The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes

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Lancet 2006; 368: 1696–705

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Glucagon-like peptide 1 (GLP-1) is a gut-derived incretin hormone that stimulates insulin and suppresses glucagon secretion, inhibits gastric emptying, and reduces appetite and food intake. Therapeutic approaches for enhancing incretin action include degradation-resistant GLP-1 receptor agonists (incretin mimetics), and inhibitors of dipeptidyl peptidase-4 (DPP-4) activity (incretin enhancers). Clinical trials with the incretin mimetic exenatide (two injections per day or long-acting release form once weekly) and liraglutide (one injection per day) show reductions in fasting and postprandial glucose concentrations, and haemoglobin A_{1c} (HbA_{1c}) (1–2%), associated with weight loss (2–5 kg). The most common adverse event associated with GLP-1 receptor agonists is mild nausea, which lessens over time. Orally administered DPP-4 inhibitors, such as sitagliptin and vildagliptin, reduce HbA_{1c} by 0·5–1·0%, with few adverse events and no weight gain. These new classes of antidiabetic agents, and incretin mimetics and enhancers, also expand β-cell mass in preclinical studies. However, long-term clinical studies are needed to determine the benefits of targeting the incretin axis for the treatment of type 2 diabetes.

Introduction

Eating provokes the secretion of multiple gastrointestinal hormones involved in the regulation of gut motility, secretion of gastric acid and pancreatic enzymes, gall bladder contraction, and nutrient absorption. Gut hormones also facilitate the disposal of absorbed glucose through the stimulation of insulin secretion from the endocrine pancreas. The observation that enteral nutrition provided a more potent insulinotropic stimulus compared with isoglycaemic intravenous challenge led to the development of the incretin concept.[1] The first incretin to be identified, glucose-dependent insulinotropic polypeptide (GIP), was purified from porcine intestinal extracts and had weak effects on gastric acid secretion but more potent insulinotropic actions in human beings.[2] GIP is a 42-aminoacid hormone synthesised in duodenal and jejunal enteroendocrine K cells in the proximal small bowel.

A second incretin hormone, glucagon-like peptide-1 (GLP-1) was identified after the cloning of the cDNAs and genes encoding proglucagon (figure 1). GLP-1 exists in two circulating equipotent molecular forms, GLP-1(7-37) and GLP-1(7-36)amide, although GLP-1(7-36)amide is more abundant in the circulation after eating. Most GLP-1 is made in enteroendocrine L cells in the distal ileum and colon, but plasma levels of GLP-1, like GIP, also increase within minutes of eating. Hence a combination of endocrine and neural signals probably promote the rapid stimulation of GLP-1 secretion well before digested food transits through the gut to directly engage the L cell in the small bowel and colon. More proximally located L cells in the duodenum and jejunum have also been described; however, the precise

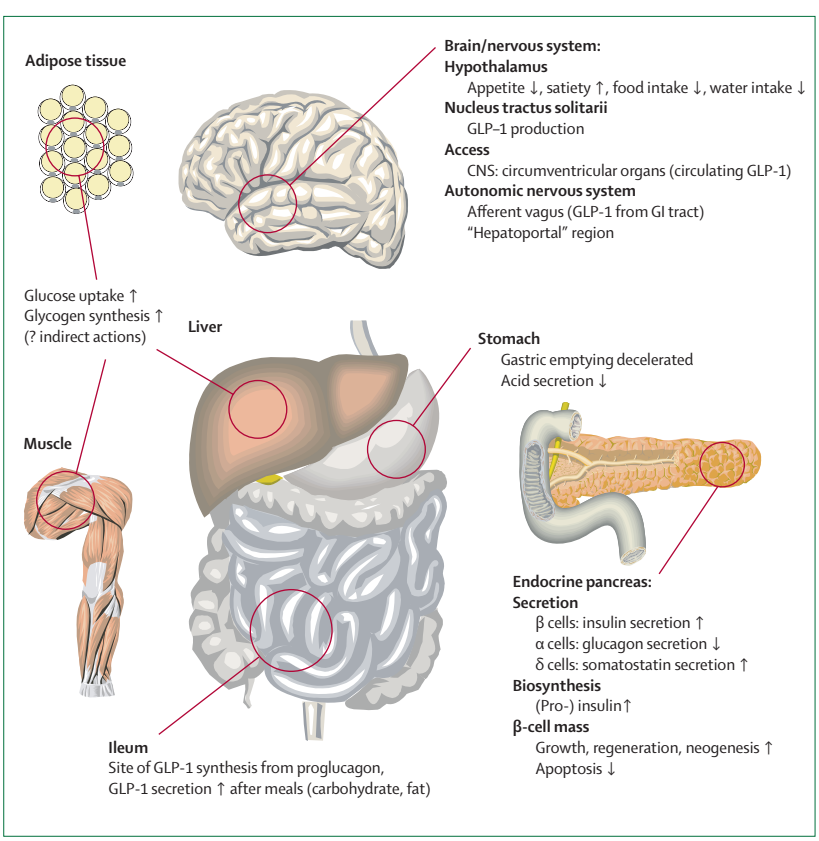

Figure 1: Physiology of GLP-1 secretion and action on GLP-1 receptors in different organs and tissues

Search strategy and selection criteria

We searched the MEDLINE and PubMed databases (1987–2006) with the search terms "glp-1", "glucagon", "glucagon-like", "gip", "incretin", "dipeptidyl peptidase-4", and "diabetes". We preferentially selected publications from the past 5 years, but did not exclude older publications that are commonly referenced or highly regarded. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant.

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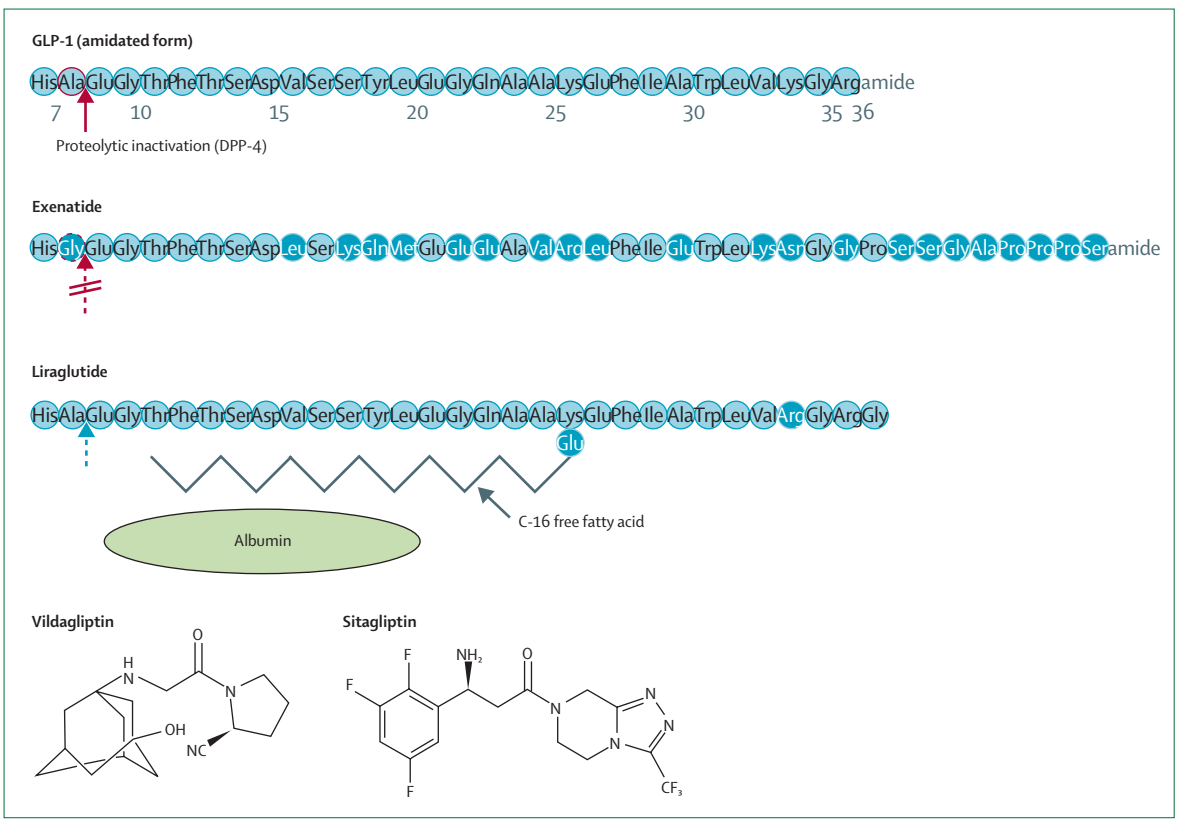

Figure 2: **Structure of GLP-1, GLP-1R agonists exenatide and liraglutide, and DPP-4 inhibitors vildagliptin and sitagliptin**

contributions of the proximal and distal L cells to the early rapid increase in plasma GLP-1 remains unclear.

Plasma levels of GLP-1 are low in the fasted state, in the range of 5–10 pmol/L, and increase rapidly after eating, reaching 15–50 pmol/L. The circulating levels of intact GLP-1 and GIP decrease rapidly because of enzymatic inactivation, mainly dipeptidyl peptidase-4 (DPP-4), and renal clearance.[3] Whether additional proteases, such as human neutral endopeptidase 24·11, are also essential determinants of GLP-1 inactivation is being investigated. Both GIP and GLP-1 contain alanine at position 2, and hence are excellent substrates for DPP-4. Indeed, DPP-4 is essential for incretin inactivation, and mice with targeted inactivation of the DPP-4 gene have raised levels of plasma GIP and GLP-1, increased insulin secretion, and reduced glucose excursion after glycaemic challenge.[4] As a result of DPP-4 activity, intact, biologically active GLP-1 represents only 10–20% of total plasma GLP-1.[5]

Both GIP and GLP-1 exert their actions by the engagement of structurally distinct G-protein-coupled receptors (GPCRs). The GIP receptor is predominantly expressed on islet β cells, and to a lesser extent, in adipose tissue and in the central nervous system. By contrast, the GLP-1 receptor (GLP-1R) is expressed in islet α and β cells and in peripheral tissues, including the central and peripheral nervous systems, heart, kidney, lung, and gastrointestinal tract (figure 1). Activation of both incretin receptors on β cells leads to rapid increases in levels of cAMP and intracellular calcium, followed by insulin exocytosis, in a glucose-dependent manner.[6] More sustained incretin receptor signalling is associated with activation of protein kinase A, induction of gene transcription, enhanced levels of insulin biosynthesis, and stimulation of β-cell proliferation.[7] Both GLP-1R and GIP receptor activation also promote resistance to apoptosis and enhanced β-cell survival, in both rodent[8] and human islets.[9] Consistent with the distribution of GLP-1R expression, GLP-1 also inhibits glucagon secretion, gastric emptying, and food ingestion, and promotes enhanced glucose disposal through neural mechanisms,[10] actions that also contribute to the control of glucoregulation. Notably, effects on glucagon secretion, like those on insulin secretory responses, are glucose-dependent, whereas counter-regulatory release of glucagon in response to hypoglycaemia is fully preserved even in the presence of pharmacological concentrations of GLP-1.[11]

The physiological importance of endogenous GIP and GLP-1 for glucose homoeostasis has been investigated in studies with receptor antagonists, or gene-knockout mice. Acute antagonism of GIP or GLP-1 lowers insulin secretion and increases plasma glucose after glycaemic challenge in rodents. Similarly, mice with inactivating mutations in the GIP or GLP-1 receptors also have

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defective glucose-stimulated insulin secretion and impaired glucose tolerance.[12,13] GLP-1, but not GIP, is also essential for control of fasting glycaemia, since acute antagonism or genetic disruption of GLP-1 action leads to increased levels of fasting glucose in rodents.[13] Furthermore, GLP-1 is essential for glucose control in human beings: studies with the antagonist exendin(9-39) show defective glucose-stimulated insulin secretion, reduced glucose clearance, increased levels of glucagon, and quicker gastric emptying after disruption of GLP-1 action.[14]

The pleiotropic actions of GLP-1 and GIP on the control of blood glucose have fostered considerable interest in the use of these agents for the treatment of type 2 diabetes. Whereas in healthy human beings oral glucose elicits a considerably higher insulin secretory response than does intravenous glucose (even if leading to the same glycaemic increments), this incretin effect is substantially reduced or even lost in patients with type 2 diabetes.[15] As an explanation for the acquired incretin defect, GIP but not GLP-1 shows noticeably attenuated insulinotropic action in patients with type 2 diabetes.[16] Furthermore, those with type 2 diabetes show a small but significant reduction in meal-stimulated levels of GLP-1.[17] Since GLP-1 action remains relatively preserved in diabetic patients, most pharmaceutical efforts directed at potentiation of incretin action for the treatment of type 2 diabetes have focused on GLP-1R agonists.

	Biological actions of incretin hormone in type 2 diabetes	Native GLP-1*	Incretin mimetics		DPP-4 inhibitors (eg, vildagliptin, sitagliptin)
			Exenatide	Liraglutide	
Characteristic features of type 2 diabetes					
Defective glucose-stimulated insulin secretion	Glucose-dependent stimulation of insulin secretion	Yes[16]	Yes[45]	Yes[46]	Yes[47]
Lack of biphasic response†	Restoration of biphasic responses	Yes[48]	Yes[49]	Not tested	Not tested
Slow insulin secretory response to meals[50]	More adequate insulin secretory response after meals‡	Yes[21,51]	Yes[45]	Yes[46]	Yes[47]
Reduction in or absence of incretin effect[15]	Replacement of incretin activity, greater incretin effect§	Yes‡	Yes‡	Yes‡	Not tested, but probable
Hyperglucagonaemia[52]	Suppression of glucagon secretion	Yes[16]	Yes[45]	Yes[46]	Yes[47]
Hypoglycaemia counter-regulation	Glucagon secretion, when plasma glucose is low	Yes[11]	Yes[53]	Yes[54]	Not tested
Reduced pancreatic β-cell insulin content	Increased synthesis of proinsulin	Yes[55]	Yes	Yes	Yes
Reduced endocrine pancreatic β-cell mass[56,57]	Increase in pancreatic islet β-cell mass	Yes[58]	Yes[59]	Yes[60]	Yes[61]
	Differentiation of islet precursor cells into β cells	Yes[62]	Yes	Yes	Unknown
Abnormally high rate of β-cell apoptosis[57]	Inhibition of toxin-induced|| β-cell apoptosis	Yes[8,63]	Yes[64]	Yes[65]	Probable[66]
Normal, decelerated or accelerated[67] gastric emptying	Deceleration in gastric emptying	Yes[68]	Yes[69]	Yes[46]	Marginal[70,71]
Hypercaloric energy intake/obesity[72]	Suppression of appetite/induction of satiety	Yes[73]	Yes[74]	Yes[75]	No obvious effect
	Weight loss (figure 3)	Yes[22]	Yes[25-27]	Yes[32]	No weight change[34]
Pharmacological characteristics					
Mode of administration		Intravenous, subcutaneous	Subcutaneous	Subcutaneous	Orally
Frequency of administration		Continuous	Twice daily	Once daily	Once (or twice) daily
Predominant adverse event		Nausea	Nausea	Nausea	None noted

*GLP-1 exists as glycine-extended (7–37) and amidated form (7–36)amide, with both forms having similar properties; †Biphasic response is only seen under artificial conditions leading to rapid rise in glucose concentrations (glucose bolus injection or "squarewave stimulus" when starting hyperglycaemic clamp); ‡As judged by improvement (normalisation) of postprandial glucose excursions; §By definition, GLP-1 and incretin mimetics replace incretin activity; ¶These actions have only been reported from animal or in vitro (eg, islet) studies; methods to assess human β-cell mass in vivo are not available; ||Hydrogen peroxide, free fatty acids, or streptozotocin.

Table: **Type 2 diabetes and biological actions of GLP-1, incretin mimetics, and DPP-4 inhibitors**

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Antidiabetic actions of GLP-1

Short-term intravenous infusions of GLP-1 (1–1·2 pmol kg^{-1} min^{-1}, leading to pharmacological plasma concentrations of total GLP-1 of 70–150 pmol/L, and of intact biologically active GLP-1 of 10–20 pmol/L) lowers blood glucose in patients with type 2 diabetes through a transient glucose-dependent stimulation of insulin and suppression of glucagon secretion and gastric emptying.[18–21] A 6-week subcutaneous infusion of GLP-1 in patients with type 2 diabetes, achieving plasma levels of GLP-1 in the 60–70 pmol/L range,[22] produced substantial improvements in insulin secretory capacity, insulin sensitivity, a reduction in HbA_{1c} of 1·2% and modest weight loss (1·9 kg).[22] Although intravenous or subcutaneous GLP-1 infusions could be useful for the short-term control of hyperglycaemia,[23,24] the long-term treatment of type 2 diabetes needs a more feasible approach to achieve sustained activation of GLP-1 receptors. The efficacy of injectable GLP-1 receptor agonists (degradation-resistant peptides or larger proteins with more suitable pharmacokinetic properties, figure 2) and DPP-4 inhibitors (small molecules with good oral bioavailability, webtable),[25–42] has been assessed in clinical trials.

GLP-1R agonists

Exenatide

Exenatide (synthetic exendin-4) was discovered in the search for biologically active peptides in lizard venom.[43] Exendin-4 shares roughly 50% of its aminoacid sequence with mammalian GLP-1 , is encoded by a unique gene in the lizard,[44] and is a potent degradation-resistant agonist at the mammalian GLP-1R (figure 2). Exenatide has been developed for the treatment of type 2 diabetes (table).[47–75] Exenatide has a circulating half-life of 60–90 min,[69] with increases in plasma exenatide concentrations lasting 4–6 h after a single subcutaneous injection.[76,77]

Phase III trials investigated the efficacy of adding exenatide (5 or 10 µg by subcutaneous injection twice daily) to ongoing therapy in patients suboptimally controlled on oral antidiabetic agents (metformin,[25] sulphonylureas,[26] a combination of both,[27] or thiazolidinediones[28]). The starting dose of exenatide is 5 µg twice daily for 4 weeks, followed by an increase to 10 µg twice daily.[78,79] Exenatide reduced HbA_{1c} concentrations by 0·8–1·0 % (figure 3)[25–42] over 30 weeks, with prevention of weight gain or modest weight loss of 1·5–3 kg. Patients continuing in an open-label extension lost more weight, with the total weight loss reaching 4–5 kg after 80 weeks.[80] The commonest adverse events with exenatide were gastrointestinal (nausea, or more rarely vomiting or diarrhoea[25–27]) (figure 3). However, exenatide was rarely discontinued because of side-effects, and the occurrence of nausea lessened the longer the duration of therapy.[25–27] An increased number of mild to moderate hypoglycaemic events was noted in patients given exenatide and sulphonylureas,[26,27] but not in those given exenatide and metformin,[25] despite a similar reduction in glycaemia.

40–50% of patients receiving exenatide develop antibodies with weak binding affinity and low titres.[25–27] Antibody formation has not been associated with impaired antidiabetic effectiveness of exenatide in most of those treated. However, the drug might not be as effective in the few patients with high-titre antibodies.

Exenatide has been compared with insulin glargine in an open-label study as additional treatment for diabetic patients not achieving effective glucose control on metformin and a sulphonylurea.[29] Fasting glucose concentrations were reduced more in patients receiving insulin glargine, but postprandial glucose reduction was greater with exenatide, especially after breakfast and dinner. Both exenatide and insulin glargine reduced levels of HbA_{1c} by 1·1% over 26 weeks.[29] No significant differences in overall rates of hypoglycaemia were seen in the different treatment groups, although nocturnal hypoglycaemia was less frequent with exenatide and daytime hypoglycemia was less common in patients given insulin glargine. Gastrointestinal side-effects, such as nausea and vomiting, were more often reported with exenatide than with insulin glargine, and the dropout rate was also higher in the exenatide-treated cohort. However, patients receiving insulin glargine gained an average of 1·8 kg compared with a 2·3 kg weight loss in exenatide-treated patients.[29] Exenatide was approved by the US Food and Drug Administration for the treatment of type 2 diabetes in April, 2005. In Europe, exenatide is expected to be approved by the end of 2006 or early 2007 for use in patients with type 2 diabetes that is not well controlled on oral agents.

See Online for webtable

Liraglutide

Liraglutide, a partly DPP-4-resistant GLP-1 analogue, contains a Arg34Lys substitution, and a glutamic acid and 16-C free-fatty-acid addition to Lys26 (figure 2).[81] The acyl moiety promotes non-covalent binding to albumin with 1–2% of liraglutide circulating as the non-albumin-bound free peptide.[82] Liraglutide has a half-life of about 10–14 h after subcutaneous administration in human beings,[83,84] and can be given as a once daily injection. Early phase II studies were done with up to 0·75 mg per day of liraglutide,[31,85] but more recent studies with weekly escalating dose-titration have investigated the efficacy of doses up to 2·0 mg.[32] Liraglutide reduces fasting and postprandial glucose, and levels of HbA_{1c} by up to 1·75 % (figure 3),[33] while preventing weight gain or inducing modest but significant weight loss.[32,33] Nausea, vomiting, and diarrhoea were the most prominent adverse events but were generally mild, transient, and rarely caused discontinuation of liraglutide treatment.[32,33] So far, no studies of exposure to liraglutide have reported antibody formation, and phase III testing was started earlier this year.

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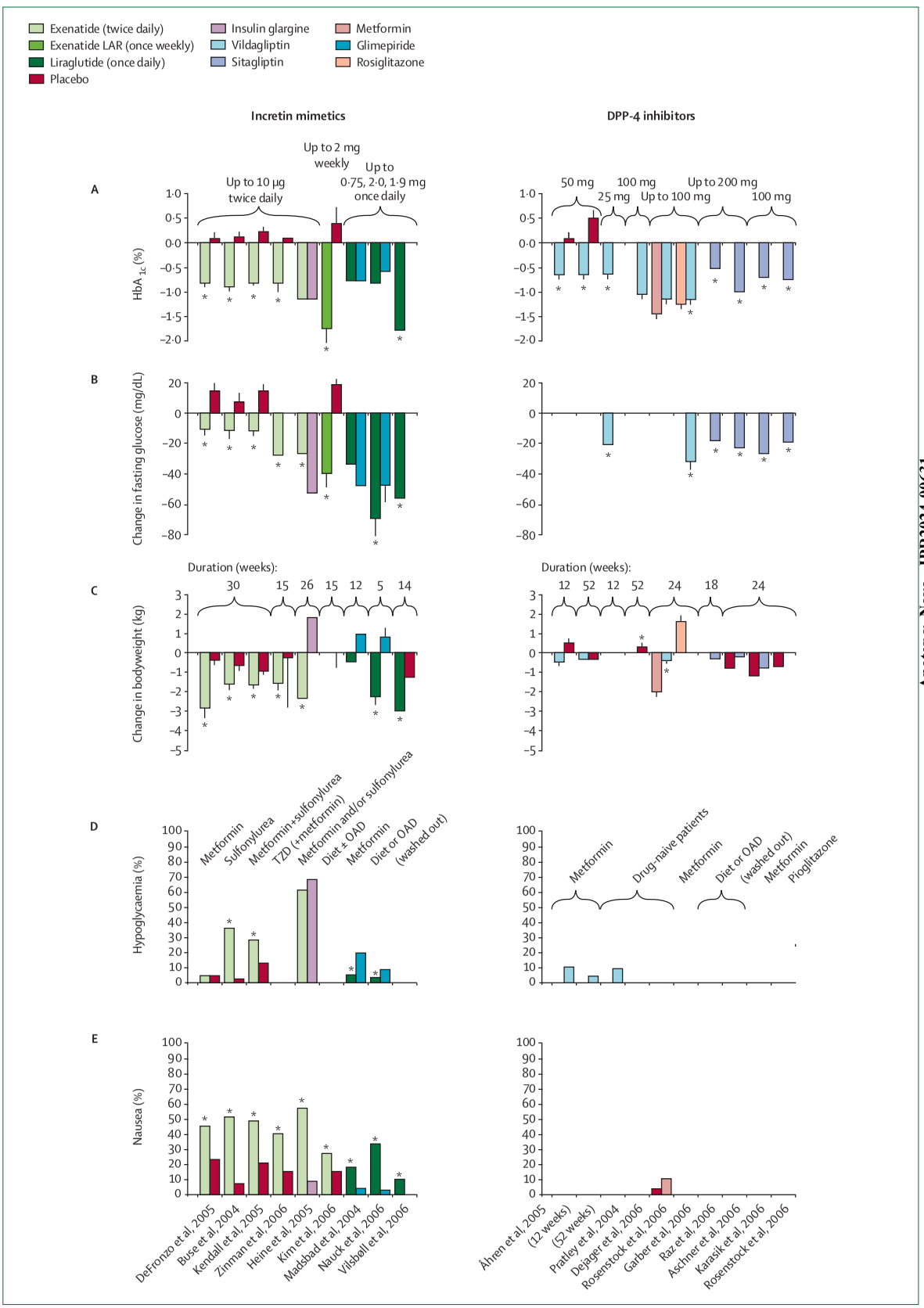

***Figure 3*: Clinical effects of GLP-1R agonists (incretin mimetics) and DPP-4 inhibitors (incretin enhancers) on HbA_{1c}, fasting glucose concentrations, bodyweight, hypoglycaemic episodes, and nausea**

Doses are indicated in top panels (A); concomitant medication is shown in lower panel (D). Results are from phase II or III studies on: exenatide;[25-29] exenatide LAR;[30] liraglutide;[31-33] vildagliptin;[34-38] and sitagliptin.[39-42] *Significant differences to placebo or respective comparator; if no comparator is shown, results are depicted as placebo-subtracted differences. Bars are mean and SE. OAD=oral antidiabetic agents.

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Long-acting GLP-1R agonists

Because one subcutaneous injection of exenatide does not produce effective glucose control for more than 6–8 h, there is considerable interest in the development of long-acting GLP-1R agonists that need less frequent parenteral administration. Exenatide long-acting release (LAR) is a polylactide-glycolide microsphere suspension containing 3% exendin-4 peptide that shows sustained dose-dependent glycaemic control in diabetic fatty Zucker rats for up to 28 days after one subcutaneous injection.[86] Preliminary experience with exenatide LAR in 45 patients with type 2 diabetes indicates a much greater reduction in fasting glucose concentrations and HbA_{1c} after once weekly administrations of exenatide LAR for 15 weeks compared with exenatide twice daily.[30] However, long-term experience with the drug in larger numbers of patients has not yet been reported. Exenatide LAR is currently being assessed in a phase III head-to-head trial against twice-daily exenatide.

Additional strategies for development of long-acting GLP-1R agonists include the use of chemical linkers to form covalent bonds between GLP-1 (CJC-1131) or exendin-4 (CJC-1134).[87] Similarly, recombinant albumin-GLP-1 proteins have been developed that mimic the full range of GLP-1 actions in preclinical studies.[88] Although these drugs are expected to have an extended pharmacokinetic profile suitable for once weekly dosing in diabetic patients, little clinical information is available about the efficacy and safety of these albumin-based drugs in human beings.

DPP-4 inhibitors

The observation that GLP-1 is rapidly degraded by DPP-4[5,89,90] has fostered the development of specific protease inhibitors that prevent the rapid fall of GLP-1 in circulating plasma after eating. DPP-4 is a ubiquitous membrane-spanning cell-surface aminopeptidase widely expressed in many tissues, such as liver, lung, kidney, intestinal brush-border membranes, lymphocytes, and endothelial cells.[91–93] The extracellular domain of DPP-4 can also be cleaved from its membrane-anchored form and circulate in plasma, where it retains its full enzymatic activity. DPP-4 preferentially cleaves peptides with a proline or alanine residue in the second aminoterminal position. Many gastrointestinal hormones, neuropeptides, cytokines, and chemokines are substrates for DPP-4,[91,93] among them both GIP[89,90,94] and GLP-1.[5,89,90,95] In preclinical studies, DPP-4 inhibitors mimic many of the actions ascribed to GLP-1R agonists, including stimulation of insulin and inhibition of glucagon secretion, and preservation of β-cell mass through stimulation of cell proliferation and inhibition of apoptosis.[7,96] By contrast, DPP-4 inhibitors are generally not associated with a deceleration of gastric emptying or weight loss, perhaps due to the modest stabilisation of postprandial levels of intact biologically active plasma GLP-1 (doubled to 15–25 pmol/L) seen after DPP-4 inhibition (table).

Many small-molecule DPP-4 inhibitors have been developed that specifically and potently inhibit DPP-4 activity after oral administration. Typically, these agents reduce serum DPP-4 activity by more than 80%, with some inhibition maintained for 24 h after one dose or with once daily treatment.[47,97] DPP-4 inhibition is accompanied by a rise in postprandial levels of intact GLP-1.[47,97,98] Most published studies used vildagliptin.[99]

Vildagliptin and sitagliptin

At a dose of 100 mg once daily, fasting and postprandial glucose concentrations were reduced after 4 weeks of vildagliptin treatment.[47] Plasma glucagon concentrations were suppressed after vildagliptin treatment, together with an increase in the ratio of insulin to glucose.[47] In clinical studies of longer duration, the addition of vildagliptin to patients already given metformin reduced HbA_{1c} by 0·8% after 12 weeks, compared with placebo,[34] and this difference was maintained during an open-label extension for 52 weeks[34] (figure 3). Indirect evidence from modelling experiments suggests that β-cell function is improved with vildagliptin treatment over 1 year in patients with type 2 diabetes.[100] Preliminary reports of longer phase III clinical studies with vildagliptin monotherapy, either 50 mg twice daily or 100 mg once daily, showed sustained efficacy but slight non-inferiority compared with metformin[36] after 1 year of therapy, although vildagliptin was better tolerated than metformin. Similarly, vildagliptin was as effective as rosiglitazone in direct comparison monotherapy study[37] and also produced significant reductions in HbA_{1c} when used in combination with metformin[38] (figure 3).

Clinical studies have also been reported for sitagliptin[97] (figure 3). Phase III clinical trial data presented at the American Diabetes Association meeting in June, 2006, indicated that sitagliptin is well-tolerated at doses of 100 mg once daily, either as monotherapy, or in combination with metformin or pioglitazone, without significant hypoglycaemia or weight gain.[40–42] Fewer data are available for other DPP-4 inhibitors in development such as saxagliptin[101] or denagliptin.[102] Thus whether various chemically distinct DPP-4 inhibitors will show significant differences in pharmacokinetic profiles, side-effects, or clinical activity cannot be predicted. Sitagliptin was approved for the treatment of type 2 diabetes in the USA in October, 2006.

No characteristic pattern of adverse events has been associated with the use of vildagliptin[34,47] or other DPP-4 inhibitors,[103-105] despite the large number of potential substrates for DPP-4.[91,93] In view of the widespread expression of DPP-4 on many cell types, including lymphocytes, there is considerable interest in the long-term safety profile of DPP-4 inhibitors. Although highly selective DPP-4 inhibition seems to be well tolerated in preclinical studies and DPP-4 inhibitors do not substantially inhibit cell proliferation in experiments with human lymphocytes in vitro,[106] considerable

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additional clinical experience with these agents will be needed before any theoretical safety concerns emerge. Furthermore, given the large number of chemically distinct DPP-4 inhibitors under clinical development, it seems likely that one or more of these agents could be associated with adverse events arising as a result of unique properties attributable to the individual chemical structure, as opposed to a class effect arising as a consequence of inhibition of DPP-4 activity. Non-selectivity for actions on the related enzymes DPP-8, DPP-9, or both, could be of particular importance.[106]

Contrasting properties of GLP-1R agonists and DPP-4 inhibitors

Twice daily exenatide through subcutaneous injection is indicated for the treatment of patients with type 2 diabetes mellitus in whom one or more oral agents do not work, often as an alternative to insulin treatment. By contrast, once daily DPP-4 inhibitors could be used as first-line therapy, or as add-on therapy to patients failing one or more oral agents. While there does not seem to be a great difference in the HbA_{1c}-lowering capacity of GLP-1R agonists compared with DPP-4 inhibitors, the obvious difference between these classes of drugs is their effect on bodyweight. Weight loss is a common outcome of therapy with native GLP-1,[22] exenatide,[25–27] and liraglutide,[32,75] whereas treatment with DPP-4 inhibitors is associated with prevention of weight gain[34,47,103,104] (figure 3). By contrast, gastrointestinal side-effects, predominantly nausea, are often reported after treatment with injectable GLP-1R agonists but have not been described with DPP-4 inhibition.[34,47,102–105] These differences might be explained in part by the relatively modest stabilisation of postprandial GLP-1 seen after DPP-4 inhibition, compared with the pharmacological increases in circulating levels of GLP-1R agonists exemplified by exenatide. Hence therapy with DPP-4 inhibitors might not be associated with weight loss perhaps partly because of the relative levels of GLP-1 achieved after treatment with these agents. Although nausea is a common side-effect of exenatide therapy, many patients lose weight independently of nausea. Consistent with the above differences in circulating levels of GLP-1, GLP-1R agonists, but not DPP-4 inhibitors, greatly decelerate gastric emptying.[69,107,108]

Future developments

Liraglutide and exenatide are first-generation GLP-1 receptor agonists, requiring once or twice daily parenteral administration, respectively. Much effort continues to be directed towards improvement of the pharmacokinetic profile of GLP-1R agonists, to minimise peak levels of the drug and thus reduce the extent of nausea. Longer-acting GLP-1R agonists should ideally provide more uniform and sustained GLP-1R activation over a 24-h period, but require less frequent administration.

Furthermore, there is great interest in determining whether chronic therapy with GLP-1R agonists will be associated with sustained long-term control of HbA_{1c} and improvement in β-cell function beyond that achievable with existing agents. Similar questions pertain to the DPP-4 inhibitors, which also indirectly target β cells; however, long-term clinical data assessing the durability and efficacy of these agents in the treatment of type 2 diabetes are not yet available. Because patients with type 2 diabetes have increased risks of cardiovascular morbidity and mortality, the observation that GLP-1R agonists improve myocardial function in human patients after myocardial infarction[109] highlights the need for studies that assess cardiovascular endpoints in patients treated with DPP-4 inhibitors or GLP-1R agonists. Overall, agents that enhance incretin action show great promise for the treatment of type 2 diabetes by recruitment of new, often physiologically based mechanisms of action for glucoregulation, in the context of a currently favourable safety profile. Nevertheless, long-term clinical studies are needed to compare these agents with existing oral therapies or insulin, or both, to permit a greater understanding of the true benefits and role of these drugs for the treatment of diabetes mellitus.

Conflict of interest statement

D J Drucker is an inventor or co-inventor on patents related to the field of type 2 diabetes that are licensed to Amylin Pharmaceuticals Inc or Arisaph Pharmaceuticals Inc. He has served as a consultant or adviser within the past 12 months to Abbott Laboratories, Amgen Inc, Amylin Pharmaceuticals, Bayer Inc, Chugai Inc, Conjuchem Inc, Eli Lilly Inc, GlaxoSmithKline, Glenmark Inc, Johnson & Johnson, Merck Research Laboratories, Novartis Pharmaceuticals, NPS Pharmaceuticals Inc, PPD Inc, Takeda Inc, Transition Pharmaceuticals Inc, and Arisaph Pharmaceuticals Inc. M A Nauck has received grants for the support of product-related studies from Amylin Pharmaceuticals, Eli Lilly & Co, Novartis Pharma, and NovoNordisk and consulting honoraria from Amgen, Amylin Pharmaceuticals, Bayer, ConjuChem, Eli Lilly & Co, GlaxoSmithKline, Merck, Sharp & Dohme, Novartis Pharma, NovoNordisk, and Takeda. He has received speaker's honoraria from Amylin Pharmaceuticals, ConjuChem, Eli Lilly & Co, Merck, Sharp & Dohme, Novartis Pharma, and NovoNordisk. He is a co-inventor on a patent related to the clinical use of GLP-1 that is licensed to Amylin Pharmaceuticals Inc. Neither author, nor their family members, hold stock directly or indirectly in any of these companies.

Acknowledgments

We thank Sabine Petrick for secretarial assistance. M A Nauck's studies received support from the Deutsche Forschungsgemeinschaft (grant Na 203/6-1), the Deutsche Diabetes-Gesellschaft, and the Nationales Aktionsforum Diabetes mellitus. D J Drucker is supported by a Canada Research Chair in Regulatory Peptides and work in the Drucker Laboratory on incretin hormones is supported by operating grants from the Juvenile Diabetes Research Foundation and the Canadian Diabetes Association. Research in the Drucker Laboratory is supported in part by grants from Novartis Inc, Amylin-Eli Lilly Inc, Merck Frosst Canada, and Novo Nordisk Inc.

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