1, have shown promising results in clinical trials. The application of GLP-1 to clinical use fulfills a long-standing interest in adapting endogenous insulinotropic hormones to the treatment of diabetes.

glucose tolerance; insulin secretion

IT HAS LONG BEEN KNOWN that the assimilation of glucose is more efficient when it is given orally than when it is given intravenously. The primary explanation for this is that factors released from the gastrointestinal (GI) tract regulate insulin secretion and glucose homeostasis. Thus circulating insulin levels are significantly higher after glucose is ingested than when it is administered intravenously, and the enhanced insulinotropic potency of glucose absorbed through the GI tract is attributed to the actions of hormones released from the gut. These hormones are termed incretins, and the augmentation of insulin secretion with oral compared with intravenous glucose is termed the incretin effect. There are two known hormones that act as incretins, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1). These peptides are produced by specialized cells in the intestinal mucosa and secreted in response to carbohydrate- and lipid-containing meals. There are specific GIP and GLP-1 receptors that are expressed on islet cells, as well as in other tissues, and deletion of these receptors in mouse models leads to glucose intolerance (13). These data and corroborating studies using GIP and GLP-1 receptor antagonists have demonstrated that so-called “enteroinsular” signaling is a physiological process that is necessary for normal glucose homeostasis (15, 21, 42, 99).

The physiological actions of the incretins raise the possibility that these naturally occurring peptides could be harnessed for the treatment of diabetes. However, although there is considerable homology between GIP and GLP-1, and the peptides seem to act through similar mechanisms in β-cells, there is a great divergence in the clinical potential of the incretins. GIP is relatively ineffective in eliciting insulin secretion in individuals with type 2 diabetes (26, 56) and so has not been intensively pursued as a therapeutic agent. On the other hand, GLP-1 is insulinotropic in diabetic as well as nondiabetic humans and also seems to promote glucose homeostasis beyond the enhancement of insulin secretion. In a number of experimental settings, GLP-1 has been very effective in correcting the hyperglycemia of diabetic subjects, and several pharmacological agents that act by enhancing GLP-1 signaling are in advanced development.

This minireview will summarize the physiological actions of GLP-1 that are involved in controlling blood glucose levels in healthy and diabetic humans, discuss the evidence that these effects are due to an integration of GLP-1 actions on several organ systems, and briefly describe the development of GLP-1-based pharmaceuticals. For more information on the underlying molecular and cellular physiology of the incretins and their synthesis and secretion, several excellent reviews have been published in the recent past (17, 19, 36, 40).
GLP-1: A GI Hormone That Regulates Blood Glucose

Because GLP-1 has been identified as an incretin, it is often characterized primarily as an insulin secretagogue. However, whereas stimulation of β-cell secretion is probably a prominent physiological action of GLP-1, it is better classified as a hormone that regulates glucose homeostasis rather than as just an incretin. For example, when the action of GLP-1 is blocked in humans or nonhuman primates during glucose ingestion, the most notable response is an increase in blood glucose (15, 21). In humans this response is accompanied by a small increase in plasma insulin. In nonhuman primates there is equivalent insulin secretion, compared with controls without GLP-1 receptor blockade (Fig. 1). Given the consensus role of GLP-1 as a stimulus for postprandial insulin release, these findings appear at first paradoxical. One interpretation of these data is that the increase in circulating glucose levels that occurs when GLP-1 signaling is abolished or blunted stimulates increased insulin secretion directly or by increasing the gain of other postprandial β-cell stimuli. In fact, the effect of even small increases in plasma glucose levels to potentiate GIP-stimulated insulin secretion has recently been demonstrated (95). A second interpretation of the more pronounced effect of GLP-1 blockade on blood glucose than on insulin concentrations is that GLP-1 regulates other functions contributing to glucose tolerance beyond insulin secretion. Indeed, there is considerable evidence that GLP-1 regulates gastric function, glucagon secretion, and possibly other systems that govern circulating glucose concentrations. The action of GLP-1 is thus a composite of several processes acting on blood glucose during the postprandial state, and the role of any one of these can be difficult to discern in vivo. Most probably, elements of both of these explanations of the effects of GLP-1 blockade are true. Nonetheless, when the physiology and pharmacology of GLP-1 are considered, plasma glycemia is generally the parameter most reflective of GLP-1 effects.

Physiological Actions of GLP-1 That Promote Glucose Homeostasis

Signaling Through the GLP-1 Receptor

A specific GLP-1 receptor has been cloned from pancreatic islet cells (40) and is the only known mediator of GLP-1 signaling in mammals. The mRNA for this receptor has been demonstrated in specific regions of the stomach, heart, kidney, and lung as well as islet cells (6). The GLP-1 receptor is also expressed in specific regions of the brain, where it mediates a number of behaviors, such as satiety and the response to illness (78, 88). There are also emerging data suggesting that the GLP-1 receptor is expressed by visceral afferent nerves (55, 61), and several studies suggest that some of the actions of GLP-1 secreted from the GI tract could be mediated via autonomic neural pathways (4, 8, 37, 100).

The GLP-1 receptor is a member of the secretin-VIP family of seven transmembrane G protein-coupled receptors (36, 40). Ligand binding by this receptor is highly specific, and there is little affinity for glucagon or GIP. However, exendin-4, a peptide found in the venom of the Gila monster (Heloderma suspectum), and its derivative exendin-4-(9–39), are naturally occurring GLP-1 receptor agonist and antagonist, respectively (54). In cultured β-cells, GLP-1 mediates its effects through G proteins linked to adenylyl cyclase, formation of intracellular cAMP, and activation of protein kinase A (PKA) (32). Foremost among these effects are synergism with glucose to close ATP-sensitive channels, augmentation of glucose-induced increases in intracellular calcium, and promotion of secretory granule exocytosis. In addition, it has recently been shown that a significant component of GLP-1 signaling is independent of PKA and acts through the cAMP-regulated guanine nucleotide exchange factor II pathway (4, 39).

A hallmark of the insulinotropic effect of GLP-1 is the dependence on ambient glucose levels, and GLP-1 has only minimal activity on insulin secretion at fasting or basal glucose concentrations (40). The mechanism conferring glucose dependence is not fully understood, but it has been suggested to result from independent effects of GLP-1 to facilitate ATP generation from glucose (87), differential effects of PKA in states of high or low intracellular ADP (46), and/or the effect of GLP-1 to inhibit voltage-dependent potassium channels that are quiescent at basal glucose levels but activated by hyperglycemia (49). Regardless, the attenuated insulinotropic effect of GLP-1 at basal glycemia can be seen as a physiological adaptation to protect against incretin-induced hypoglycemia.
This distinguishes β-cell signaling through the GLP-1 receptor from other insulin secretagogues such as sulfonylureas, which induce insulin secretion independently of the glucose concentration.

*Effects of GLP-1 on β-Cell Function*

Administration of GLP-1 to animals and humans increases insulin secretion when blood glucose is increased above basal levels. Because this effect occurs at concentrations of GLP-1 immunoreactivity that are similar to those observed in the circulation after meals, it has been assumed that this represents a physiological action. Indeed, two studies of rats given the GLP-1 receptor antagonist exendin-(9–39) demonstrated decreased insulin levels and glucose intolerance during the absorption of glucose from the gut (42, 99). Similarly, male mice with a targeted deletion of the GLP-1 receptor gene also had hyperglycemia and a mild impairment of insulin release after a glucose gavage (77). These results in rats and mice diverge from the effects of GLP-1 receptor blockade in other species, since monkeys given exendin-(9–39) during intragastric glucose tolerance tests had elevated postprandial glucose but with overall insulin secretion that was comparable to that of controls (15), and humans given this GLP-1 receptor blocker had increased postprandial glycemia associated with increased plasma insulin (21). The reason for the difference in findings between rodents and primates has not been explained and might suggest a greater importance of GLP-1 in the regulation of insulin secretion in rats and mice. Regardless, when the data from studies in mammals are considered as a whole, they indicate that GLP-1 is necessary for normal glucose tolerance and postprandial insulin release.

In addition to abnormalities in the insulin and glucose responses to ingested glucose, GLP-1 receptor-deficient mice have fasting hyperglycemia and impaired insulin secretion in response to parenteral glucose (77). Although this latter finding is puzzling at first glance, since GLP-1 levels in the circulation are low except during meal absorption, recent studies in vitro (79) and in humans (75) suggest that basal levels of GLP-1 may play a role in β-cell function. The observation that GLP-1 receptor knockout mice have decreased pancreatic insulin and insulin mRNA content (65) is also consistent with the notion that basal, or the long-standing integrated, levels of GLP-1 have important effects on β-cell function. Other studies have shown that GLP-1 increases insulin biosynthesis and stimulates the transcription of other β-cell genes, including glucokinase and the GLUT2 glucose transporter (98). GLP-1 also increases the capacity of individual β-cells to respond to stimulation by glucose, and this effect to activate glucose-insensitive cells has been termed induction of glucose competence (36). Furthermore, a recent study in rats with β-cell damage after streptozotocin treatment supported a role for α-cell-derived GLP-1 in the promotion of insulin secretion (59). These cumulative data suggest that GLP-1 may have important effects on β-cell function beyond incretin action as an acute insulin secretagogue.

*Other Actions of GLP-1 that Promote Glucose Homeostasis*

Importantly, GLP-1 has been shown to have effects on tissues other than the pancreatic β-cell, and these extraislet actions are ones that promote glucose homeostasis. In general, the extraislet functions of GLP-1 have been most clearly demonstrated in studies using exogenous peptide, and functions in normal physiology have not been conclusively established. Nonetheless, a reasonable case can be made that GLP-1 has a broad role to minimize fluctuations in blood glucose levels by regulating some of these extra-β-cell processes.

GLP-1 lowers fasting and postprandial glucagon concentrations in humans, animals, and cultured islets (40). Although the GLP-1 receptor has been demonstrated on α-cells, it is also possible that the effect of GLP-1 on glucagon secretion is mediated in a paracrine manner via insulin or somatostatin. Because fasting glucagon levels increase when the GLP-1 receptor is blocked with exendin-(9–39), at a time when GLP-1 levels are at basal it appears that there may be tonic regulation of the α-cell by GLP-1 (15, 75). These data indicate that GLP-1 coordinates the secretion of islet hormones in a manner that minimizes elevations in blood glucose.

Doses of GLP-1 estimated to mimic postprandial plasma concentrations inhibit antral contractions, increase pyloric tone, and substantially lower the rate of gastric emptying of both liquid and solid meals (74). This effect is sufficient to minimize the rise in meal-induced glucose and insulin levels, and supraphysiological doses of GLP-1 virtually abolish gastric emptying over the course of several hours. However, two recent studies demonstrated that GLP-1 also relaxes the proximal stomach and increases gastric capacity (16, 76). These effects of GLP-1 on gastric motility, as well as an action to inhibit gastric acid secretion, are likely mediated through vagal afferent nerves (37, 100). The complex actions of GLP-1 on gastric function suggest that this is a physiological role for the peptide, but this has not been proven. In humans given infusions of GLP-1 to mimic physiological concentrations, gastric emptying of solid meals was significantly delayed (31). However, in nonhuman primates given exendin-(9–39) during oral glucose tolerance tests, no difference in delivery of carbohydrate to the intestine was noted (15), suggesting that, with small liquid meals, the effect of GLP-1 to slow gastric emptying may be small. Although more work is needed to establish the physiological role of GLP-1 on gastric function, it is clear that exogenous GLP-1 has powerful effects on the stomach.

GLP-1 is produced by a discrete set of neurons in the hindbrain, and administration of GLP-1 into the cerebroventricular system of rats decreases food intake (88). This raises the possibility that GLP-1 may have a regulatory role in satiety or body weight regulation. Because short-term intravenous administration of GLP-1 to humans suppresses consumption of a subsequent lunch (30, 34), it appears that at least some of the satiety effects of GLP-1 are mediated by peripherally, rather than centrally, derived peptide. One possibility is that effects of GLP-1 on food intake are mediated through the same visceral neural circuits that regulate gastric emptying. Although there is still some question as to whether GLP-1 regulates energy balance and body weight, reduction of food intake can be viewed as another mechanism by which GLP-1 minimizes postprandial glucose excursions.

There have been several studies in humans demonstrating that GLP-1 decreases blood glucose concentrations independently of the islet hormones (Table 1 and Refs. 14, 24, 33, 51, 52, 80, and 90). However, a number of other studies designed to determine whether there are extraislet actions of GLP-1 have been negative (Table 1 and Refs. 73, 84, 91, 92). It is likely that
some of the discrepancy in this area is explained by the variation in experimental methods used by different investigators and the relatively small effect of reported extraislet effects, generally <15% of glucose disposition. There are several studies indicating that GLP-1 does not acutely affect insulin sensitivity in humans (1, 14, 63, 73, 87, 88), although there are some reports of GLP-1 augmenting insulin action (24, 51). The several reports suggesting that GLP-1 has independent effects to promote glucose disposal are consistent with in vitro studies showing that GLP-1 promotes glucose uptake in cultured cells (25, 62) and in animals (60). It has recently been reported that GLP-1 suppressed fasting glucose production while insulin and glucagon levels were fixed with a clamp technique (67). Although this finding would appear to be at odds with solid evidence that the GLP-1 receptor is not expressed in hepatocytes (6), it is plausible that GLP-1 effects on hepatic glucose production could also be regulated by visceral nerves similar to gastric function. Overall, although islet-independent actions of GLP-1 to regulate plasma glucose continue to be both elusive and controversial, this area of investigation remains intriguing because of its novel physiological implications and potential therapeutic application.

Incretins and Islet Growth

An exciting new aspect of GLP-1 biology is an apparent role in pancreatic islet growth and development. Recent studies in rodents have shown that GLP-1 and its analogs directly stimulate β-cell growth and replication to promote an increase in islet mass (18, 81, 101). These initial reports have been buttressed by a series of recent studies indicating that GLP-1 receptor agonists cause the differentiation of pancreatic duct cells into insulin-producing cells (7, 35). In addition, there is now evidence that GLP-1 inhibits β-cell apoptosis, another action that would promote expansion of β-cell mass (28, 45, 97). In contrast to the primary role of cAMP in the acute stimulation of insulin secretion, GLP-1-mediated β-cell growth is likely activated by the phosphatidylinositol 3-kinase pathway as a proximal signaling step (9, 10, 48).

Because mice with a targeted deletion of the GLP-1 receptor have only slightly decreased islet size (47), signaling by GLP-1 does not appear to be essential for β-cell and islet development. Although it is possible that there is sufficient plasticity in islet development for some compensation for loss of GLP-1 signaling, it may be that the role of GLP-1 to regulate islet cell mass is primarily in response to external challenges. Thus GLP-1 could function as part of a homeostatic system to match insulin production with chronic nutrient demands. Indeed, support for this view can be drawn from recent studies implicating GLP-1 signaling in the compensatory β-cell hypertrophy that develops with insulin resistance (89). However, the most compelling question raised by the recent findings of GLP-1 effects on β-cell mass is whether this action can be used clinically for the treatment of diabetes. If the GLP-1 effects to increase β-cell mass are present in diabetic humans, as they are in diabetic rodents, it would raise the possibility of a novel pharmacology that could alter the progressive course of type 2 diabetes.

**EFFECTS OF GLP-1 TO LOWER BLOOD GLUCOSE IN DIABETIC SUBJECTS**

Impaired GLP-1 signaling is not likely to contribute substantially to the metabolic abnormalities of diabetes. However, recent studies suggest that the secretion of GLP-1 during meal absorption is slightly but significantly lower in people with type 2 diabetes (85, 94). In addition, the sensitivity of the β-cell to GLP-1 is attenuated in diabetic individuals compared with nondiabetic persons (41). However, GLP-1 improves hyperglycemia in diabetic patients, sometimes dramatically. Continuous intravenous administration of GLP-1 to hyperglycemic patients with moderate to poorly controlled type 2 diabetes decreases fasting hyperglycemia to near-normal levels within 3–4 h (58, 86). This effect of intravenous GLP-1 to normalize fasting glucose is robust, occurs in almost all patients (86), and has been attributed to increased insulin release and decreased glucagon levels (58). Interestingly, fasting hyperglycemia was also significantly improved in a group of type 1 diabetic subjects with minimal insulin-secretory reserve who were given intravenous GLP-1, most likely due to suppressed glucagon secretion (12). Thus, despite having a primary role in postprandial physiology, exogenous GLP-1 has potent glucose-lowering effects in fasted diabetic patients.

That GLP-1 is a potent insulin secretagogue in patients with type 2 diabetes distinguishes it from other insulinotropic gut peptides such as GIP, CCK, and secretin, which are not effective in persons with diabetes. In diabetic patients, intravenous GLP-1 improves the responsiveness of the β-cell to glucose (56), causes a partial restitution of the first phase of insulin secretion (68, 69), and increases the maximal secretory capacity (1). Thus GLP-1 treatment corrects several of the fundamental defects in diabetic β-cell function. And because the insulinotropic effect of GLP-1 is glucose dependent, hyperglycemia has rarely been reported in studies with diabetic patients.

GLP-1 has been administered to diabetic patients by subcutaneous injection before meals, and this route of administration caused a significant decrease in the postprandial blood glucose excursions (20, 83). Despite doses of GLP-1 in these studies that were in the pharmacological range, the insulin response was not greatly enhanced, and the most significant GLP-1 effect was inhibition of gastric emptying. These studies demonstrate the potential benefit of the gastric effects of GLP-1 in the treatment of diabetes, although symptoms of nausea have been reported in some patients. Continuous subcutaneous infusion of GLP-1 via a portable pump to subjects with type 2 diabetes caused significant improvements in their glycemic levels for ≤1 wk and was well tolerated (44). More recently, diabetic subjects were given GLP-1 by continuous subcutaneous infusion for a period of 6 wk (103). In this study, fasting and postprandial glucose levels were consistently lower, and

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**Table 1. Effects of GLP-1 on glucose metabolism independent of islet hormones: summary of human studies**

<table>
<thead>
<tr>
<th>Mechanism of GLP-1 Action</th>
<th>Studies Reporting Effect (Ref no.)</th>
<th>Studies Not Finding Effect (Ref no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin action</td>
<td>24, 51</td>
<td>1, 14, 63, 73, 87, 88</td>
</tr>
<tr>
<td>Glucose effectiveness</td>
<td>14, 52</td>
<td>87</td>
</tr>
<tr>
<td>Glucose uptake</td>
<td>33, 90</td>
<td>81</td>
</tr>
<tr>
<td>Glucose production</td>
<td>67, 80</td>
<td>52, 87, 88</td>
</tr>
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GLP-1, glucagon-like peptide 1.
insulin secretion was improved, in GLP-1-treated patients compared with saline-treated controls. This study demonstrates that chronic GLP-1 administration is effective and persistent, and it serves as a proof of principle for the application of the GLP-1-signaling system to diabetes.

PHARMACOLOGICAL APPLICATION OF GLP-1 TO THE TREATMENT OF DIABETES

The major limitation of using GLP-1 to treat diabetic patients is the short half-life of the native compound. The two NH₂-terminal amino acids are cleaved from GLP-1 by the ubiquitous enzyme dipeptidyl peptidase IV (DPP-IV), and the circulating half-life of intact GLP-1 is only ∼1–2 min (19, 40). Overcoming this hurdle with agents that can give more prolonged stimulus to the GLP-1 receptor has been a major challenge in drug development. There are now several compounds in various stages of preclinical or clinical development for the treatment of type 2 diabetes that utilize the GLP-1-signaling pathway. These include GLP-1 receptor agonists with extended biological half-lives, and inhibitors of DPP-IV that act to increase circulating levels of endogenous, intact, and bioactive GLP-1.

GLP-1 Analogs

Several peptide analogs of GLP-1 that are resistant to degradation by DPP-IV have been identified and have advanced to clinical trial. The reptilian peptide exendin-4 has 53% sequence homology to GLP-1, is a full agonist at the GLP-1 receptor (82), and is resistant to the actions of DPP-IV, resulting in a greatly extended duration of action compared with GLP-1 (22). The antidiabetic actions of exendin-4 have been confirmed in a variety of rodent strains with diabetes syndromes, as well as in spontaneously diabetic rhesus monkeys (102). Furthermore, administration of exendin-4 has been shown to increase pancreatic insulin content and β-cell mass in diabetic rats and mice (96, 101).

In subjects with type 2 diabetes, single subcutaneous injections of exendin-4 have similar effects to overnight administration of intravenous GLP-1 (43). Thus fasting hyperglycemia decreased from values of near 12 mM to ∼7 mM over 3 h and was maintained in this range for ≥8 h. The improvement in fasting glycemia was associated with an increase in plasma insulin and decrease in plasma glucagon, suggesting that GLP-1-like effects on islet hormone secretion played a major role. In addition, exendin-4 given to diabetic individuals before a mixed-nutrient liquid meal significantly lowered the postprandial glycemia excursion (43). Similar to GLP-1, the effects of exendin-4 on meal-induced glycemia appeared to be the result of decreased gastric emptying and inhibition of glucagon, in addition to potentiation of insulin secretion. In fact, the insulin response was actually smaller after exendin-4 than after placebo, in all likelihood because of the much lower blood glucose. In that study (43), exendin-4 appeared to be equally effective in lowering blood glucose in subjects with poorly controlled diabetes as it was in subjects with good glycemic control.

Two longer studies of exendin-4 treatment of diabetic patients have been published (23, 29). In the first, exendin-4 was given once or twice daily for 4 wk. Treated patients had significant reductions in Hb A₁c, from 9.1 to 8.3%, noteworthy in a study of only 1 mo (23). More recently, patients with type 2 diabetes treated with the combination of sulfonylurea and metformin, but with poor glycemic control (average Hb A₁c >9%), were given synthetic exendin-4 for 4 wk (29). Treated subjects had significantly reduced postprandial glucose compared with placebo-treated individuals and a reduction in Hb A₁c of nearly 1% over the month of treatment. Importantly, serious hypoglycemia was uncommon in both of these trials, with most events noted in patients taking concurrent sulfonylurea. However, nausea occurred in 15–30% of subjects, although in general this symptom too was relatively mild.

A long-acting derivative of GLP-1, NN2211, is another agent in advanced clinical development (11, 38). This compound is composed of GLP-1 covalently linked to a hexadecyl residue. With the addition of this fatty acid, the GLP-1 complex binds to serum albumin, increasing the duration of action of NN2211 relative to native GLP-1. Albumin-bound GLP-1 is less susceptible to degradation by DPP-IV, and it has reduced renal elimination. The half-life of NN2211 in healthy volunteers is ∼12 h (27), so that a single daily injection can deliver biologically active amounts of GLP-1 for an entire 24-h period.

Similar to exendin-4 and GLP-1, chronic administration of NN2211 to diabetic mice decreased glucose levels and increased β-cell proliferation and β-cell mass (72). In addition, acute or chronic administration of NN2211 reduced glucose and increased insulin levels, suppressed glucagon release, and delayed gastric emptying in glucose-intolerant minipigs, resulting in a marked reduction of serum fructosamine levels (71).

In patients with type 2 diabetes, a single subcutaneous injection of NN2211 reduced glucose levels to near-normal levels overnight and lowered postprandial glucose excursions, at least partly, by enhancing increased meal-stimulated insulin secretion (38). Suppression of meal-stimulated glucagon levels and delay of gastric emptying were also confirmed in patients with type 2 diabetes, and the plasma half-life of NN2211 was similar (10 h) to that reported previously in healthy volunteers. However, as with exendin-4 or native GLP-1, nausea and vomiting are the most common side effects and are generally a function of the dose administered. For example, in healthy volunteers given NN2211 to assess tolerability of the drug, the incidence of nausea and vomiting occurred in all of the subjects receiving the highest dose (20 μg/kg) and decreased at lower doses (27). In a study of diabetic patients, nausea was reported in 2 of 11 patients after injection of 10 μg/kg (38).

In sum, the GLP-1 receptor agonists exendin-4 and NN2211 are promising agents that have been shown to share the multiple positive metabolic effects of GLP-1 (stimulation of insulin release in a glucose-dependent manner, suppression of glucagon release, and delay of gastric emptying) in patients with type 2 diabetes. Their extended duration of action permits once or twice a day administration and similar effectiveness to continuously infused GLP-1. Although these agents are well tolerated over short trials, it remains to be seen whether the relatively frequent GI side effects will limit their utility.

DPP-IV Inhibitors

Given the rapid inactivation of GLP-1 by DPP-IV, methods to inactivate this protease are a second major strategy to increase plasma GLP-1 levels, and several have been devel-
oped. Because DPP-IV metabolizes a large number of regulatory peptides, including GIP (53), the effects of these agents cannot be entirely attributed to GLP-1. However, most of the other known peptides acted on by DPP-IV do not have known roles in glucose homeostasis, and GIP has been consistently shown to be inactive in diabetic patients. Because plasma levels of intact GLP-1 increase after inhibition of DPP-IV, much of the clinical effect of DPP-IV inhibitors has been ascribed to GLP-1.

Several orally effective inhibitors of DPP-IV have been identified that exert antidiabetic actions in various hyperglycemic animal models. For example, acute administration of DPP-IV inhibitors to Zucker fatty rats increased the percentage of intact GLP-1 from ~20 to 100%, stimulated insulin release, and improved glucose tolerance (3). When Zucker fatty rats were treated with a DPP-IV inhibitor for 3 mo, there was improved glucose tolerance as well as enhanced insulin secretion and insulin action (66). DPP-IV inhibition was also effective in obese, glucose-intolerant monkeys (93). Similar to GLP-1 and GLP-1 analogs, DPP-IV inhibitors do not appear to exhibit tachyphylaxis. For example, there was no waning of effectiveness to improve glucose tolerance over 8-wk treatment of glucose-intolerant mice (70).

Several DPP-IV inhibitors are in clinical trials. Recently the results from a trial of NVP-DPP728 have been reported (2). In this study, NVP-DPP728 (100 mg 3 times a day or 150 mg twice a day) or placebo was administered for 4 wk in patients with type 2 diabetes and relatively mild hyperglycemia (fasting plasma glucose ~8.6 mmol/l, Hb A1c ~7.4%) who were not treated with medications. Treatment with the DPP-IV inhibitor significantly reduced glucose levels throughout the day, and insulin levels were also slightly reduced. However, in the context of lower glucose, it is likely that the β-cell responsiveness to glucose was actually increased, a finding often reported for GLP-1. Fasting plasma glucose was modestly but significantly reduced in patients receiving NVP-DPP728, and Hb A1c decreased by 0.5% after 4 wk. Treatment with NVP-DPP728 was well tolerated: one of 61 patients had an episode of confirmed hypoglycemia, and two patients reported mild nausea during active treatment.

Because DPP-IV metabolizes a number of regulatory peptides, there has been some concern about using agents that inhibit this enzyme for prolonged periods. However, except for GLP-1, there seem to be alternative enzymatic pathways for the degradation of most DPP-IV substrates. Rats with a spontaneous null mutation of the DPP-IV gene and mice with targeted deletions of DPP-IV are normal except for a tendency toward enhanced glucose tolerance (50, 64).

It seems likely that both GLP-1 analogs and DPP-IV inhibitors will have a place in the treatment of diabetes. The analogs have specific actions that can be attributed to GLP-1 receptor signaling and can be administered in pharmacological doses. However, current versions of these agents must be injected, and side effects, particularly nausea, are potentially limiting. DPP-IV inhibitors are orally available and have been well tolerated, with only minimal adverse effects noted in the clinical experience to date. However, the potency of these agents is limited by the production of endogenous GLP-1 (and potentially other peptides). How these strengths and weaknesses of GLP-1-related treatments shape their clinical application will be an interesting outcome of further clinical trials and postmarketing follow-up.

**SUMMARY**

GLP-1 is an incretin that is essential for normal glucose tolerance. It is the first insulinotropic GI hormone to be identified that is effective in diabetic as well as nondiabetic persons. The effect of GLP-1 to lower blood glucose is likely due to effects on several processes, including gastric motility, food intake, and possibly glucose production and/or glucose uptake, as well as islet hormone secretion. Although the mechanisms by which GLP-1 controls these processes in vivo are still being clarified, it appears that some, like gastric emptying and satiety, could be mediated through a visceral neural pathway. One tenable hypothesis is that this neural circuit, initiated from sites innervated by vagal afferents, integrates the spectrum of GLP-1 effects. Pharmacological administration of GLP-1 or GLP-1 receptor agonists, or elevation of circulating GLP-1 with DPP-IV inhibitors, offers promise that the GLP-1 system can be effectively used for the treatment of diabetes. Given the range of responses that are mediated through the GLP-1 receptor, these new agents will add new and complementary options for diabetic patients.

**GRANTS**

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