Incretin-Based Therapies in Type 2 Diabetes Mellitus

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Context: Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide are incretins secreted from enteroendocrine cells postprandially in part to regulate glucose homeostasis. Dysregulation of these hormones is evident in type 2 diabetes mellitus (T2DM). Two new drugs, exenatide (GLP-1 mimetic) and sitagliptin [dipeptidyl peptidase (DPP) 4 inhibitor], have been approved by regulatory agencies for treating T2DM. Liraglutide (GLP-1 mimetic) and vildagliptin (DPP 4 inhibitor) are expected to arrive on the market soon.

Evidence Acquisition: The background of incretin-based therapy and selected clinical trials of these four drugs are reviewed. A MEDLINE search was conducted for published articles using the key words incretin, glucose-dependent insulinotropic polypeptide, GLP-1, exendin-4, exenatide, DPP 4, liraglutide, sitagliptin, and vildagliptin.

Evidence Synthesis: Exenatide and liraglutide are injection based. Three-year follow-up data on exenatide showed a sustained weight loss and glycosylated hemoglobin (HbA_{1c}) reduction of 1%. Nausea and vomiting are common. Results from phase 3 studies are pending on liraglutide. Sitagliptin and vildagliptin are orally active. In 24-wk studies, sitagliptin reduces HbA_{1c} by 0.6–0.8% as monotherapy, 1.8% as initial combination therapy with metformin, and 0.7% as add-on therapy to metformin. Vildagliptin monotherapy lowered HbA_{1c} by 1.0–1.4% after 24 wk. Their major side effects are urinary tract and nasopharyngeal infections and headaches. Exenatide and liraglutide cause weight loss, whereas sitagliptin and vildagliptin do not.

Conclusions: The availability of GLP-1 mimetics and DPP 4 inhibitors has increased our armamentarium for treating T2DM. Unresolved issues such as the effects of GLP-1 mimetics and DPP 4 inhibitors on β-cell mass, the mechanism by which GLP-1 mimetics lowers glucagon levels, and exactly how DPP 4 inhibitors lead to a decline in plasma glucose levels without an increase in insulin secretion, need further research. (***J Clin Endocrinol Metab*** **93: 3703–3716, 2008)**

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), termed "incretins," are enteroendocrine hormones released into the bloodstream from L and K cells dispersed throughout the gastrointestinal tract in response to ingested nutrients. They provide the additional stimulus to insulin secretion during oral glucose ingestion that is not present with iv glucose infusion (1, 2). These incretins increase insulin secretion in a glucose-dependent manner through activation of their specific receptors on β-cells.

In newly diagnosed type 2 diabetes mellitus (T2DM) with relatively good glycemic control [glycosylated hemoglobin (HbA_{1c}) ~6.9%], both GIP and GLP-1 secretion in response to glucose and mixed meal challenges are the same or even increased when compared with healthy subjects (3, 4). However, in long-standing T2DM with poor glycemic control (HbA_{1c} ~8–9%), the GLP-1 response is decreased, whereas GIP secretion is unchanged (5–7). In addition, insulin response to exogenous GLP-1 is 3- to 5-fold lower in T2DM. However, acute GLP-1 administration is able to increase insulin secretion to normal levels and to lower plasma glucose effectively (8, 9). In contrast, exogenous GIP, even at supraphysiological doses, has markedly reduced insulinotropic actions with little or no glucose-lowering effects in T2DM (9, 10). Therefore, therapeutic strategies for T2DM within the incretin field focused on the use of GLP-1, GLP-1

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Abbreviations: aGLP-1, Active glucagon-like peptide-1; DPP, dipeptidyl peptidase; FPG, fasting plasma glucose; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; GLP-1R, glucagon-like peptide-1 receptor; HbA_{1c}, glycosylated hemoglobin; NEP, neutral endopeptidase; PPG, postprandial glucose; tGLP-1, total glucagon-like peptide-1; T2DM, type 2 diabetes mellitus.

analogs, and GLP-1 receptor (GLP-1R) agonists or GLP-1 mimetics, and not GIP.

GLP-1, when administered at pharmacological doses, also has other noninsulinotropic effects beneficial for treating T2DM: suppression of glucagon secretion in the presence of hyperglycemia and euglycemia, but not hypoglycemia, leading to improved hepatic insulin resistance and glycemic control (11, 12); slowing of gastric emptying and gut motility, causing delayed nutrient absorption and dampened postprandial glucose (PPG) excursion (13); and increasing the duration of postprandial satiety, leading to lower food intake, weight loss, and improved insulin resistance (14–16). More importantly, acute GLP-1 infusion normalized fasting plasma glucose (FPG) in patients with long-standing, uncontrolled T2DM who were no longer responsive to sulfonylureas or metformin (17).

One major drawback of GLP-1 treatment is its short half-life (2 min) (18). GLP-1 is rapidly degraded by dipeptidyl peptidase (DPP) 4, which cleaves the N-terminal dipeptides (His^7-Ala^8) from GLP-1 (7–36) and renders the resulting major metabolite GLP-1 (9–36) inactive (Fig. 1) (19, 20). In addition, neutral endopeptidase (NEP) 24.11 hydrolyzes GLP-1 at six different places (21). With short half-life, bolus sc injections resulted in only a transient effect on insulin secretion and plasma glucose levels (22).

Nonetheless, in patients with T2DM, bolus sc administration of GLP-1 before breakfast, lunch, and dinner for 7 d significantly improved PPG and decreased plasma lipid levels (23). Overnight iv GLP-1 infusions lowered FPG and PPG to near-normal levels, markedly improved β-cell function, and restored first-phase insulin secretion, the absence of which is a hallmark of T2DM (24).

Continuous sc GLP-1 infusion via a pump for 6–12 wk improved glucose-induced insulin secretion, enhanced insulin-mediated glucose disposal, and increased insulin pulse mass and pulsatile insulin secretion in T2DM (25, 26). Six weeks of GLP-1 infusion also restored first-phase insulin secretion in T2DM, therefore, demonstrating the insulinotropic potency of long-term GLP-1 treatment (15).

Recent animal studies suggest that exogenous GLP-1 has the ability to increase islet size, enhance β-cell proliferation, inhibit β-cell apoptosis, and regulate islet growth (27, 28). These effects have tremendous implication in the treatment of T2DM because they directly address one of the fundamental defects in T2DM, *i.e.* β-cell failure.

Collectively, the aforementioned studies demonstrated the potential of using GLP-1-based therapy for treating T2DM. Two options for GLP-1-based therapies are GLP-1 mimetics resistant to DPP 4 activity, therefore, a longer half-life, and agents such as DPP 4 inhibitors, which increase plasma endogenous GLP-1 levels. In this review we will focus on: 1) exenatide (GLP-1 mimetic) and sitagliptin (DPP 4 inhibitor), which have been approved by regulatory agencies for treatment of T2DM, as well as liraglutide (GLP-1 mimetic) and vildagliptin (DPP 4 inhibitor), which are expected to arrive on the market soon; and 2) issues that are still open for debate regarding the actions of these agents.

GLP-1 Mimetics

Given that DPP 4 cleaves peptides with an alanine, proline, or hydroxyproline in the penultimate N-terminal position, various modifications of GLP-1 at His^7, Ala^8, or Glu^9 have been investigated (29). Additional mid-chain modifications of GLP-1 to prevent NEP hydrolysis are also being investigated to provide longer plasma half-life. Exenatide and liraglutide are two compounds that exhibit these characteristics.

Exenatide

Exenatide (synthetic exendin-4) is the only GLP-1R agonist approved by regulatory agencies as an adjunct therapy to patients with T2DM not achieving satisfactory glycemic control. It is a 39-amino acid peptide produced in the salivary glands of the Gila monster (*Heloderma suspectum*) with 53% amino acid homology to full-length GLP-1. It binds more avidly to GLP-1R than GLP-1 in GLP-1R-expressing cells (30). There appears to be no specific exendin-4 receptor. Exendin-4 is not a substrate for DPP 4 because it has a Gly^8 in place of an Ala^8 (Fig. 1). In addition, it lacks some of the target bonds for NEP, and its secondary and tertiary structures may also prevent NEP hydrolysis. Exenatide, being a peptide, must be injected sc, and is eliminated by the kidneys through glomerular filtration (31). It has a mean half-life of 3.3–4 h, is detected in the plasma 15 h after sc injection, and has biological effect 8 h after dosing (32).

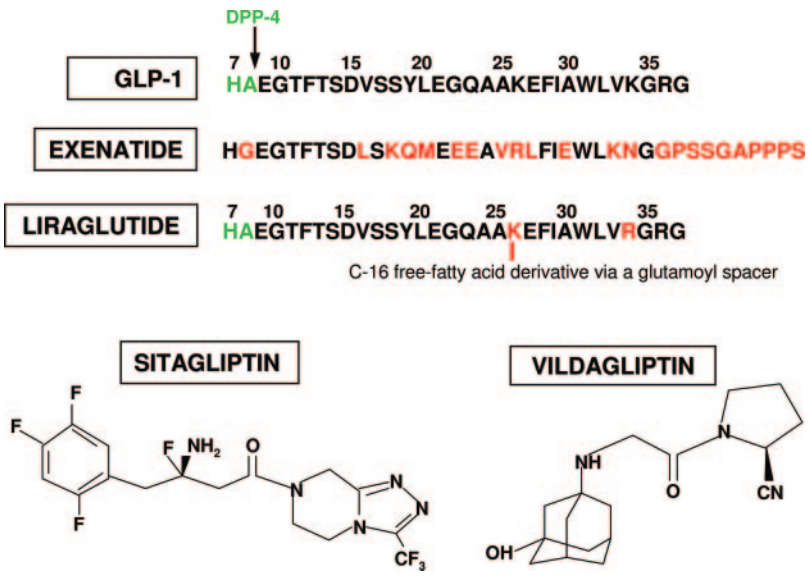

FIG. 1. Structure of native GLP-1, exenatide, liraglutide, sitagliptin, and vildagliptin. The N-terminal dipeptide "HA" of GLP-1 is cleaved by DPP 4, and the remaining fragment does not increase insulin secretion. For exenatide the substitution of glycine for alanine at position 8 prevents the degradation by DPP 4. The free-fatty acid derivative that is attached to liraglutide is thought to promote noncovalent binding of liraglutide to albumin.

Selected clinical studies

Clinical trials investigating exenatide as adjuvant therapy to patients with T2DM

not achieving adequate glycemic control on metformin and/or sulfonylurea, metformin and/or thiazolidinedione, as well as comparison trials with insulin glargine and biphasic insulin aspart, are summarized in Table 1 (33–39). With exenatide 10 μg twice daily as adjuvant therapy to oral hypoglycemic agents, a significant number of patients (32–62%) achieved HbA_{1c} of 7% or less when compared with placebo (7–13%), glargine (48%), and biphasic insulin aspart (24%), and HbA_{1c} reductions of 0.8–1.1% were sustained up to 3 yr. Progressive weight loss from 1.6–2.8 kg noted at 30 wk to 5.3 kg at 3 yr was also noted. Antiexenatide antibodies were detected in 41–49% of patients in the treatment arms but were not associated with glycemic control (33–38).

Side effects

A metaanalysis on the randomized controlled trials with exenatide showed that severe hypoglycemia was rare. Mild to moderate hypoglycemia was 16 *vs.* 7% (exenatide *vs.* placebo) and more common with coadministration with a sulfonylurea. The most common side effects of exenatide were nausea (57%) and vomiting (17%). Nausea was usually mild to moderate in nature, and being most common during the initial 8 wk therapy and declined thereafter. Overall, 4% of patients withdrew from the studies because of gastrointestinal side effects (40).

Liraglutide

Liraglutide is a long-acting GLP-1 analog with a substitution of Lys^{34} with Arg^{34}, and an attachment of a C-16 free-fatty acid derivative via a glutamoyl spacer to Lys^{26} (Fig. 1). The free-fatty acid derivative is thought to promote noncovalent binding of liraglutide to albumin, therefore, increasing plasma half-life through protection from renal clearance and slow absorption rate from injection site (41). Like GLP-1 and exenatide, liraglutide needs to be injected sc. After sc injection, maximum plasma concentrations are reached after 10–14 h, and it has a half-life of 11–13 h (42, 43).

Selected clinical trials

In a 5-wk dose-escalation study, liraglutide/metformin combination was associated with a 0.8% reduction in HbA_{1c} and a 70 mg/dl reduction in fasting glucose when compared with metformin alone. In addition, liraglutide/metformin significantly reduced fasting glucose (21.6 mg/dl) and body weight (2.9 kg) when compared with the metformin/glimepiride group, and liraglutide/placebo significantly reduced fasting glucose (25.2 mg/dl) when compared with the metformin/placebo group (Table 1) (44). In a 14-wk study of liraglutide *vs.* placebo, liraglutide significantly reduced HbA_{1c} by 1.45, 1.40, and 0.98% in the 1.90, 1.25, and 0.65-mg groups, respectively, whereas placebo group had an increase of 0.29% in HbA_{1c}. The percentages of patients that achieved HbA_{1c} of 7% or less were 46, 48, 38, and 5 in the 1.9, 1.25, 0.65-mg groups and the placebo group, respectively (Table 1) (45). The results from phase 3 trials have not been presented at scientific meetings or published in peer-reviewed journals.

Side effects

Most frequently reported adverse events were nausea and vomiting, especially at the higher doses (40, 45). There is also no development of antibodies noted in trials up to 14 wk (45–47).

Unresolved Issues Regarding GLP-1 and GLP-1 Mimetics

1. Does GLP-1 and GLP-1 mimetics have favorable effects on β-cell mass in humans?

Studies have shown that exenatide has favorable effects on parameters of β-cell function in humans using indirect measures such as first-phase insulin secretion and homeostasis model assessment β-cell index (48, 49). In rodent studies, GLP-1 induced glucose sensitivity in glucose-resistant β-cells (50). Exenatide given to rodents in pharmacological doses appeared to have beneficial effects on β-cell mass not seen with other antidiabetic agents. However, whether exenatide has a favorable effect on β-cell mass in humans is unknown.

Exenatide prevented cytotoxic agent-induced apoptosis of rodent islets (51), and chronic treatment increased β-cell turnover in rodents (52). GLP-1 also inhibited nonchemically induced β-cell apoptosis in freshly isolated human islets (53). Both decreased apoptosis and increased β-cell turnover should and do lead to increases in islet size and β-cell numbers. The trophic effects of exenatide on β-cells in rodents are seen with concentrations not achieved in clinical practice. Although markers of β-cell function show improvement in humans with chronic exenatide use of up to 3 yr (39), this improvement in function may be due to the restoration of glucose-competence to β-cells and the insulinotropic, glucose-lowering, and weight-loss effects of exenatide, and not because of any direct effect of exenatide on β-cell mass.

2. What is the mechanism by which GLP-1 and GLP-1 mimetics lower glucagon secretion from α-cells?

Elevated fasting and postprandial plasma glucagon levels throughout the day are a feature of T2DM (54), and exenatide treatment lowers both (55). The ability for exenatide and GLP-1 to lower glucagon levels in patients with T2DM most likely contributes to its overall glucose-lowering effect. In addition, by virtue of enhancing endogenous insulin secretion concurrently with suppressing glucagon secretion, a more physiological insulin to glucagon ratio in the portal vein should be established, resulting in better suppression of hepatic glucose output. Whether GLP-1 and GLP-1 mimetics lower glucagon secretion from α-cells through direct or indirect mechanisms is still unclear.

The presence of GLP-1R on human α-cells has not been directly investigated. Overnight iv GLP-1 administration to fasted subjects with type 1 diabetes mellitus resulted in the lowering of plasma glucagon levels that was postulated to be a direct effect of GLP-1 on α-cells (56). However, given that plasma C-peptide levels were doubled by GLP-1 infusion, an indirect action mediated by the stimulatory effect of GLP-1 on residual neighboring β (or δ) cells resulting in intraislet paracrine inhibition of gluca-

TABLE 1. Summaries of selected clinical trials on exenatide, liraglutide, sitagliptin, and vildagliptin

Prior glycemic treatment	Length	Trial design	Intervention	No. of subjects randomized	No. of subjects completed	Baseline HbA_{1c} (%)	Baseline FPG (mg/dl)	Δ HbA_{1c} (%) baseline	Baseline HbA_{1c} (%)[d]	% Achieved HbA_{1c} ≤7%	Δ FPG (mg/dl) baseline	Δ Weight (lb) baseline
Exenatide												
Sulfonylurea (34) (trial A)	30 wk	Randomized, triple-blind, placebo-controlled	Placebo plus sulfonylurea	123	74	8.7 (1.2)	194 (58)	+0.1 ± 0.1		9	+7.2 ± 5.4	−0.6 ± 0.3
			Exenatide 5 μg bid plus sulfonylurea	125	95	8.5 (1.1)	180 (45)	−0.5 ± 0.1		33	−5.4 ± 3.6	−0.9 ± 0.3
			Exenatide 10 μg bid plus sulfonylurea	129	91	8.6 (1.2)	178 (50)	−0.9 ± 0.1		41	−10.8 ± 5.4	−1.6 ± 0.3
Metformin (33) (trial B)	30 wk	Randomized, triple-blind, placebo-controlled	Placebo plus metformin	113	89	8.2 (1.0)	170 (40)	+0.1 ± 0.1		13	+14.4 ± 4.2	−0.3 ± 0.3
			Exenatide 5 μg bid plus metformin	110	90	8.3 (1.1)	176 (43)	−0.4 ± 0.1		32	−7.2 ± 4.6	−1.6 ± 0.4
			Exenatide 10 μg bid plus metformin	113	93	8.2 (1.0)	168 (46)	−0.8 ± 0.1		46	−10.1 ± 4.4	−2.8 ± 0.5
Sulfonylurea/metformin (35) (trial C)	30 wk	Randomized, double-blind, placebo-controlled	Placebo plus metformin/sulfonylurea	247	188	8.5 (1.0)	180 (49)	+0.2 ± 0.1		9	+14.4 ± 3.6	−0.9 ± 0.2
			Exenatide 5 μg bid plus metformin/sulfonylurea	245	206	8.5 (1.0)	182 (52)	−0.6 ± 0.1		27	−9.0 ± 3.6	−1.6 ± 0.2
			Exenatide 10 μg bid plus metformin/sulfonylurea	241	199	8.5 (1.1)	178 (43)	−0.8 ± 0.1		34	−10.8 ± 3.6	−1.6 ± 0.2
TZD with/without metformin (36)	16 wk	Randomized, double-blind, placebo-controlled	Placebo plus TZD with/without metformin	112	96	7.9 (0.8)	159 (34)	+0.1 ± 0.1		16	+1.8 ± 3.8	−0.2 ± 0.3
			Exenatide 10 μg bid plus TZD with/without metformin	121	86	7.9 (0.9)	164 (47)	−0.9 ± 0.1		62	−28.6 ± 4.0	−1.8 ± 0.3
Sulfonylurea/metformin (37)	26 wk	Randomized, open-label, controlled	Exenatide 10 μg bid plus metformin/sulfonylurea	282	228	8.2 (1.0)	182 (47)	−1.1		46	−25.7	−2.3
			Glargine approximately 25 U/d plus metformin/ sulfonylurea	267	242	8.3 (1.0)	187 (52)	−1.1		48	−51.5	+1.8
Sulfonylurea/metformin (38)	52 wk	Randomized, open-label, noninferiority	Exenatide 10 μg bid plus metformin/sulfonylurea	253	199	8.6 (1.0)	198 (49)	−1.0 ± 0.1		32	−32.4 ± 3.6	−2.5 ± 0.2
			Biphasic aspart (30% insulin aspart) plus metformin/ sulfonylurea	248	223	8.6 (1.1)	203 (50)	−0.9 ± 0.1		24	−30.6 ± 3.6	+2.9 ± 0.2
Metformin and/or sulfonylurea (39)	≥3 yr	Trials A–C (above) and their open-label extensions were folded into one open-ended, open-label trial	Exenatide 10 μg bid plus metformin and/or sulfonylurea	527	217	8.2 (1.0)	172 (45)	−1.0 ± 0.1		46	−23.5 ± 3.8	−5.3 ± 0.4

(Continuous)

TABLE 1. (Continued)

Prior glycemic treatment	Length	Trial design	Intervention	No. of subjects randomized	No. of subjects completed	Baseline HbA_{1c} (%)	Baseline FPG (mg/dl)	Δ HbA_{1c} (%) baseline	Baseline HbA_{1c} (%)[d]	% Achieved HbA_{1c} ≤7%	Δ FPG (mg/dl) baseline	Δ Weight (lb) baseline
Liraglutide												
Two or less oral hypoglycemic agents (except TZD) (44)	5 wk	Randomized, double-blind (liraglutide titration 0.5–2.0 mg in 0.5 mg increment weekly) plus 2-wk run-in with metformin	Liraglutide plus metformin 1000 mg bid	36	34	9.5 (1.0)	238 (45)	−0.8[a]			−70.2[a]	−2.2
			Liraglutide plus placebo	36	30	9.4 (0.8)	239 (45)	−0.2[a]			−25.2[a]	−2.1
			Metformin 1000 mg bid plus placebo	36	25	9.4 (0.8)	243 (52)					−1.7
		Randomized, open label	Metformin 1000 mg bid plus glimepiride 4 mg qd	36	36	9.4 (1.2)	234 (47)	−0.3[b]			−21.6[b]	+0.8
One oral hypoglycemic agent (45)	14 wk	Randomized, double-blind, placebo-controlled (previous hypoglycemic agent discontinued)	Placebo	40	29	8.2 (0.7)	203 (40)	+0.3		5		
			Liraglutide 0.65 mg qd	40	35	8.1 (0.6)	203 (49)	−1.0		38	−48.6[c]	
			Liraglutide 1.25 mg qd	42	39	8.3 (0.8)	214 (43)	−1.4		48	−61.2[c]	
			Liraglutide 1.90 mg qd	41	37	8.5 (0.9)	221 (56)	−1.5		46	−61.2[c]	−3.0
Sitagliptin												
Diet or one oral hypoglycemic agent (72, 77)	24 wk	Randomized, double-blind, placebo-controlled (washout period)	Placebo	253	216	8.0 (0.8)	176.4 (41.4)	+0.2		17	+5.4	−1.1 ± 0.2
			Sitagliptin 100 mg qd	238	209	8.0 (0.9)	171.0 (43.2)	−0.6		41	−12.6	−0.2 ± 0.2
			Sitagliptin 200 mg qd	250	214	8.1 (0.9)	174.6 (45.0)	−0.8		45	−16.2	−0.1 ± 0.2
	30-wk extension	Randomized	Sitagliptin 100 mg qd	188		7.9		−0.6		41		
			Sitagliptin 200 mg qd	194		8.0		−0.6		46		
Diet and exercise (73, 78)	24 wk	Randomized, double-blind, placebo-controlled, parallel-group	Placebo	176	127	8.7 (1.0)	196.3 (47.4)	+0.2		9	+5.8	−0.9
			Sitagliptin 100 mg qd	179	142	8.9 (1.0)	201.4 (49.4)	−0.7		20	−17.5	0.0
			Metformin 500 mg bid	182	153	8.9 (1.0)	205.2 (50.6)	−0.8		23	−27.3	−0.6 to −1.3
			Metformin 1000 mg bid	182	156	8.7 (0.9)	197.0 (46.8)	−1.1		38	−29.3	−0.6 to −1.3
			Sitagliptin 50 mg bid plus metformin 500 mg bid	190	164	8.8 (1.0)	203.9 (51.7)	−1.4		43	−47.1	−0.6 to −1.3
			Sitagliptin 50 mg bid plus metformin 1000 mg bid	182	164	8.8 (1.0)	196.7 (48.2)	−1.9		66	−63.9	−0.6 to −1.3
	30-wk extension	Double-blind, active-controlled phase	Sitagliptin 100 mg qd	100		Mean HbA_{1c} 8.7%		−0.8		23		
			Metformin 500 mg bid	122		Mean HbA_{1c} 8.7%		−1.0		25		
			Metformin 1000 mg bid	137		Mean HbA_{1c} 8.7%		−1.3		44		
			Sitagliptin 50 mg bid plus metformin 500 mg bid	148		Mean HbA_{1c} 8.7%		−1.4		48		
			Sitagliptin 50 mg bid plus metformin 1000 mg bid	157		Mean HbA_{1c} 8.7%		−1.8		67		
Pioglitazone (74)	24 wk	Randomized, double-blind, placebo-controlled, parallel group	Placebo plus pioglitazone 30–45 mg qd	178	158	8.0 (0.8)	165.6 (39.9)	−0.2		23	+1.0	+1.5
			Sitagliptin 100 mg qd plus pioglitazone 30–45 mg qd	175	149	8.1 (0.8)	168.3 (39.5)	−0.9		45	−16.7	+1.8

(Continuous)

TABLE 1. (Continued)

Prior glycemic treatment	Length	Trial design	Intervention	No. of subjects randomized	No. of subjects completed	Baseline HbA_{1c} (%)	Baseline FPG (mg/dl)	Δ HbA_{1c} (%) baseline	Baseline HbA_{1c} (%)[d]	% Achieved HbA_{1c} ≤7%	Δ FPG (mg/dl) baseline	Δ Weight (lb) baseline
Sitagliptin (continued)												
Metformin (75)	24 wk	Randomized, double-blind, placebo-controlled, parallel group	Placebo plus metformin ≥1500 mg/d	237	192	8.0 (0.8)	172.8 (41.4)	0.0		18	+9.0	
			Sitagliptin 100 mg qd plus metformin ≥1500 mg/d	464	416	8.0 (0.8)	169.2 (41.4)	−0.7		47	−16.2	
	30-wk extension	Double-blind, active-controlled (placebo switched to glipizide)	Glipizide 5–15 mg/d plus metformin ≥1500 mg/d	157		7.9		−0.9		61		+1.5
			Sitagliptin 100 mg qd plus metformin ≥1500 mg/d	387		7.9		−0.7		51		−0.9
Glimepiride or glimepiride/ metformin (76)	24 wk	Randomized, double-blind, placebo-controlled, parallel group	Placebo plus glimepiride ≥ 4 mg/d	106	87	8.4 (0.8)	184.9 (42.3)	+0.3		9	+18.4	0.0
			Placebo plus glimepiride ≥ 4 mg/d plus metformin ≥1500 mg/d	113	92	8.3 (0.7)	178.4 (42.6)	+0.3		1	+12.9	−0.7
			Sitagliptin 100 mg qd plus glimepiride ≥4 mg/d	106	83	8.4 (0.8)	182.6 (33.1)	−0.3		11	−0.88	+1.1
			Sitagliptin 100 mg qd plus glimepiride ≥4 mg/d plus metformin ≥1500 mg/d	116	102	8.3 (0.7)	179.4 (41.6)	−0.6		23	−7.8	+0.4
Metformin (80)	52 wk	Randomized, double-blind, active-controlled, parallel-group, noninferiority trial	Sitagliptin 100 mg qd plus metformin ≥1500 mg/d	588	386	7.5 (0.8)	157.7 (33.7)	−0.7		63	−10.1	−1.5
			Glipizide 5–20 mg/d plus metformin ≥1500 mg/d	584	412	7.5 (0.9)	159.1 (38.5)	−0.7		59	−7.6	+1.1
Vildagliptin												
Drug naive (91, 92)	52 wk	Randomized, double-blind, placebo-controlled, parallel group	Placebo	150	131	6.8 (0.4)	129.6 (21.6)	+0.1 ± 0.1			+9.0 ± 1.8	−0.2 ± 0.3
			Vildagliptin 50 mg qd	156	133	6.7 (0.4)	127.8 (21.6)	−0.2 ± 0.1			+3.6 ± 1.8	−0.5 ± 0.3
	4-wk washout, 52-wk extension		Placebo	63	50	6.7 (0.4)	126.0 (18.0)	+0.5 ± 0.1			+21.6 ± 5.4	−0.3 ± 0.4
			Vildagliptin 50 mg qd	68	58	6.6 (0.4)	122.4 (18.0)	+0.1 ± 0.1			+10.8 ± 5.4	−1.1 ± 0.5
Drug naive (93)	24 wk	Randomized, double-blind, placebo-controlled, parallel group	Placebo	160	119	8.4 (0.8)	178.2 (45.0)	−0.3 ± 0.1			−1.8	−1.4 ± 0.4
			Vildagliptin 50 mg qd	163	130	8.2 (0.8)	176.4 (43.2)	−0.8 ± 0.1			−18.0	−1.8 ± 0.4
			Vildagliptin 50 mg bid	152	128	8.6 (0.8)	181.8 (39.6)	−0.8 ± 0.1			−14.4	−0.3 ± 0.4
			Vildagliptin 100 mg qd	157	134	8.4 (0.8)	178.2 (41.4)	−0.9 ± 0.1			−14.4	−0.8 ± 0.4
Drug naive (94)	52 wk	Randomized, double-blind, active-controlled, parallel group	Vildagliptin 50 mg bid	526	378	8.7 (1.1)	189.0 (52.2)	−1.0 ± 0.1			−16.2 ± 1.8	+0.3 ± 0.2
			Metformin 1000 mg bid	254	191	8.7 (1.1)	189.0 (52.2)	−1.4 ± 0.1			−34.2 ± 3.6	−1.9 ± 0.3
Drug naive (95)	24 wk	Randomized, double-blind, active-controlled, parallel group	Vildagliptin 50 mg bid	519	446	8.7 (1.1)	185.4 (48.6)	−1.1 ± 0.1			−23.4 ± 1.8	−0.3 ± 0.2
			Rosiglitazone 8 mg qd	267	232	8.7 (1.1)	185.4 (52.2)	−1.3 ± 0.1			−41.4 ± 3.6	+1.6 ± 0.3
Drug naive (96)	24 wk	Randomized, double-blind, active-controlled, parallel group	Pioglitazone 30 mg qd	161	133	8.7 (1.0)	189.0 (55.8)	−1.4 ± 0.1		43	−34.2 ± 3.6	+1.5 ± 0.3
			Vildagliptin50 mg qd plus pioglitazone 15 mg qd	144	115	8.8 (0.9)	192.6 (48.6)	−1.7 ± 0.1		54	−43.2 ± 3.6	+1.4 ± 0.3
			Vildagliptin100 mg qd plus pioglitazone 30 mg qd	148	129	8.8 (1.1)	196.2 (48.6)	−1.9 ± 0.1		65	−50.4 ± 3.6	+2.1 ± 0.3
			Vildagliptin 100 mg qd	154	136	8.6 (1.0)	190.8 (48.6)	−1.1 ± 0.1		43	−23.4 ± 3.6	+0.2 ± 0.3
Drug naive (97)	24 wk	Randomized, double-blind, active-controlled, parallel group	Vildagliptin 50 mg bid	441	399	8.6 (0.9)	180.0 (43.2)	−1.4 ± 0.1		46	−21.6 ± 1.8	−0.4 ± 0.1
			Acarbose up to 100 mg tid	220	192	8.6 (1.0)	183.6 (45.0)	−1.3 ± 0.1		47	−27.0 ± 3.6	−1.7 ± 0.2

(Continuous)

TABLE 1. (Continued)

Prior glycemic treatment	Length	Trial design	Intervention	No. of subjects randomized	No. of subjects completed	Baseline HbA_{1c} (%)	Baseline FPG (mg/dl)	Δ HbA_{1c} (%) baseline	Baseline HbA_{1c} (%)[d]	% Achieved HbA_{1c} ≤7%	Δ FPG (mg/dl) baseline	Δ Weight (lb) baseline
Vildagliptin (continued)												
Sulfonylurea (98)	24 wk	Randomized, double-blind, placebo-controlled	Placebo plus glimepiride 4 mg qd	176	108	8.5 (1.0)	185.4 (52.2)	+0.1 ± 0.1		12	+3.6 ± 3.6	−0.4 ± 0.3
			Vildagliptin 50 mg qd plus glimepiride 4 mg qd	170	113	8.5 (0.9)	189.0 (54.0)	−0.6 ± 0.1		21	−5.4 ± 3.6	−0.1 ± 0.3
			Vildagliptin 50 mg bid plus glimepiride 4 mg qd	169	111	8.6 (1.0)	189.0 (48.6)	−0.6 ± 0.1		25	−7.2 ± 3.6	+1.3 ± 0.3
Metformin (99)	24 wk	Randomized, double-blind, placebo-controlled, parallel group	Placebo plus metformin ≥1500 mg/d	182	152	8.3 (0.9)	181.8 (43.2)	+0.2 ± 0.1	≤7.9 7.9–8.5 >8.5	14 13 2		
			Vildagliptin 50 mg qd plus metformin ≥1500 mg/d	177	153	8.4 (0.9)	174.6 (39.6)	−0.5 ± 0.1	≤7.9 7.9–8.5 >8.5	50 22 8		
			Vildagliptin 50 mg bid plus metformin ≥1500 mg/d	185	157	8.4 (1.0)	178.2 (46.8)	−0.9 ± 0.1	≤7.9 7.9–8.5 >8.5	54 31 16		
TZD (100)	24 wk	Randomized, double-blind, placebo-controlled, parallel group	Placebo plus pioglitazone 45 mg qd	158	128	8.7 (1.2)	181.8 (54.0)	−0.3 ± 0.1		15	−9.0 ± 3.6	
			Vildagliptin 50 mg qd plus pioglitazone 45 mg qd	147	124	8.6 (1.0)	185.4 (52.2)	−0.8 ± 0.1		29	−14.4 ± 3.6	
			Vildagliptin 50 mg bid plus pioglitazone 45 mg qd	158	124	8.7 (1.2)	180.0 (59.4)	−1.0 ± 0.1		36	−19.8 ± 3.6	
Insulin (101)	24 wk	Randomized, double-blind, placebo-controlled, parallel group	Placebo plus insulin	152	124	8.4 (1.1)	156.6 (55.8)	−0.2 ± 0.1			−3.6 ± 7.2	0.6 ± 0.3
			Vildagliptin 50 mg bid plus insulin	144	114	8.4 (1.0)	167.4 (55.8)	−0.5 ± 0.1			−14.4 ± 5.4	1.3 ± 0.3
Metformin (102)	24 wk	Randomized, double-blind, active-controlled	Vildagliptin 50 mg bid plus metformin ≥1500 mg/d	295	262	8.4 (1.0)	196.2 (46.8)	−0.9 ± 0.1		27%	−25.2 ± 1.8	+0.3 ± 0.2
			Pioglitazone 30 mg qd plus metformin ≥1500 mg/d	281	244	8.4 (0.9)	198.0 (48.6)	−1.0 ± 0.1		36%	−37.8 ± 1.8	+1.9 ± 0.2

Data are presented as mean (SD) or mean ± SE. bid, Twice daily; qd, every day; tid, three times a day; TZD, thiazolidinedione.

[a] Change relative to metformin therapy.

[b] Change relative to liraglutide and metformin combination therapy.

[c] Change relative to placebo.

[d] This column only applies to the Vildagliptin trial (99).

gon release is also plausible, though at considerably lower insulin concentrations than in healthy or T2DM subjects. A transgenic model of β-cell dysfunction also favors a paracrine effect of GLP-1 on glucagon secretion. Mice with a β-cell-specific mutation of the *pdx-1* gene had defective insulin secretory and glucagon suppressive responses to exenatide, both of which were present in wild-type mice (57). This strongly suggests that a β-cell secreted factor is absolutely necessary for GLP-1-mediated suppression of glucagon secretion.

Rodent data on the presence or absence of GLP-1R on α-cells are not convincing either way. Neither GLP-1Rs nor their transcripts could be detected in purified rat α-cells (58, 59). Direct GLP-1 application to rat α-cells did not alter glucagon secretion or cause an increase in cAMP levels. However, GLP-1R expression was detected by immunocytochemistry in a subpopulation (20%) of glucagon-positive cells in dispersed rat islets (60). Because this is a small number of cells and the cells were not obtained with precise methodology, such as laser-captured microscopy, contaminating cells may be the source of the GLP-1R expression.

Furthermore, GLP-1 was also recently reported to elicit an increase in the cAMP content and glucagon secretion in an α-cell line transfected with the GLP-1Rs (61). Therefore, if α-cells actually contain GLP-1Rs, increased glucagon secretion would be the expected response to elevated plasma GLP-1 levels or exenatide therapy. Finally, neuronal control of glucagon secretion through the autonomic nervous system is well recognized, and this pathway may be mediated by GLP-1. Therefore, GLP-1 and exenatide infusion may cause glucagon suppression *in vivo* via feedback from vagal afferents where neuronal networks are intact but not *in vitro* from dispersed α-cells or cell lines. Regardless, the mechanism underlying suppressed plasma glucagon levels by exenatide is an interesting area of research and may offer insights as to how glucagon secretion might be controlled in T2DM.

DPP 4 Inhibitors

If pharmacological levels of exogenous GLP-1 can lower blood glucose in T2DM, it is logical to assume that supraphysiological levels of endogenous active GLP-1 (aGLP-1) can also lower blood glucose. No secretagogue of L cells has been specifically developed, though clear headway has been made in elucidating how food products bring about GLP-1 secretion from L cells (Fig. 2) (62–64). Compared with wild-type mice, DPP knockout mice have elevated fasting incretin levels, lower plasma glucose, and higher plasma insulin levels after a glucose challenge (65). There has been immense interest at disrupting DPP 4 activity in humans to increase plasma aGLP-1 levels. Sitagliptin and vildagliptin are two such DPP 4 inhibitors.

Sitagliptin

Sitagliptin, an organic molecule, appears to be selective for DPP 4 and not interact with other closely related proteases (Fig. 1) (66). Sitagliptin is rapidly absorbed, achieving peak plasma levels 1–6 h after dosing. Its half-life is 8–14 h with bioavailability of 87%, with or without food (67, 68). About 80% of the dose is excreted unchanged by the kidney, with 15% of the bioavailable drug metabolized by CYP3A4 and CYP2C8 in the liver (67, 69). At 100 mg daily, greater than 80% of plasma DPP 4 activity is inhibited over a 24-h period (67, 70). A dose reduction to 50 mg is needed if creatinine clearance is less than 50 ml/min and to 25 mg if creatinine clearance is less than 30 ml/min (71).

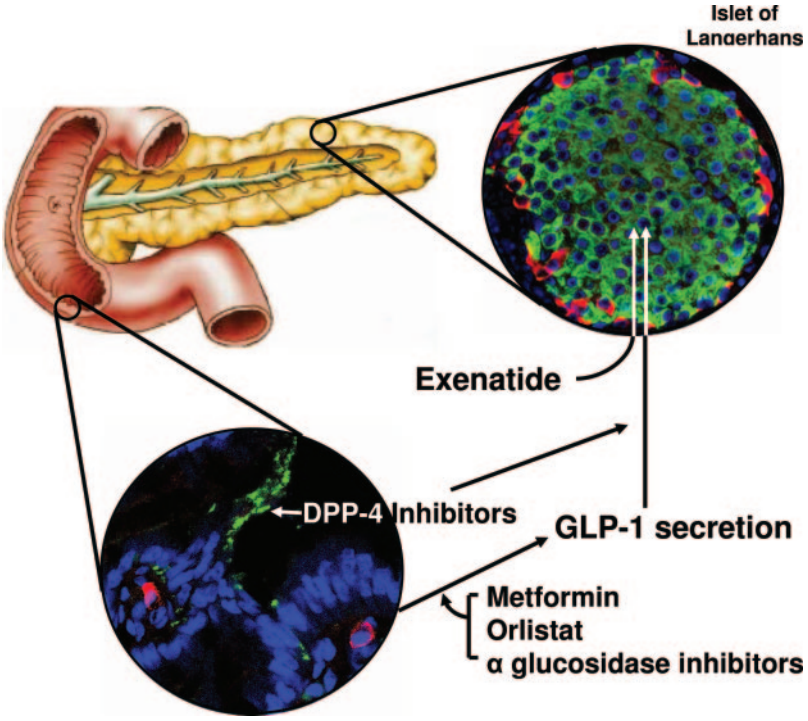

FIG. 2. Mechanism of action of sitagliptin, vildagliptin, and exenatide. GLP-1 is released from L cells (stained *red*) of the gut, and is subject to DPP 4 (stained *green* on endothelial cells of blood vessels of the gut) degradation in both gut and blood. Sitagliptin and vildagliptin inhibit DPP 4 action in blood and on endothelial cells. Metformin, orlistat, and α-glucosidase inhibitors increase GLP-1 secretion. Exenatide, a GLP-1R agonist, increases insulin secretion from β-cells (stained *green*) in islets of Langerhans. The α-cells in islets are stained *red*.

Selected clinical studies

Five 24-wk trials in T2DM patients examined the following: sitagliptin monotherapy; comparison of sitagliptin monotherapy, metformin monotherapy, and initial combination therapy of sitagliptin and metformin; sitagliptin added to ongoing pioglitazone; sitagliptin added to ongoing metformin; and sitagliptin added to ongoing sulfonylurea and/or metformin (Table 1) (72–76). As initial therapy, sitagliptin/metformin combination therapy worked better than either sitagliptin or metformin monotherapy with an HbA_{1c} reduction of 1.9% compared with 0.6–0.7% and 1.13% after 24 wk. As adjuvant therapy, sitagliptin in combination

with metformin, glipizide, or pioglitazone yielded an HbA_{1c} reduction of 0.6–0.7% when compared with placebo.

Preliminary results from 30-wk extension trials on sitagliptin monotherapy, initial sitagliptin combination therapy with or without metformin, and sitagliptin as adjuvant therapy to metformin showed that the reduction in HbA_{1c} was sustained at wk 54 (77–79). A 52-wk trial on sitagliptin *vs.* glipizide as adjuvant therapy to metformin showed a reduction in HbA_{1c} of 0.7% in both groups, however, the maximal HbA_{1c} reduction was observed at 24–30 wk with a gradual increase in HbA_{1c} from wk 30–52, which raises the issue of declining sitagliptin efficacy (80). Sitagliptin is reported to be weight neutral. Currently, there is an ongoing study on adding sitagliptin to exogenous insulin in patients with or without metformin treatment (81).

Side effects

A pooled analysis of 5141 patients in clinical trials for 2 yr or less showed that sitagliptin monotherapy or combination therapy (metformin, pioglitazone, sulfonylurea, or sulfonylurea and metformin) was well tolerated, and hypoglycemia occurred in the setting of combination therapy (82). The adverse events that were higher with sitagliptin compared with nonexposed groups included nasopharyngitis, contact dermatitis, and osteoarthritis. A systematic review and metaanalysis of incretin therapies showed that sitagliptin has no risk of gastrointestinal adverse events but has an increase risk for urinary track infection, headache, and especially nasopharyngitis (40), and may reflect a lack of DPP 4 activity required for immunosurveillance.

Vildagliptin

Vildagliptin, a selective, reversible, and competitive inhibitor of DPP 4, is a low molecular weight compound suitable for oral dosing (83, 84). After dosing, vildagliptin is rapidly absorbed and achieves peak plasma levels in 1–2 h. Its half-life of 2 h is shorter than sitagliptin (85, 86). Its bioavailability is 85% (87), and its pharmacokinetics is not affected by food (88). At 100 mg daily, it inhibits 98% of DPP 4 activities 45 min after dosing and 60% at 24 h. Approximately 85% of vildagliptin is metablolized in the liver to LAY151 by hydrolysis: LAY151 is inactive. The remaining 15% is eliminated unchanged by the kidneys (89). A study suggested that there was no significant difference in exposure to vildagliptin in patients with various degrees of hepatic impairment (89). In 2007, the Food and Drug Administration requested additional data on patients with renal impairment before granting final approval of vildagliptin (90).

Selected clinical trials

Six clinical trials evaluated vildagliptin as initial monotherapy in comparison to placebo, metformin, rosiglitazone, or acarbose, and also as initial combination therapy with pioglitazone in comparison to vildagliptin monotherapy in drug-naive patients with T2DM (Table 1) (91–97). Patients with worse glycemic control (HbA_{1c} ~8.4 *vs.* 6.7%) had bigger HbA_{1c} reduction over 24 wk. Data from the extension study on the group with better glycemic control showed that maximum HbA_{1c} reduction occurred around 24–30 wk, followed by a gradual increase thereafter until wk 108 (92). As monotherapy, vildagliptin 50 mg twice daily was as effective as rosiglitazone 8 mg once daily and acarbose 100 mg thrice daily in lowering HbA_{1c} but not as effective as metformin 1000 mg twice daily (94, 95, 97). Initial combination therapy with vildagliptin and pioglitazone provided better glycemic control than either vildagliptin or pioglitazone monotherapy (96).

Vildagliptin is effective as adjuvant therapy when administered to patients inadequately controlled with sulfonylurea, metformin, thiazolidinedione, or insulin therapy with HbA_{1c} reduction of 0.6, 0.9, 1.0, and 0.5%, respectively (98–101). In addition, vildagliptin and pioglitazone were equally effective as adjuvant therapy for patients who were inadequately controlled on metformin, in which HbA_{1c} reductions of 0.9 and 1.0% were noted, respectively (102).

Side effects

The side effects from vildagliptin are comparable to that of sitagliptin. In a systematic review and metaanalysis of incretin therapies, vildagliptin has no risk of gastrointestinal adverse events but has an increase risk for urinary track infection and headache (40).

Unresolved Issues Regarding DPP 4 Inhibitors

1. Do DPP 4 inhibitors have favorable effects on β-cell mass in humans?

Exenatide appears to have beneficial effects on β-cell mass when given in pharmacological doses to rodents (51, 52). The effect of DPP 4 inhibitors on β-cell mass is less clear. Three-month treatment of high-fat-fed diet streptozotocin-induced diabetic mice with des-fluoro-sitagliptin preserved β-cells from apoptosis with no increase in β-cell mass (103). β-Cells of DPP 4 knockout mice are also reported to be more resistant to the toxic effects of streptozotocin (104). But against DPP 4 inhibitors being trophic factors, 8-wk treatment with vildagliptin had no obvious effects on β-cell turnover or β-cell mass in mice (105).

2. Is the modest increase in aGLP-1 levels the sole modulator of glycemia using DPP 4 inhibitors?

DPP 4 inhibitors were developed to augment biologically active, endogenously secreted plasma GLP-1. In humans, sitagliptin, both after a single dose and after a once-daily dose for 10 d, resulted in about a 2-fold increase in aGLP-1 after meal (67, 106). Furthermore, sitagliptin decreased total GLP-1 (tGLP-1) in the presence of increased aGLP-1 (107). However, whether the 2-fold increase in aGLP-1 is sufficient to explain the glucose-lowering effect with reduction of HbA_{1c} in patients on chronic sitagliptin therapy is controversial.

If DPP 4 inhibitors did lower blood glucose as a direct consequence of increased aGLP-1 levels, plasma insulin levels would be expected to increase as well. However, fasting and postprandial plasma insulin and C-peptide levels were not different before and after 10 d DPP 4 inhibition in both healthy and T2DM subjects (106, 108, 109). Indeed, infusions of GLP-1 that result in comparable plasma aGLP-1 levels attained by DPP 4 inhibition do not induce insulin secretion in T2DM (10). Some re-

viewers noted that with DPP 4 inhibitors, the same amount of insulin is secreted at a lower glucose level, or insulinogenic index is improved (110). However, any treatment that lowers plasma glucose without increasing insulin secretion, such as weight loss, metformin, or α-glucosidase inhibitors, also improves insulinogenic indices (111, 112).

Another surprising finding is that DPP 4 inhibition does not slow gastric emptying (108) when slowed gastric emptying is a consistent finding with exogenous GLP-1 and exenatide treatments (13, 113). An explanation offered in some reviews is that the degree of elevation of aGLP-1 is not of sufficient magnitude to inhibit gastric emptying (110, 114). However, by the same rationale, one can extrapolate that the elevation in aGLP-1 from DPP 4 inhibition is also not sufficient to bring about an increase in insulin secretion (108).

3. How might DPP 4 inhibition lead to a decline in plasma glucose levels without an increase in insulin secretion?

DPP 4 inhibition results in lower postprandial plasma glucagon levels (108, 109, 115). However, the reduced glucagon secretion is not evident in the fasting state when it would be most beneficial to decrease nocturnal hepatic glucose output. The postprandial glucagon suppressive effects of DPP 4 inhibitors, whereas significantly different from placebo, are small and short lived, and the levels are much higher than in nondiabetic subjects, therefore, unlikely to account for the full antihyperglycemic effect.

The following is speculation by the authors. Many endogenous compounds are subject to DPP 4 modification, resulting in their activation or inactivation, and any of these unknown qualities might have effects on glucose homeostasis (116, 117). If indeed the glucose-lowering effects of DPP 4 inhibition are mediated by GLP-1, one would expect to see maximum clinical effects of one dose of DPP 4 inhibitor on PPG and insulin levels immediately after a meal when GLP-1 secretion is at its maximum. However, this is not the case because no clinical effects on glucose, insulin, glucagon, or C-peptide levels over a 2-h postmeal period were observed after one dose of sitagliptin (67). However, after 4 wk sitagliptin, PPG levels were significantly reduced over a 24-h period in the treatment group, but insulin and C-peptide levels were comparable between treatment and placebo groups (118). This phenomenon may signify accumulation, over time, of one or more DPP 4 products that have effects on glucose uptake.

GLP-1 is known to have effects on the gut-hepatoportal-brain neural axis. Sitagliptin should directly inhibit DPP 4 activity at the level of the vascular endothelium in the gut, resulting in greater activation by GLP-1 of sensory neurons originating in the nodose ganglion, where GLP-1R gene expression has been shown to occur (119, 120). It should also cause higher aGLP-1 levels to enter the portal system after eating with subsequent activation of the vagal hepatic nerves (121). GLP-1R mRNA is present on nerve terminals of the portal vein in rodents (120), and there are GLP-1-modifiable glucose sensors in the hepatoportal bed (122). Dog studies had shown that direct infusion of GLP-1 into the portal vein results in increased glucose uptake (123, 124). Against gut-neuronal pathways being the likely cause of the improved glucose homeostasis with DPP 4 inhibition is this – gastric emptying is not altered. GLP-1 is thought to influence gastric emptying through interacting with afferent sensory neurons. Therefore, if DPP 4 inhibition were of such magnitude as to influence neuronal pathways through greater GLP-1R activation, one would also expect to see effects on gastric emptying, which is not the case.

4. Was the development of DPP 4 inhibitors, which are not specific for GLP-1 and actually resulted in decreased tGLP-1 secretion, really needed to increase plasma aGLP-1 levels?

There are other hypoglycemic agents that cause a minor increase in plasma GLP-1 levels but were thought to not contribute to their antihyperglycemic effect. Three-day treatment with phenformin resulted in elevated levels of gut-derived glucagon-like immunoreactivity (measured before a RIA specific for GLP-1 was available) both during fasting and in response to intraduodenal glucose infusions in T2DM (125). One-week metformin treatment in healthy subjects resulted in dramatic increases in postprandial glucagon-like immunoreactivity levels when compared with baseline (126). Furthermore, a 2-wk course of metformin in obese nondiabetic volunteers resulted in a statistically significant increase in aGLP-1 levels during an oral glucose load performed under euglycemic-hyperinsulinemic clamp when compared with baseline (127). aGLP-1 levels during both fasting and after the oral glucose load did not change after a single 850 mg dose of metformin but were significantly increased after 4 wk metformin in obese patients with and without T2DM (128). Subsequently, metformin was found to inhibit DPP 4 activity in patients with T2DM (129). Similarly, metformin was found to decrease DPP 4 activity, increase aGLP-1 levels, and improve insulin secretory capability to exogenous GLP-1 administration in diabetic mice (130). However, on a molar basis, specific DPP 4 inhibitors are 15–20 times more effective at reducing DPP 4 activity than metformin. A recent study of healthy subjects showed the following: both postprandial tGLP-1 and aGLP-1 levels were increased 2-fold with metformin; aGLP-1 levels were increased 2-fold but tGLP-1 levels were diminished by a third with sitagliptin; and aGLP-1 levels were increased 4-fold and tGLP-1 increased by 1.6-fold with metformin/sitagliptin (107).

These data suggest that metformin and sitagliptin increase aGLP-1 levels through different mechanisms. Most likely metformin increases GLP-1 levels through both inhibition of DPP 4 and secretion from L cells. The mechanism by which metformin might increase GLP-1 secretion is speculative. Biguanides have inhibited glucose absorption (131, 132). We hypothesize that this decrease in glucose absorption would prolong exposure of the sweet taste receptors on intestinal L cells (recently found to be the modulators of GLP-1 secretion from L cells) to glucose, resulting in the prolonged activation of the sweet taste receptors and secretion of GLP-1 (Fig. 2) (62).

Although metformin increases GLP-1 secretion, it is still unclear whether this increase has any glucose-lowering effect. It is well accepted that metformin lowers glucose levels by suppressing hepatic glucose output, mediated through kinase LKB1 in the

liver (133, 134). Therefore, it is also reasonable to ask whether sitagliptin, which increases aGLP-1 by the same amount as metformin, is actually lowering glucose through aGLP-1. However, given the synergistic effect of metformin and sitagliptin, both in terms of increase in aGLP-1 levels and lowering of HbA_{1c} (0.8% with sitagliptin alone, 1.3% with metformin alone, and 1.8% with metformin/sitagliptin), combination therapy might actually have a meaningful impact in glucose lowering through the GLP-1 mechanism (73, 78, 107).

Summary

Exenatide, as adjuvant therapy in T2DM, led to sustained HbA_{1c} reduction of 1.0%, and improved β-cell function and weight loss. It is inconvenient to use, but long-acting forms with once-weekly injection, such as long-acting release exenatide formulation are under development (135). Liraglutide lowered HbA_{1c} by 1.5% in a 14-wk study, but phase 3 studies are not yet available in peer-reviewed journals.

The advantage of DPP 4 inhibitors is their availability in oral form. Sitagliptin monotherapy led to HbA_{1c} reduction of 0.6–0.7% after 54 wk. Vildagliptin monotherapy lowered HbA_{1c} by 0.9–1.4% after 24 wk. However, patients with mild T2DM on low-dose vildagliptin showed a return of HbA_{1c} to pretreatment levels after 108 wk. A similar trend was seen in sitagliptin. Long-term data on sitagliptin and vildagliptin are needed to evaluate whether their glucose-lowering effects are sustained. Both DPP 4 inhibitors are weight neutral, and their effects on other DPP 4 substrates need further research.

A better understanding of the effects of GLP-1 and GLP-1 mimetics on β-cell mass in humans and the mechanism of action by which they lower glucagon secretion from α-cells are needed. Finally, more work is needed to elucidate how DPP 4 inhibitors improve insulin sensitivity in humans.

Acknowledgments

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