Glucagon-like peptide 1 receptor agonists and dipeptidyl peptidase IV inhibitors: new therapeutic agents for the treatment of type 2 diabetes

Elaine M. Sinclair and Daniel J. Drucker

Purpose of review

Current treatments for type 2 diabetes are effective, but a substantial number of patients continue to have difficulty in achieving and maintaining satisfactory control of blood glucose. The available data suggest that enhancing the action of glucagon-like peptide 1 through the use of glucagon-like peptide 1 receptor agonists, or by preventing the degradation of glucagon-like peptide 1 by inhibition of dipeptidyl peptidase IV, may be useful therapeutic approaches for the treatment of type 2 diabetes. Herein we focus on the status of current approaches, based on enhancement of incretin action, for the treatment of type 2 diabetes.

Recent findings

Degradation-resistant glucagon-like peptide 1 receptor agonists acutely lower blood glucose in human beings by improvement in β cell function, inhibition of gastric emptying, and reduction of glucagon secretion. Treatment with these agents added to existing diabetes therapies, as exemplified by studies of the injectable glucagon-like peptide 1 receptor agonist exenatide, demonstrates significant reduction in HbA1c, together with prevention of weight gain and, in many individuals, significant weight loss over a 30-week study period. Dipeptidyl peptidase IV inhibitors are orally available effective antidiabetic agents that seem to be well tolerated but may not produce weight loss. Less information is currently available about the consequences of long-term treatment with Dipeptidyl peptidase IV inhibitors.

Summary

Both glucagon-like peptide 1receptor agonists and dipeptidyl peptidase IV inhibitors represent promising new approaches for the treatment of type 2 diabetes. The long-term safety and efficacy of these agents remain to be determined, but the available evidence suggests that these new drug classes will provide novel therapeutic alternatives for the management of diabetes.

Keywords

dipeptidyl peptidase IV, glucagon-like peptide 1, glucose-dependent insulinotropic polypeptide, incretin

Curr Opin Endocrinol Diabet 12:146–151. © 2005 Lippincott Williams & Wilkins.

Department of Medicine, Banting and Best Diabetes Centre, Toronto General Hospital and the University of Toronto, Toronto, Ontario M5G 2C4, Canada

DJD is a consultant to Amylin Pharmaceuticals Inc, Conjuchem Inc, Merck Research Laboratories, Novartis, Aventis, Syrrx Inc, and Bristol Myers Squibb.

DJD is supported in part by a Canada Research Chair in Regulatory Peptides and by operating grants from the Juvenile Diabetes Research Foundation, the Canadian Diabetes Association, and the Canadian Institutes for Health Research.

Correspondence to Daniel J. Drucker, Toronto General Hospital, Banting and Best Diabetes Centre, 200 Elizabeth Street, MBRW4R-402, Toronto, Canada M5G 2C4
Tel: 416 340 4125; fax: 416 978 4108; e-mail: d.drucker@utoronto.ca

Current Opinion in Endocrinology and Diabetes 2005, 12:146–151

Abbreviations

DPP-IV	dipeptidyl peptidase IV
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide 1
GLP-1R	glucagon-like peptide-1 receptor

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Introduction

The oral administration of glucose causes a greater release of insulin than when glucose is infused intravenously to achieve comparable levels of glycemia [1,2]. The enhanced insulin release after enteral rather than parenteral nutrient administration is due to the release of gut peptides known as incretins. These incretins, subsequently identified as specific enteroendocrine-derived peptides, are thought to be physiologically important for the control of blood glucose excursion after meal ingestion. The predominant incretins are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). GIP is produced in and secreted from intestinal K cells localized to the duodenum and proximal small bowel. GIP is secreted in response to a meal rich in carbohydrate and fat and stimulates insulin secretion in a glucose-dependent manner [3]. GLP-1 is synthesized in and secreted from enteroendocrine L cells in the distal regions of the gastrointestinal tract, predominantly in the ileum and colon. Nevertheless, levels of circulating GLP-1 rise rapidly within minutes of nutrient ingestion; hence, GLP-1 secretion is controlled by both neural and endocrine signals initiated upon nutrient arrival into the proximal gastrointestinal tract [4–6]. The observation that the incretin effect is impaired in patients with type 2 diabetes has generated interest in the question as to whether a defective incretin response contributes to the pathophysiology of type 2 diabetes [7]. Although the action of GLP-1 is preserved in diabetic individuals, patients with type 2 diabetes have a markedly blunted response or absence of response to the infusion of exogenous GIP [8,9]. The mechanisms underlying the defective GIP response in patients with diabetes remain unknown, but experiments

using experimental models of diabetes demonstrate a reduction in islet cell GIP receptor expression [10].

Dipeptidyl peptidase IV

Both GLP-1 and GIP are rapidly degraded *in vivo* by the protease dipeptidyl dipeptidase IV (DPP-IV). DPP-IV, also known as the lymphocyte cell surface protein CD26, cleaves the N-terminal portion of peptides after X-proline or X-alanine [11,12]. DPP-IV is widely expressed as both a soluble and a membrane-bound protein. It is estimated that more than 50% of GLP-1 that leaves the intestinal circulation has already been degraded by DPP-IV [13]. The product of DPP-IV–mediated GLP-1 degradation, GLP-1-(9-36)-amide, has been shown to promote insulin-independent glucose clearance in pigs [14]. GLP-1 (9-36)-amide, however, had no effect on glucose homeostasis in comparable studies carried out in mice [15]. Similarly, no actions of GLP-1(9-36)-amide were detected in studies with humans [16].

Glucagon-like peptide 1 receptor agonists

The administration of native GLP-1 for 6 weeks by continuous subcutaneous infusion produced considerable improvement in multiple parameters of diabetic control, including reduced fasting glucose, decreased HbA1c, decreased levels of free fatty acids, and modest but significant weight loss [17]. Levels of fasting insulin rose modestly from 65 pmol/L at baseline to 98 pmol/L at the end of the 6-week treatment period. GLP-1-treated individuals also had significant improvements in β cell function and insulin sensitivity at the end of the 6-week study [17]. The GLP-1 treatment was remarkably well tolerated, with few individuals describing significant nausea or vomiting, likely because of the significant but slowly progressive elevations in GLP-1 levels (from 19 pmol/L at the start of the study to 282 pmol/L by week 6; saline-treated patients had no change in their mean plasma GLP-1 levels of ~10 pmol/L) achieved with subcutaneous infusion [17].

To circumvent the limitations of using the native GLP-1 peptide as a therapeutic agent, current efforts are directed at using degradation-resistant GLP-1 receptor agonists for the treatment of diabetes. Exendin-4 isolated from the saliva of the Gila monster lizard is a potent GLP-1 receptor agonist [18]. It shares 53% amino acid identity with GLP-1 and is highly resistant to DPP-IV degradation because of the presence of an NH_2 penultimate glycine residue. In part because of DPP-IV resistance and its different amino acid structure, exendin-4 has a longer plasma half-life and increased duration of action relative to native GLP-1 [19,20]. After the administration of a single 0.08 μg/kg injection of exenatide (synthetic exendin-4), plasma drug levels peak between 2 and 3 hours later, with a mean half-life calculated to be approximately 226 ± 170 minutes at the end of a 28-day study in patients with type 2 diabetes [21•]. Furthermore, ongoing research efforts are directed at further prolonging the duration of action of native exendin-4, either through the use of sustained release microsphere technology (exenatide LAR) or through polyethylene glycol modification of the exendin-4 peptide to extend the duration of peptide action [22].

Clinical experience with exenatide

Exenatide has been examined in both short-term and long-term studies of persons with type 2 diabetes. Short-term administration of exendin-4 reduced both fasting and postprandial glucose, decreased gastric emptying, and reduced energy intake in normal healthy volunteers [23]. Twice-daily administration of exenatide for 5 days resulted in reduced glycemic excursion, in association with decreased levels of insulin and glucagon [24].

The antidiabetic actions of exendin-4 were examined in a 1-month study of 10 patients with diabetes given twice-daily injections with dosing individually titrated for each patient to a maximum of 96 pmol/kg. Exendin-4 treatment improved blood glucose and lowered HbA1c, together with an improvement in β cell sensitivity to glucose [25]. The efficacy of exenatide administered twice or three times daily in combination with oral antidiabetic agents (metformin and/or sulfonylurea) was examined in a 28-day study. The mean entry HbA1c in study participants was just over 9%. Exenatide treatment reduced levels of fructosamine and HbA1c and improved β cell function as assessed by homeostasis model assessment [21•]. No significant improvement was seen in fasting glucose or body weight, and in 19% of patients, low titer anti–exendin-4 antibodies developed in the 28-day study. Nausea was the most common adverse event, generally observed in the first few days of the study and reported by 31% of exenatide-treated patients [21•].

To explore approaches that might reduce the acute nausea associated with the administration of GLP-1R agonists, patients were treated with placebo or exenatide, given three times daily, with exenatide dosing increased slowly and progressively every 3 days over 35 days in patients with type 2 diabetes. At the end of the initial 35-day titration period, all patients in the placebo and exenatide arms then received 3 days of higher-dosage parenteral exenatide (0.24 μg/kg) three times daily. Consistently with the study hypothesis, patients pretreated with increasing doses of exenatide reported less nausea and vomiting than did those in the exenatide-naive group [26].

The effect of exenatide added to metformin alone, sulfonylurea alone, or metformin plus sulfonylurea was examined in a series of three phase 3 trials in patients with type 2 diabetes not currently achieving optimal glucose control in their current antidiabetic regimens. These studies, designated the AMIGO trials (AC2993: Diabetes

Management for Improving Glucose Outcomes), have been reported in part in abstract presentations and publications. Patients taking sulfonylureas treated with exenatide 10 μg twice daily for 6 months had a significant reduction in HbA1c of 0.86% at the end of the study period. Then, 377 patients were randomized to additional treatment with either placebo (n = 123), exenatide 5 μg twice daily (n = 125), or exenatide 10 μg twice daily (n = 129). Of the patients receiving the 10-μg twice-daily dose, 41% achieved an HbA1c of 7%, in contrast to 9% of patients receiving sulfonylurea alone. A modest decrease in fasting glucose (0.6 mM) and a mean weight loss of 1.6 kg was observed at the end of the 6-month treatment period. The two most common treatment-associated adverse events were nausea (51%) and hypoglycemia (36%), with nausea more commonly observed in the first 8 weeks of exenatide treatment [27•]. Only 3% of exenatide-treated patients withdrew from the study because of nausea, and no cases of severe hypoglycemia were observed. At the end of the study, 41% of the patients treated with exenatide had detectable anti-exenatide antibodies, but the presence or absence of antibodies did not correlate with clinical outcomes.

The efficacy of exenatide in combination with metformin, compared with metformin alone, was also examined in a 6-month study in patients with type 2 diabetes treated with either 5 or 10 μg of exenatide twice daily. In this study, 336 patients were randomized to additional treatment with either placebo (n = 113), exenatide 5 μg twice daily (n = 110), or exenatide 10 μg twice daily (n = 113). At the end of the 6-month treatment period, patients receiving 10 μg twice a day achieved a reduction in HbA1c of 0.78%, together with a mean weight loss of 2.8 kg. Of patients receiving 10 μg twice daily, 46% achieved an HbA1c of 7% or less, with exenatide therapy achieving a relatively greater reduction in postprandial *versus* fasting glucose even after 30 weeks of therapy. Weight loss was observed in exenatide-treated patients independently of the starting body mass index; although nausea was the most commonly reported side effect, there was no correlation between the rate of reported nausea and the extent of weight loss achieved. Mild to moderate hypoglycemia was reported in approximately 5% of patients receiving either exenatide or placebo, and 43% of patients had detectable anti-exenatide antibodies at the end of the 30-week study period.

The third AMIGO study compared the efficacy of sulfonylurea plus metformin treatment with or without the addition of exenatide, 5 or 10 μg twice daily for 30 weeks. In this study, 733 patients were randomized to receive additional therapy with either placebo (n = 247), exenatide 5 μg twice daily (n = 245), or exenatide 10 μg twice daily (n = 241). Exenatide reduced levels of HbA1c by approximately 0.8%, with a mean weight loss of 1.6 kg at the end of the study period. Mild to moderate hypoglycemia was reported in 28% of patients treated with 10 μg of exenatide twice daily, and study investigators were allowed to decrease the dose of sulfonylurea during the study in the event of suspected or documented hypoglycemic events. The most frequently reported adverse events were nausea and mild to moderate hypoglycemia, with 49% of exenatide-treated patients having antibody positivity at the end of the 30-week study period.

Glucagon-like peptide 1R agonists with prolonged pharmacokinetics based on albumin

Liraglutide is a fatty acylated GLP-1 analog, which binds human serum albumin in a noncovalent manner, thus prolonging the circulating half-life of GLP-1 and resulting in improved glucose control after once-daily subcutaneous administration [28•]. Mild initial and transient nausea and vomiting was reported after liraglutide administration. The treatment of 13 patients with type 2 diabetes with liraglutide 6 μg/kg once daily for 1 week resulted in a marked improvement in 24-hour glycemia as a result of increased glucose clearance, reduced glucose release due to decreased glycogenolysis, decreased glucagon release, and an improved first-phase insulin response [29•]. No effect of liraglutide was observed on gastric emptying. A longer-term study examined the effects of a single daily dose of 0.6 mg liraglutide in 21 patients with type 2 diabetes for 8 weeks [30]. Liraglutide reduced fasting glucose and decreased HbA1c (0.33%) but was not associated with a significant change in body weight or energy expenditure [30].

There is considerable interest in the development of longer-acting GLP-1R agonists, and several strategies use either covalent bonding to albumin, or the generation of a recombinant albumin-GLP-1 protein, to take advantage of the long circulating half-life of albumin *in vivo*. CJC-1131 is a GLP-1 analogue with a chemical linker attached to the C terminus allowing for covalent binding to endogenous albumin at a specific cysteine residue on albumin. CJC-1131 mimics GLP-1R–dependent actions *in vivo*, including stimulation of insulin secretion and biosynthesis, inhibition of food intake, and stimulation of islet neogenesis in a mouse model of type 2 diabetes [31•]. CJC-1131 is currently being examined in phase 2 human clinical trials; preliminary data suggest that it exerts a prolonged duration of action and is efficacious in human patients but that it is associated with the development of nausea after parenteral administration.

Albugon is a recombinant GLP-1-albumin protein that has been examined in preclinical models of type 2 diabetes. Although albugon is not expected to rapidly cross the blood–brain barrier because of its large size, peripheral administration of albugon inhibited food intake and gastric emptying and activated c-fos expression in the central nervous system of normal mice. Hence, although both

GLP-1 and exendin-4 rapidly penetrate the brain, it seems that many of the acute effects of GLP-1R agonists may not require direct access to the central nervous system [32,33,34•].

Dipeptidyl peptidase IV inhibitors

The rapid degradation of both GLP-1 and GIP by DPP-IV has fostered interest in the development of DPP-IV inhibitors for the treatment of type 2 diabetes. DPP-IV inhibitors have shown efficacy in several experimental models of diabetes [35–37]. Furthermore, genetic disruption or mutation of the DPP-IV gene in mice or rats results in improved glucose tolerance and increased levels of intact bioactive GLP-1 and confers resistance to diet-induced obesity [38–40]. DPP-IV inhibitors lower blood glucose and HbA1c in short-term clinical studies [41]. Multiple DPP-IV inhibitors, including LAF237 and MK0431, are now in late-stage clinical development (phase 2/3). Although preclinical studies have suggested that improvement in glycemic control correlates with the degree and chronicity of DPP-IV inhibition, the extent and duration of DPP-IV inhibition over a 24-hour time period that will prove optimal for the safe treatment of diabetes in humans has not yet been precisely determined [42,43].

The most advanced DPP-IV inhibitor in phase 3 clinical trials is LAF237. A 4-week study examined the efficacy of LAF237 in human patients with diet-controlled type 2 diabetes, a mean initial HbA1c of 7.2%, and a body mass index of 27.5 [44•]. A single daily oral dose of 100 mg LAF237 significantly increased the postprandial circulating levels of intact bioactive GLP-1 and reduced the levels of plasma DPP-IV activity, with the extent of the inhibition approximately 60% of baseline activity when measured 24 hours after a single dose [44•]. Although LAF237 treatment did not affect body weight, a significant improvement in the insulin–glucose ratio and a reduction in levels of meal-stimulated glucagon were observed after 4 weeks of drug administration. The ongoing administration LAF237 has been examined in 12-week studies of patients receiving both metformin and LAF237, 50 mg daily. The mean reduction in HbA1c was approximately 0.6%, and preliminary information from open-label extension studies continued for as long as 1 year has demonstrated a sustained but modest reduction in HbA1c.

Conclusion

Both GLP-1R agonists and DPP-IV inhibitors exert both overlapping and contrasting effects (Table 1) in humans. The available information from both preclinical and clinical studies suggests that sustained activation of GLP-1 receptor signaling produces rapid and considerable improvement in glucose control, in association with modest reduction in body weight. Peptide-based drugs acting through the GLP-1 receptor, such as exenatide and liraglutide, are generally well tolerated and safe but have a narrow therapeutic window, with nausea being the most troublesome initial side effect after short-term drug administration. Although the current generation of GLP-1R peptide agonists requires once-daily or twice-daily parenteral administration, treatment-associated weight loss or prevention of weight gain with these agents may provide an attractive clinical benefit, beyond simple reduction in HbA1c, that is difficult to achieve with most currently available oral antidiabetic agents. Furthermore, active ongoing efforts are directed at the development of long-acting GLP-1R agonists, potentially suitable for once-weekly administration.

Short-term studies of GLP-1R agonists in patients with type 2 diabetes demonstrate significant improvements in β cell function as assessed by analyses of glucose-stimulated insulin secretion [29,45]. Little information is available, however, about the long-term effects of these agents on the preservation and potential sustainability of improved β cell function.

The GLP-1 receptors are expressed on pancreatic ductal cells and islet β cells. Treatment of rodents or islet cells with GLP-1R agonists enhances β cell proliferation, leading to expansion of β cell mass [46–48]. Furthermore, the GLP-1 receptor activates signal transduction pathway coupled to cell preservation *via* regulation of genes and corresponding proteins regulating programmed cell death [49•,50,51]. Although the proliferative and cytoprotective pathways activated by the GLP-1R remain incompletely understood, GLP-1R agonists increase the expression of adenylate cyclase, cyclic amp response element binding protein, Akt, and IRS-2, which contribute to preservation of β cell mass [47,48,52].

The GLP-1 receptor is also expressed outside the pancreas in the central nervous system, lung, kidney, stomach,

Table 1. Comparison of GLP-1R agonists with DPP-IV inhibitors

GLP-1R agonists	DPP-IV inhibitors
Injectable	Orally available
Defined MOA	Incompletely understood MOA
Defined safety profile in 6–12-month studies	Safety profile currently being determined
Associated with nausea, which diminishes over time	Well tolerated
Treatment prevents weight gain or induces weight loss	Weight neutral

GLP-1R, glucagon-like peptide-1 receptor; DPP-IV, dipeptidyl peptidase IV; MOA, mechanisms of action.

and heart [53]. GLP-1 rapidly normalizes blood glucose and stimulates insulin secretion, and GLP-1R agonists are therefore also being explored for the treatment of additional clinical indications, such as normalization of glucose, free fatty acids, and related metabolic abnormalities in acutely ill hospitalized patients [54,55]. Furthermore, GLP-1 may also have favorable effects on cardiomyocyte metabolism and survival, and GLP-1 infusion in patients with acute myocardial infarction and left ventricular dysfunction improved clinical outcomes after acute coronary ischemia and angioplasty in a pilot study [56•]. Whether the effects of GLP-1 in these clinical scenarios are due strictly to improved metabolic control, or perhaps indirectly *via* effects on other tissues, remain uncertain.

Although the antidiabetic effects of DPP-IV inhibitors are being assessed in phase 3 clinical trials, comparatively less is known about their mechanism of action and potential for improvement in glycemic control. DPP-IV inhibitors exert their effects in part though the prevention of incretin degradation. Consistent with these findings, gene tic elimination of both GLP-1 and GIP receptor signaling abrogates the acute glucose-lowering actions of DPP-IV inhibitors in mice [57•]. Nevertheless, the mechanisms of action of DPP-IV inhibitors remain incompletely understood, and it seems likely that additional substrates will continue to be identified that contribute to the antidiabetic effect of these agents after prolonged administration *in vivo* [58]. Furthermore, the large number of proteins with an alanine or a proline at position 2, encompassing neuropeptides, chemokines, and regulatory peptides, raises the possibility that the long-term inhibition of DPP-IV activity might potentially be associated with unknown changes in one or more systems unrelated to the treatment of diabetes. The clinical experience to date suggests that selective DPP-IV inhibitors seem to be safe, and are an attractive new approach to enhancing incretin action that obviates the need for frequent once or twice daily injections. Nevertheless, it remains uncertain how potent these drugs will be in lowering blood glucose, or how safe they will prove to be with long-term administration, and the available data suggests that DPP-IV inhibitor therapy may not be associated with weight loss in human studies. It seems reasonable to expect that one or more classes of new drugs that exert their effects through enhancing incretin action may soon be approved for the treatment of type 2 diabetes.

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