Enhancing Incretin Action for the Treatment of Type 2 Diabetes

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OBJECTIVE — To examine the mechanisms of action, therapeutic potential, and challenges inherent in the use of incretin peptides and dipeptidyl peptidase-IV (DPP-IV) inhibitors for the treatment of type 2 diabetes.

RESEARCH DESIGN AND METHODS — The scientific literature describing the biological importance of incretin peptides and DPP-IV inhibitors in the control of glucose homeostasis has been reviewed, with an emphasis on mechanisms of action, experimental diabetes, human physiological experiments, and short-term clinical studies in normal and diabetic human subjects.

RESULTS — Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) exert important effects on β-cells to stimulate glucose-dependent insulin secretion. Both peptides also regulate β-cell proliferation and cytoprotection. GLP-1, but not GIP, inhibits gastric emptying, glucagon secretion, and food intake. The glucose-lowering actions of GLP-1, but not GIP, are preserved in subjects with type 2 diabetes. However, native GLP-1 is rapidly degraded by DPP-IV after parenteral administration; hence, degradation-resistant, long-acting GLP-1 receptor (GLP-1R) agonists are preferable agents for the chronic treatment of human diabetes. Alternatively, inhibition of DPP-IV–mediated incretin degradation represents a complementary therapeutic approach, as orally available DPP-IV inhibitors have been shown to lower glucose in experimental diabetic models and human subjects with type 2 diabetes.

CONCLUSIONS — GLP-1R agonists and DPP-IV inhibitors have shown promising results in clinical trials for the treatment of type 2 diabetes. The need for daily injections of potentially immunogenic GLP-1–derived peptides and the potential for unanticipated side effects with chronic use of DPP-IV inhibitors will require ongoing scrutiny of the risk-benefit ratio for these new therapies as they are evaluated in the clinic.

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After meal ingestion, nutrient entry into the stomach and transit through the proximal gastrointestinal (GI) tract stimulates activation of neural and hormonal signals that control gastric emptying and gut motility, nutrient absorption, and hormonal regulation of energy disposal and storage. The mucosal epithelium of the GI tract is one of the earliest integrators of information relevant to digestion and assimilation of nutrient loads. Highly specialized enteroendocrine cells dispersed along the length of the GI tract play an important role in controlling the rate of gastric emptying and small bowel motility, pancreatic enzyme secretion, and the growth and differentiated absorptive function of the small and large bowel epithelium. The aim of this review is to examine our current understanding of the physiological actions of two gut hormones, glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic polypeptide (GIP), with an emphasis on the biological importance and pharmaceutical potential of these peptides for the treatment of type 2 diabetes.

INTRODUCTION TO THE INCRETIN CONCEPT

— The development and application of the insulin radioimmunoassay to clinical investigation has permitted the assessment of β-cell secretory function after meal ingestion in normal and diabetic subjects. The observation that food ingestion or enteral glucose administration provoked a greater stimulation of insulin release compared with similar amounts of energy (glucose) infused intravenously (1,2) led to the development of the incretin concept. Hence, it was postulated that gut-derived signals stimulated by oral nutrient ingestion represent potent insulin secretagogues responsible for the augmentation of insulin release when energy is administered via the gut versus the parenteral route (3). Although several neurotransmitters and gut hormones possess incretin-like activity, the considerable evidence from immunoneutralization, antagonist, and knockout studies suggests that GIP and GLP-1 represent the dominant peptides responsible for the majority of nutrient-stimulated insulin secretion. The observation that patients with type 2 diabetes exhibit a significant reduction in the magnitude of meal-stimulated insulin release underlies the interest in determining whether defective incretin release or resistance to incretin action contributes to the pathophysiology of β-cell dysfunction in diabetic subjects.

INCRETIN SYNTHESIS, SECRETION, AND DEGRADATION

— GIP and GLP-1 are members of the glucagon peptide superfamily and share considerable amino

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Abbreviations: DPP, dipeptidyl peptidase IV; GI, gastrointestinal; GIP, glucose-dependent insulinotropic peptide; GIPR, GIP receptor; GLP, glucagon-like peptide; GLP-1R, GLP-1 receptor.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
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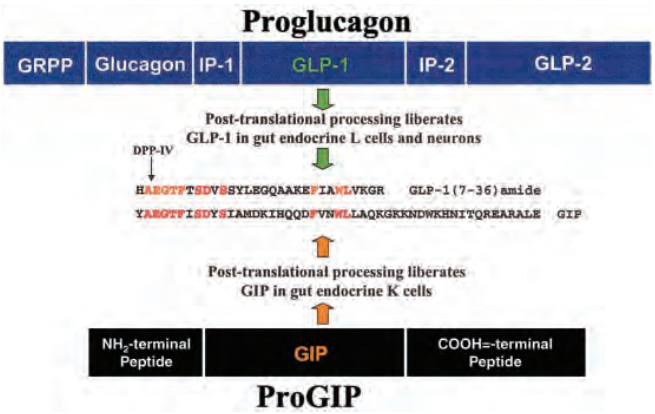

Figure 1—*Structure of preproglucagon and preproGIP encoding GLP-1 and GIP, respectively, is shown. The arrow designates the position of the DPP-IV–mediated cleavage after the position 2 alanine residue. GRPP, glicentin-related pancreatic peptide; IP, intervening peptide.*

acid identity. GIP is a single 42–amino acid peptide encoded within a larger 153–amino acid precursor (Fig. 1) (4). GIP-secreting enteroendocrine K-cells are concentrated in the duodenum and proximal jejunum; hence, these cells are anatomically situated in an ideal location for sensing and responding to nutrient ingestion. GLP-1 is derived from a larger proglucagon precursor that encodes not only GLP-1 but also the related proglucagon-derived peptides glucagon, GLP-2, oxyntomodulin, and glicentin (Fig. 1) (5). The two forms of GLP-1 secreted after meal ingestion, GLP-1(7-37) and GLP-1(7-36)amide differ by a single amino acid. Both peptides are equipotent and exhibit identical plasma half-lives and biological activities acting through the same receptor (6,7); however, the majority (~80%) of circulating active GLP-1 appears to be GLP-1(7-36)amide (8). In contrast to the more proximal location of GIP-producing K-cells, the majority of GLP-1 is synthesized within L-cells located predominantly in the ileum and colon, although GLP-1–producing L-cells have also been identified more proximally in the duodenum and jejunum. Despite the more distal location of most L-cells, circulating levels of GLP-1 also increase rapidly within minutes of food ingestion. Hence, GLP-1 secretion from the distal gut is controlled by both neural and endocrine signals initiated by nutrient entry in the proximal GI tract, as well as by subsequent direct contact of open-type L-cells with digested nutrients. Ingestion of a mixed meal or a meal enriched with specific fats and complex carbohydrates is particularly effective in stimulating GIP and GLP-1 release in human subjects (9,10). Although the vagal nerve, via M1 muscarinic receptors, and several neuroendocrine peptides contribute to the regulation of GLP-1 release in rodents (11,12), the factors responsible for rapid nutrient-stimulated GLP-1 release in human subjects are largely unknown.

The levels of total circulating GIP and GLP-1 immunoreactivity reflect a combination of intact, full-length active and NH_2-terminally truncated inactive peptides, with GIP(3-42) and GLP-1(9-36)amide contributing to >50% of total immunoreactive GIP and GLP-1 in both the fasting and the postprandial states (13,14). Plasma levels of both GIP and GLP-1 immunoreactivity are low in the fasting state and rise rapidly within minutes of food ingestion. Initial studies of circulating levels of GIP and GLP-1 relied principally on radioimmunoassays incapable of distinguishing the biologically active full-length peptides from inactive COOH-terminal peptide fragments generated as a result of proteolytic cleavage. Studies have demonstrated that both GIP and GLP-1 were cleaved at the position 2 alanine by the widely expressed aminopeptidase dipeptidyl peptidase IV (DPP-IV) (15,16). These findings have prompted a reanalysis of the circulating molecular forms of GIP and GLP-1 using newer radioimmunoassays more specific for the full-length bioactive peptides in normal and diabetic subjects.

The disappearance of exogenously administered GIP and GLP-1 has been studied in normal and diabetic human subjects using antisera capable of discriminating the full-length from the NH_2-terminally cleaved peptides. The $t_{1/2}$ of infused GIP is ~7 and 5 min in normal and diabetic human subjects, respectively (14). In contrast, the $t_{1/2}$ of exogenously infused intact GLP-1 is considerably shorter (13), with intravenously administered GLP-1 eliminated with a half-life of ~2 min in both normal and obese diabetic human subjects (17). Although the NH_2-terminally truncated peptides GIP(3-42) and GLP-1(9-36)amide function as weak antagonists of their respective receptors (18,19), there is little evidence that these truncated peptides exert physiologically important actions in human subjects in vivo. Despite observations that GLP-1(9-36)amide may function as an activator of insulin-independent glucose clearance in pigs (20), this peptide does not exert significant glucose-lowering properties in human subjects (21).

Circulating levels of GIP(1-42) are normal or slightly increased in type 2 diabetic subjects in the basal or postprandial states (22). In contrast, subjects with diabetes or impaired glucose tolerance exhibit modest but significant reductions in levels of meal-stimulated circulating GLP-1 (22,23). Furthermore, meal-induced increases in GIP and GLP-1 secretion are inversely correlated with the extent of insulin resistance detected in human subjects (24). The lower levels of circulating GLP-1 detected in diabetic subjects are not attributable to altered GLP-1 clearance (17). Whether levels of meal-stimulated GLP-1 may be restored toward normal with improved control of diabetes remains unknown.

GIP ACTION: INSIGHTS FROM PRECLINICAL AND HUMAN STUDIES— GIP was originally observed to inhibit gastric acid secretion (gastric inhibitory polypeptide), predominantly at supraphysiological dosages. Subsequent studies have demonstrated potent glucose-dependent insulin stimulatory effects from GIP administration in dogs and rodents. GIP also regulates fat metabolism in adipocytes, including stimulation of lipoprotein lipase activity, fatty acid incorporation, and fatty acid synthesis (25). Unlike GLP-1, GIP does not inhibit glucagon secretion or gastric emptying. GIP does promote β-cell proliferation and cell survival

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in islet cell line studies (26,27); whether GIP also induces β-cell growth or survival in diabetic rodents remains unclear.

The physiological actions of GIP have been deduced using GIP peptide antagonists, GIP receptor antisera, and GIP receptor knockout mice. NH_2-terminally truncated or modified GIP peptides such as GIP(6-30)amide, GIP(7-30)amide, or (Pro^3)GIP block GIP binding to the GIP receptor with varying effectiveness, and attenuate the insulinotropic effects of exogenous GIP in vitro and endogenous GIP in vivo (28–30). Similarly, immunopurified antisera against the extracellular domain of the GIP receptor block GIP binding and attenuate glucose-dependent insulin secretion after oral glucose loading in rats and mice (31,32). Complementary evidence for the incretin-like actions of GIP is derived from analysis of GIP receptor−null mice, which exhibit mild glucose intolerance after oral glucose loading (33). Surprisingly, $GIPR^{-/-}$ mice exhibit resistance to diet-induced obesity after months of high-fat feeding. Moreover, the $GIPR^{-/-}$ genotype attenuates obesity in the *ob/ob* mouse, possibly because of reduced fat storage and altered lipid metabolism as a direct result of absent GIP receptor (GIPR) action in adipocytes (34). Whether GIPR action significantly modulates adipocyte biology, lipoprotein synthesis, and weight accretion in humans is not known.

In contrast to the potent glucose-lowering actions of GIP in normal rodents, exogenous GIP administration is comparatively less insulinotropic in obese diabetic rodents. GIP levels are increased in some models of experimental rodent diabetes, and continuous GIP infusion for 4 h produces GIPR desensitization in normal rats (35). ZDF rats exhibit normal levels of GIP, absent insulinotropic responses to exogenous GIP and reduced expression of the GIPR in isolated islets (36). Recent studies with more potent GIP analogs engineered for resistance to DPP-IV have demonstrated improved insulinotropic and glucose-lowering properties after peptide administration to both normal and diabetic rodents (37–39).

Infusion of porcine or human GIP into patients with type 2 diabetes has produced variable insulinotropic responses, ranging from preserved (40) to attenuated or near absent insulin secretion (41–45). The potential for β-cell GIP responsivity to improve with treatment in type 2 diabetic subjects is intriguing, but has not been extensively examined (46). The GIP defect in insulin secretion seems most pronounced in the late phase of insulin secretion (47). Moreover, ~50% of normoglycemic first-degree relatives of type 2 diabetic subjects exhibit reduced insulin secretion after exogenous GIP infusion (48). Hence the reduced insulinotropic action of GIP in diabetes likely reflects a combination of genetic and acquired defects. Whether the pancreatic effects of GIP on β-cell proliferation and survival are also diminished in experimental or clinical diabetes is not known.

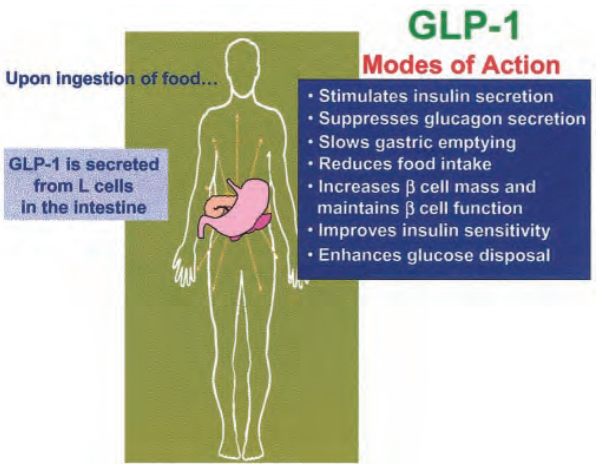

Figure 2—*The major biological actions of GLP-1.*

GLP-1 PRECLINICAL STUDIES AND PHYSIOLOGICAL ACTIONS

— Original observations elucidating a role for GLP-1 in the potentiation of glucose-dependent insulin secretion (49–51) and insulin gene expression (52) were followed by experiments demonstrating that GLP-1 also inhibits glucagon secretion (53,54) and gastric emptying (55) (Fig. 2). Acute intracerebroventricular (56) injection of GLP-1 or GLP-1 receptor (GLP-1R) agonists produces transient reduction in food intake, whereas more prolonged intracerebroventricular or peripheral GLP-1R agonist administration is associated with weight loss in some (57–60), but not all (61) studies. GLP-1 actions on food intake appear related in part to overlapping actions on central nervous system aversive signaling pathways, which remains a topic of intense interest (62–66). In contrast to GIP, the spectrum of actions delineated for GLP-1 that promote glucose lowering (regulation of insulin and glucagon secretion, inhibition of gastric emptying, and reduction of food intake) appear comparable in diabetic versus nondiabetic animals of various ages.

GLP-1 exerts actions on β-cells independent of acute stimulation of insulin secretion. Incubation of isolated rat islet cells with GLP-1 recruited nonresponsive glucose-resistant β-cells to a functional state of glucose-responsive insulin secretion, designated glucose competence (67,68). GLP-1R agonists also promote insulin biosynthesis, β-cell proliferation, and survival (69–71), and stimulate differentiation of exocrine cells or islet precursors toward a more differentiated β-cell phenotype (72–74). The GLP-1R–dependent augmentation of β-cell mass has been demonstrated in diverse experimental models, including neonatal rats administered streptozotocin and exendin-4 (75) and normal Wistar rats ages 6 and 22 months infused with native GLP-1 for 5 days (76). Similarly, GLP-1R agonists promote β-cell proliferation and expansion of functional islet mass after partial pancreatectomy in rats aged 4–5 weeks (69) or in neonatal rat pups subjected to experimental intrauterine growth retardation (77). The expansion of β-cell mass after GLP-1R agonist administration prevents or delays the occurrence of diabetes in *db/db* mice (78) and GK diabetes-prone rats (79). Furthermore, the induction of islet proliferation after GLP-1R activation has been seen with a broad range of GLP-1R agonists,

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including native GLP-1 (76,79,80), exendin-4, NN2211 (81), and CJC-1131 (82).

GLP-1R agonists also activate anti-apoptotic pathways coupled to a reduction in β-cell death. *db/db* mice treated with exendin-4 for 2 weeks exhibited decreased numbers of apoptotic β-cells, reduced pancreatic caspase-3 activation, and increased Akt1 expression (78). Reduced islet apoptosis has been observed in GLP-1–treated Zucker diabetic rats (83) and in exendin-4–treated mice after streptozotocin-induced β-cell injury (70). The anti-apoptotic actions of GLP-1R agonists are likely direct, as GLP-1 reduced peroxide-induced apoptosis in Min6 insulinoma cells (84) and exendin-4 significantly attenuated cytokine-induced apoptosis in cultures of purified rat β-cells (70). Hence, the GLP-1R–dependent activation of both proliferative and anti-apoptotic pathways in the pancreas provides complementary mechanisms for preserving and enhancing functional β-cell mass.

The physiological importance of GLP-1 action has been studied using GLP-1R antagonists. Infusion of the peptide exendin(9-39) into rats, mice, baboons, and humans produces an increase in fasting glucose and glycemic excursion after oral glucose loading in association with reduced levels of circulating insulin (32,85–87). Exendin(9-39) also produces abnormal glycemic excursion after nonenteral glucose loading in mice (32). These findings illustrate that transient disruption of GLP-1 action consistently perturbs the incretin and nonincretin actions of GLP-1 on glucoregulation. Acute intracerebroventricular injection of exendin(9-39) increases food intake in satiated rats (56), whereas repeated daily intracerebroventricular administration of exendin(9-39) increases food intake and weight gain (57). Similarly, acute exendin(9-39) administration increases gastric emptying after glucose ingestion in fistulized rats (88). Comparable studies with exendin(9-39) in humans have demonstrated the essential role of GLP-1 action for glucose control via regulation of glucagon and insulin secretion (89,90). Hence, the majority of actions observed after exogenous administration of GLP-1R agonists are also physiologically essential, as revealed by acute interruption of GLP-1 action.

Genetic disruption of GLP-1R expression in mice has produced comparable insights into the physiological importance of GLP-1 action. GLP-1R$^{-/-}$ mice exhibit abnormal glucose tolerance after both oral and intraperitoneal glucose challenge in association with diminished glucose-stimulated insulin secretion. In contrast, insulin sensitivity and the glucagon response to glucose loading or hypoglycemia are normal in the absence of GLP-1R signaling (91). Consistent with the cardiovascular effects of GLP-1 in rodents, GLP-1R$^{-/-}$ mice exhibit defective cardiovascular responses to stress (92). Despite the potential importance of GLP-1R circuits for transducing the anorectic action of leptin (93), GLP-1R$^{-/-}$ mice retain normal to enhanced leptin sensitivity (94,95). Similarly, food intake and body weight are not significantly perturbed in GLP-1R$^{-/-}$ mice in the CD1 genetic background (96,97). In contrast, GLP-1R$^{-/-}$ mice manifest subtle but detectable abnormalities in islet number and size (98) and exhibit a defective β-cell regenerative response to partial pancreatectomy (99). Hence, GLP-1R actions are physiologically important for the growth and adaptive regeneration of murine β-cells.

GLP-1R agonists and experimental models of diabetes

The glucose-lowering action of GLP-1 delineated in nondiabetic animals has been demonstrated in multiple models of experimental diabetes. A 48-h infusion of native GLP-1 lowered blood glucose in association with increased levels of circulating insulin, islet insulin content, and insulin mRNA in Wistar rats aged 22 months (100), and perfused pancreas studies have demonstrated GLP-1–dependent augmentation of insulin secretion in ZDF rats of diverse genetic backgrounds (101–103). Similarly, exendin-4 lowered glucose in *db/db* and *ob/ob* mice, ZDF rats, and diabetic rhesus monkeys in acute and chronic experiments (78,104,105) and the GLP-1 analog NN211 improved glycemic control in pigs, rats, and mice (60,81,106). Remarkably, glucose tolerance remained significantly improved in ZDF rats for weeks after a 48-h infusion of native GLP-1 (107). This "memory effect" for sustained improvement of glycemic control was also observed in *db/db* mice after discontinuation of therapy with CJC-1131, an albumin-bound GLP-1R agonist (82).

GLP-1 action in human subjects

The majority of GLP-1 actions delineated in preclinical experiments have also been demonstrated in human studies. Infusion of GLP-1(7-36)amide into normal human subjects stimulated insulin secretion, reduced glucagon secretion, and significantly reduced blood glucose in the fasting state after glucose loading or meal ingestion (6,50,108). In contrast to GIP, the insulinotropic and glucose-lowering actions of GLP-1 are preserved in human subjects with type 2 diabetes (45,109) in both the fasting and the postprandial states (7). Similarly, GLP-1 inhibits gastric acid secretion (110,111) and gastric emptying in humans (55) and the GLP-1–dependent attenuation of gastric emptying contributes to decreased glycemic excursion and, consequently, reduced glucose-stimulated insulin secretion (112,113). Consistent with the importance of gastric emptying and glucagon secretion for glycemic control, GLP-1 also lowers blood glucose in type 1 diabetic subjects (114–116). Analogous to studies demonstrating the induction of glucose competence in rodent β-cells, GLP-1 infusion enhances β-cell function and insulin secretory dynamics in human subjects with impaired glucose tolerance or type 2 diabetes (117–119). GLP-1 may also enhance glucose clearance in humans (120,121); however, the majority of these actions are likely mediated indirectly through effects on insulin and glucagon (122–124). Although several reports have described the effects of GLP-1 on muscle, liver, and fat cells, experimental evidence demonstrating expression of the GLP-1 receptor in these tissues in vivo is lacking. Hence, the indirect actions of GLP-1, leading to improvement in glycemic control and reduction in free fatty acids, may explain observations of improved insulin sensitivity in GLP-1–treated diabetic subjects (125).

The effect of GLP-1 in restoring glucose competence in rodent islets has prompted studies of GLP-1 action and β-cell function in type 2 diabetic patients. Insulin–treated diabetic subjects previously classified as "sulfonylurea nonresponders" exhibited β-cell GLP-1 responsivity, with lowering of fasting and postprandial glucose in association with enhanced insulin secretion (126). Patients treated with both GLP-1 and glibenclamide exhibited a greater degree of glucose reduction compared with the ef-

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fect of either agent alone (127). Similarly, the combination of GLP-1 and metformin was shown in a 48-h crossover study to be more effective for lowering blood glucose than monotherapy with either agent alone (128).

The GLP-1–dependent suppression of glucagon secretion raises the possibility that GLP-1 therapy will be associated with an increased risk of hypoglycemia and potentially defective counterregulation if glucagon secretion remains suppressed in the face of GLP-1–linked hypoglycemia. Rapid gastric emptying may be associated with enhanced GLP-1 release and an increased risk of hypoglycemia in postgastrectomy patients (129). Similarly, acute administration of GLP-1 (80 nmol) to nondiabetic subjects in the fasted state produced mild relative hypoglycemia in some subjects (mean glucose ~3.5 mmol/l) (130). Nevertheless, appropriate glucagon responses to hypoglycemia do not appear to be blunted in GLP-1–treated subjects (130), and GLP-1 infusion does not impair normal counterregulatory responses to hypoglycemia in healthy human subjects (131). Hence, the risk of hypoglycemia seems modest in type 2 diabetic subjects treated with GLP-1R agonists alone.

The demonstration that both intracerebroventricular and peripheral administration of GLP-1R agonists induces weight loss in preclinical experiments has fostered interest in the potential actions of these agents to diminish appetite and reduce weight gain in overweight human subjects. The majority of human studies have examined appetite and food ingestion over short (24-h) time periods after single-dose injection or continuous infusion of GLP-1. Small but statistically significant reductions in appetite and meal ingestion have been recorded in studies of normal, obese, and diabetic GLP-1–treated subjects (132–136). A meta-analysis of available data from 115 subjects demonstrated significant GLP-1–dependent reductions in energy consumption in lean and overweight subjects (137). The acute reduction in food consumption and inhibition of gastric emptying has been detected even with physiological increases in levels of circulating GLP-1 (136). Administration of GLP-1 via continuous subcutaneous infusion for 6 weeks to obese diabetic subjects was associated with reduced appetite and a small but significant mean 1.9-kg weight loss (125). Hence, GLP-1 therapy in human subjects appears associated with prevention of weight gain or modest weight loss; however, long-term data are not yet available.

Although single or repeated subcutaneous injections of native GLP-1 decrease blood glucose in human subjects (138,139), the glucose-lowering effects are transient and no longer evident 1–2 h after peptide injection (140,141). Furthermore, continuous enhancement of GLP-1 action for 24 h/day appears superior for glucose control compared with peptide infusion for 16 h (142). Continuous intravenous or subcutaneous infusion of GLP-1 in short- and long-term studies has been shown to be highly effective in lowering blood glucose in diabetic subjects (125,143,144), but this intensive and expensive approach has major limitations for the treatment of large numbers of diabetic patients. The rapid degradation and clearance of native endogenous and exogenously administered GLP-1 (145) have spurred the clinical development of degradation-resistant GLP-1 analogs with longer durations of action in vivo.

Exendin-4 is a naturally occurring 39–amino acid GLP-1R agonist isolated from the salivary gland venom of the lizard *Heloderma suspectum* (146). Exendin-4 exhibits 53% amino acid identity to mammalian GLP-1 (146,147), yet binds to and activates the GLP-1 receptor. Furthermore, exendin-4 is highly resistant to the proteolytic activity of DPP-IV and exhibits a longer duration of action in vivo. Intravenous infusion of exendin-4 lowered fasting and postprandial blood glucose in normal healthy volunteers and was associated with a 19% reduction in calorie consumption assessed during a single test meal (148). Exendin-4 exerted similar effects on insulin secretion after acute intravenous infusion in diabetic subjects (149), and subcutaneous daily administration of exendin-4 to subjects with type 2 diabetes significantly reduced blood glucose and HbA_{1c} (a decline from 9.1 to 8.3%) over a 1-month treatment period (150). Exendin-4 has been evaluated in eight phase 2 trials in 323 individuals with type 2 diabetes who received dosages of 0.05–2.0 μg/kg subcutaneously. Nausea and vomiting were the principal side effects observed (151). A 4-week treatment period produced a significant reduction in HbA_{1c} levels, with sustained reduction in postprandial glycemia maintained over the 28-day treatment period.

Exendin-4 treatment (0.08 μg/kg s.c., b.i.d. or t.i.d.) over 1 month was evaluated in 109 patients treated with sulfonylureas or metformin, alone or in combination. The treatment was generally well tolerated, with three subjects withdrawing in the first 12 days because of nausea. At the end of the study period, a significant reduction was observed in levels of serum fructosamine, HbA_{1c}, and mean postprandial glucose, but no significant change was noted in body weight or serum lipids (152). Antibodies against exendin-4 were detected in 19% of treated subjects; however, the antibodies did not affect treatment responses. In all, 15% of patients experienced hypoglycemia; all of these subjects received sulfonylureas plus exendin-4 (152). Exendin-4, recently renamed exenatide, is currently being evaluated for the treatment of type 2 diabetes in phase 3 trials in combination with metformin, sulfonylurea agents, or both.

NN2211 (liraglutide) is a fatty acid–linked DPP-IV–resistant derivative of GLP-1 designed for subcutaneous administration that exhibits a pharmacokinetic profile compatible with once-daily injection (153). NN2211 reduced fasting and postprandial glycemia in diabetic subjects after a single 10 μg/kg subcutaneous injection at 11:00 P.M., in association with inhibition of gastric emptying and reduced levels of circulating glucagon (154). NN2211 has been tested in phase 2 clinical trials. Additional approaches for prolonging the duration of action of GLP-1 derivatives include the use of albumin-bound GLP-1 molecules (82) and sustained release exendin-4 preparations; however, human data with these pharmaceutical approaches is currently limited.

Inhibition of DPP-IV for the treatment of type 2 diabetes

The observation that GLP-1 and GIP are rapidly cleaved at the position 2 alanine leading to inactivation of their biological activity (15,16) has fostered interest in the development of inhibitors of DPP-IV, the principal enzyme responsible for incretin inactivation (155,156). DPP-IV is but one member of a large family of related enzymes with overlapping enzyme specificity; however, adenosine deaminase affinity chromatography that specifically binds DPP-IV removes 95% of DPP-IV–

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Table 1—*Properties and biological actions of GIP and GLP-1*

GIP	GLP-1
42–Amino acid peptide	30/31–Amino acid peptide
Released from duodenum	Released from distal small bowel and colon
NH_2-terminal inactivation by DPP-IV	NH_2-terminal inactivation by DPP-IV
Stimulates insulin secretion	Stimulates insulin secretion
Minimal effect on gastric emptying	Inhibits gastric emptying
No effect on glucagon secretion	Inhibits glucagon secretion
No regulation of satiety and body weight	Inhibits food intake and weight gain
Promotes expansion of β-cell mass	Promotes expansion of β-cell mass
Normal GIP secretion in diabetic subjects	Reduced GLP-1 secretion in diabetic subjects
Defective GIP response in type 2 diabetes	Preserved GLP-1 response in type 2 diabetes

like activity from human sera, consistent with the dominant role for DPP-IV as the major circulating enzyme exhibiting DPP-IV–like enzymatic activity in vivo (157). Complementary evidence supporting the importance of DPP-IV as a pharmaceutical target for lowering glucose levels is derived from analysis of rodents with inactivating DPP-IV mutations. DPP-IV knockout mice and the Fischer DPP-IV mutant rat exhibit reduced levels of glycemic excursion after glucose loading in association with increased levels of circulating GLP-1 and insulin (158,159). Remarkably, DPP-IV knockout mice exhibit resistance to obesity and display improved insulin sensitivity after high-fat feeding (160). Hence, both pharmacological and genetic attenuation of DPP-IV activity is associated with enhanced incretin action, increased insulin, and lower glucose in vivo.

DPP-IV inhibitors lowered blood glucose after acute and chronic administration in preclinical studies through mechanisms predominantly dependent on incretin action, leading to potentiation of glucose-stimulated insulin secretion (161–163). Treatment of ZDF rats for 3 months with the inhibitor P32/98 resulted in progressive improvement in glycemic control, enhanced insulin secretory responses, increased insulin-stimulated muscle glucose uptake, and improved hepatic and peripheral insulin sensitivity (164,165). In one intriguing result, daily DPP-IV inhibitor therapy for 7 weeks in Wistar rats with streptozotocin-induced diabetes increased the numbers of islets and β-cells (166), consistent with the actions of GIP and GLP-1 in promoting islet neogenesis and cytoprotection (71).

Clinical experience with DPP-IV inhibitors in diabetic subjects is limited. A single-dose escalation study of P32/98 in healthy male volunteers demonstrated improved oral glucose tolerance in association with enhanced circulating levels of GLP-1 (167). A 4-week trial of NVP DPP728 administered several times a day to subjects with mild type 2 diabetes (mean entry HbA_{1c} of ~7.6%) produced significant glucose lowering in mean HbA_{1c} to 6.9% (168). A second-generation DPP-IV inhibitor, LAF237, is currently in phase 2 clinical trials and additional DPP-IV inhibitors are in clinical development. Although inhibition of DPP-IV activity is a promising approach for enhancing incretin action in diabetic subjects, DPP-IV exhibits catalytic activity against a broad number of peptide substrates (155,169). Furthermore, DPP-IV, also known as the lymphocyte cell surface transmembrane-signaling molecule CD26, is activated by external stimuli and modulates T-cell activation, producing pleiotropic effects in experimental inflammatory and neoplastic disorders (155,170). Global genetic inactivation of CD26 in mice is associated with subtle but detectable abnormalities in cytokine and immunoglobulin secretion after mitogen stimulation (171). Whether highly selective inhibition of the catalytic activity of DPP-IV will adversely perturb immune-related activity in human subjects is unclear; hence, the long-term safety of sustained DPP-IV/CD26 inhibition merits careful scrutiny.

GLP-1R agonists and DPP-IV inhibitors: unanswered questions

Although GIP and GLP-1 exhibit both overlapping and unique mechanisms of action, GLP-1 exhibits several distinct advantages desirable in a therapeutic agent for treating type 2 diabetes (Table 1). Currently, there are few clinical data to support the development of injectable GIP agonists to treat human subjects with type 2 diabetes. Chronic GLP-1R agonist administration lowers blood glucose and HbA_{1c} in diabetic subjects and has not yet been associated with receptor downregulation or tachyphylaxis, but few clinical reports are available that address this issue. Because nausea limits the dosage of GLP-1 administered in human studies, the potential for long-term prevention of weight gain or, ideally, induction of weight loss versus lack of compliance from unwanted gastrointestinal side effects will require scrutiny. Similarly, whether subsets of patients with type 2 diabetes will exhibit preferential GLP-1 responsivity or, alternatively, relative resistance to the glucose-lowering effects of GLP-1 is not known. As is the case with intensive insulin administration, the potent glucose-lowering properties of GLP-1R agonists may increase the likelihood of treatment-associated hypoglycemia in susceptible patients concomitantly treated with insulin secretagogues such as

Table 2—*Characteristics of DPP-IV inhibitors and GLP-1R agonists*

DPP-IV inhibitors	GLP-1R agonists
Orally available	Injectable
Multiple targets	Single known GPCR target
GLP-1 PK favorable	Higher levels of GLP-1 achievable, but narrow PK profile
Short- versus long-acting	Longer acting—days to weeks
Less potent agents	More potent glucose lowering
Drug overdose nontoxic	Drug overdose problematic
No central nervous system side effects	Nausea and vomiting
Less defined side effect profile	Well-described and tolerable side effect profile

GPCR, G protein–coupled receptor; PK, pharmacokinetic.

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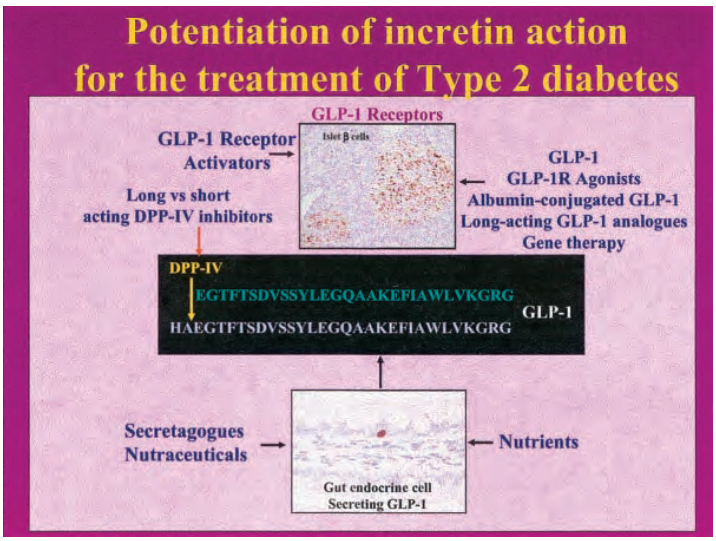

Figure 3—*Potential mechanisms for potentiation of incretin action for the treatment of type 2 diabetes.*

sulfonylureas. Although GLP-1R agonists produce remarkable effects on β-cell proliferation and cytoprotection in rodent studies, and human β-cells exhibit proliferative and cytoprotective responses to GLP-1 in vitro, the potential for GLP-1R agonists to prevent progression to β-cell failure in diabetic subjects is intriguing, but largely undocumented. Moreover, the current need for once or twice daily injections of GLP-1–based pharmaceutical agents raises acceptance and compliance issues for prolonged therapy with these agents. Whether the newer generation of long-acting GLP-1R agonists currently designed for weekly administration will be as potent as agents given once or twice daily remains unknown. Furthermore, GLP-1R agonists in the clinic exhibit <100% amino acid identity with the native peptide. The known immunogenic potential of even identical recombinant human therapeutic proteins (172) raises the specter of immunoneutralizing antibodies in some patients, which may lead to reduction in therapeutic efficacy or potential exacerbation of diabetes if the antibodies cross-react with endogenous GLP-1.

DPP-IV inhibitors represent a complementary approach for enhancing incretin action through orally available tablets. Whether these inhibitors should ideally aim for 24 h/day inhibition of DPP-IV activity is uncertain. Similarly, the observations that subjects with type 2 diabetes exhibit reduced levels of meal-stimulated circulating GLP-1 poses theoretical limitations for drugs acting in part through GLP-1–dependent mechanisms. DPP-IV inhibitors will be unable to achieve the same pharmaceutical elevation in levels of circulating GLP-1 compared with injectable GLP-1–based drugs, and are likely to be less potent compared with injectable GLP-1R agonists. A comparison of the advantages and disadvantages of DPP-IV inhibitors versus GLP-1R agonists is shown in Table 2. The broad spectrum of DPP-IV activity and the large number of potential bioactive peptide substrates pose important questions regarding unanticipated side effects associated with the long-term use of DPP-IV inhibitors. Taken together, the urgent need for diabetes therapeutic agents exhibiting new mechanisms of action and the preliminary efficacy of GLP-1R agonists and DPP-IV inhibitors in ongoing clinical trials suggest that one or both classes of agents may ultimately be approved for the treatment of type 2 diabetes. Furthermore, there remains intense interest in developing GLP-1 secretagogues or GLP-1 receptor activators (Fig. 3); hence, strategies focused on enhancing incretin action are likely to receive increasing attention if the first generation of GLP-1R agonists and DPP-IV inhibitors is approved for the treatment of type 2 diabetes.

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