Effects of dipeptidyl peptidase IV inhibition on glycemic, gut hormone, triglyceride, energy expenditure, and energy intake responses to fat in healthy males

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Herue GA, Horowitz M, Deacon CF, Feinle-Bisset C, Rayner CK, Luscombe-Marsh N, Little TJ. Effects of dipeptidyl peptidase IV inhibition on glycemic, gut hormone, triglyceride, energy expenditure, and energy intake responses to fat in healthy males. Am J Physiol Endocrinol Metab 307: E830–E837, 2014. First published September 17, 2014; doi:10.1152/ajpendo.00370.2014.—Fat is the most potent stimulus for glucagon-like peptide-1 (GLP-1) secretion. The aims of this study were to determine whether dipeptidyl peptidase IV (DPP-IV) inhibition would enhance plasma active incretin [glucose-dependent insulinotropic polypeptide (GIP), GLP-1] concentrations and modulate the glycemic, gut hormone, triglyceride, energy expenditure, and energy intake responses to intraduodenal fat infusion. In a double-blind, randomized, placebo-controlled crossover design, 16 healthy lean males received 50 mg vildagliptin (V), or matched placebo (P), before intraduodenal fat infusion (2 kcal/min, 120 min). Blood glucose, plasma insulin, glucagon, active GLP-1, and GIP and peptide YY (PYY)-(3–36) concentrations; resting energy expenditure; and energy intake at a subsequent buffet meal (time = 120–150 min) were quantified. Data are presented as areas under the curve (0–120 min, means ± SE). Vildagliptin decreased glycemia (P: 598 ± 8 vs. V: 573 ± 9 mmol·l⁻¹·min⁻¹, P < 0.05) without effecting intraduodenal lipid. This was associated with increased insulin (P: 15.964 ± 1.193 vs. V: 18.243 ± 1.257 pmol·l⁻¹·min⁻¹, P < 0.05), reduced glucagon (P: 1.008 ± 52 vs. V: 902 ± 46 pmol·l⁻¹·min⁻¹, P < 0.05), enhanced active GLP-1 (P: 294 ± 40 vs. V: 694 ± 78 pmol·l⁻¹·min⁻¹) and GIP (P: 2.748 ± 77 vs. V: 4.256 ± 157 pmol·l⁻¹·min⁻¹), and reduced PYY-(3–36) (P: 9.527 ± 754 vs. V: 4469 ± 431 pM/min) concentrations compared with placebo (P < 0.05, for all). Vildagliptin increased resting energy expenditure (P: 1.821 ± 54 vs. V: 1.896 ± 65 kcal/day, P < 0.05) without affecting energy intake. Vildagliptin 1) modulates the effects of intraduodenal fat to enhance active GLP-1 and GIP, stimulate insulin, and suppress glucagon, thereby reducing glycemia and 2) increases energy expenditure. These observations suggest that the fat content of a meal, by enhancing GLP-1 and GIP secretion, may contribute to the response to DPP-IV inhibition.

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THE INCRETIN HORMONES, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulino-tropic polypeptide (GIP), are major determinants of postprandial glycemia (27), and GLP-1 now uses energy intake (42). In health, GLP-1 and GIP account for ~70% of the insulin response to enteral glucose (19). In type 2 diabetes, the incretin effect is impaired (29), at least in part reflecting a markedly diminished insulino-tropic effect of GIP (30) and, possibly, reduced GLP-1 secretion (39). The enzyme dipeptidyl peptidase IV (DPP-IV) rapidly degrades the incretins, and inhibitors of DPP-IV have been developed as a therapeutic strategy for type 2 diabetes that is now used widely (18). DPP-IV inhibitors enhance postprandial intact GLP-1 and GIP concentrations, and in type 2 diabetes their use is associated with reductions in pre- and postprandial blood glucose and glyceded hemoglobin (HbA₁c) (2). The glucose-lowering efficacy of DPP-IV inhibitors is primarily, but not exclusively, mediated by GLP-1 (3). However, in contrast to GLP-1 receptor agonists, which promote weight loss (likely via suppression of appetite), DPP-IV-based therapy tends to be weight neutral. Given this, it is surprising that the potential effects of DPP-IV inhibition on energy intake and expenditure have received little attention.

The efficacy of DPP-IV inhibition to diminish elevated blood glucose levels is likely to be potentiated by strategies to enhance food-induced GLP-1 secretion. For example, we demonstrated in type 2 patients that a α-xylene preload given before a carbohydrate meal attenuated the postprandial glycemic response, an effect that was enhanced by DPP-IV inhibition (44). To date, the primary focus has been on carbohydrate-induced incretin secretion. However, the fat content of a meal is likely to be highly relevant to the incretin response, particularly as enteral fatty acids may be the most potent stimulus for GLP-1 secretion (35). Fat ingestion also stimulates insulin and glucagon secretion (6) and slows gastric emptying (9). Because intravenous lipid has no effect on insulin secretion (22), effects of enteral fat may be dependent on incretin release. Indeed, ingestion of a fat “preload” attenuates the glycemic response to a carbohydrate-containing meal in type 2 diabetes (14). Given the potent effect of fat on GLP-1 concentrations, it is possible that the combination of DPP-IV inhibition with enteral fat may markedly attenuate postprandial glycemia.

Clinical trials of incretin-based therapies have demonstrated potentially beneficial cardiovascular effects, including a reduction in plasma triglycerides (36). In animal studies, both GLP-1 and GIP decrease intestinal triglyceride absorption and apolipoprotein production (10, 34). Indeed, administration of vildagliptin with a high-fat meal markedly reduces postprandial triglyceride concentrations in type 2 diabetes (28). The effect of DPP-IV inhibition on postprandial triglycerides in healthy
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subjects has not, to our knowledge, been investigated. DPP-IV inhibitors have also been reported to augment postprandial lipid mobilization and fat oxidation (5), and this may explain why patients with type 2 diabetes treated with DPP-IV inhibitors do not gain weight (15). DPP-IV inhibition may promote fat oxidation (5), but the effects of DPP-IV inhibition on fat oxidation and energy expenditure require further investigation.

Exogenous administration of GLP-1 slows gastric emptying markedly (23) and suppresses food intake (42); hence, it may be expected that DPP-IV inhibition would also be associated with suppression of energy intake. Yet, despite a substantial increase in active GLP-1 concentrations following DPP-IV inhibition in type 2 diabetes, gastric emptying appears unchanged (37, 41), or only slightly slower (3), and intake of a mixed nutrient meal appears unaffected (40). However, a major limitation of the latter study was that effects on energy intake were assessed by asking subjects to drink a liquid meal until maximum tolerance, which is unlikely to be representative of intake from a typical meal. Furthermore, fat is likely to stimulate a greater GLP-1 response than a mixed nutrient meal, so the combination of fat with DPP-IV inhibition (31) would be predicted to exert greater suppressive effects on energy intake.

Therefore, the aims of this study were to determine whether DPP-IV inhibition during intraduodenal fat infusion in healthy lean volunteers would 1) increase plasma concentrations of active GLP-1 and GIP, 2) modify the glycemic, insulinemic, and triglyceride responses, 3) increase energy expenditure and fat oxidation, and 4) potentiate the suppression of energy intake. The fat was administered intraduodenally to control for variations in the rate of gastric emptying that exist between individuals, or as a result of potential drug effects. The use of DPP-IV inhibition allowed us to probe the physiological effects of prolonged elevation of active GLP-1 and GIP concentrations on responses to fat.

MATERIALS AND METHODS

Participants

Sixteen healthy males [age: 23.7 ± 1.6 (18–45) yr; body mass index: 22.6 ± 0.5 (19–25) kg/m2] were studied. Power calculations based on effect size and variance from previous studies (7, 25, 26, 33) indicated n = 16 would allow detection of a ~360-kJ (SD 482 kJ) difference in energy intake (α < 0.05, β = 0.8). All participants were unrestrained eaters (38); had no gastrointestinal disease or symptoms; were nondiabetic; had normal iron levels, creatinine clearance, and liver function tests; and were not taking medications. Consumption of a vegetarian diet, >20 g of alcohol/day, and smoking also represented exclusion criteria. The study was approved by the Royal Adelaide Hospital Research Ethics Committee and conducted in accordance with the Declaration of Helsinki. All participants provided informed written consent.

Study Design

In a double-blind, randomized, placebo-controlled crossover design separated by at least 7 days, we evaluated the effects of a 120-min intraduodenal infusion of fat, following oral ingestion of 50 mg vildagliptin or a matched placebo tablet, on blood glucose, plasma insulin, glucagon, GLP-1 [total and active GLP-1-(7–36)], GIP [total and active GIP-(1–42)], peptide YY (PYY) [total and PYY-(3–36)], triglyceride and free fatty acid concentrations, energy expenditure and fat oxidation, appetite perceptions, and energy intake. Vildagliptin and matched placebo were provided to the pharmacy by the sponsor (Novartis Pharmaceuticals Australia).

Protocol

Participants were asked to maintain normal eating habits and to refrain from vigorous exercise and alcohol intake for 24 h before visits. They were provided with a standardized beef lasagna (2,472 kJ; McCain Foods) for dinner at 1900. the night before each visit, after which they fasted from all food and fluid (except water).

On each visit, participants arrived at the Discipline of Medicine at 0800, where a silicone catheter with antral and duodenal sideholes perfused with saline, and a terminal infusion port, was inserted through an anesthetized nostril in the stomach and allowed to pass into the duodenum (16). Catheter position was monitored by measurement of the transmucosal potential difference in the stomach and duodenum (16), using a saline-filled subcutaneous cannula placed in the left forearm as a reference electrode (16). Once the catheter was positioned correctly with the infusion port 14.5 cm distal to the pylorus, fasting resting energy expenditure (REE) and respiratory quotient (RQ) were measured over 30 min by indirect calorimetry, using a clear ventilated hood and the TrueOne 2400 metabolic monitoring system (Parvo Medics, East Sandy, UT). After 30 min, the plastic hood was removed, and an intravenous cannula was inserted in an antecubital vein for blood sampling.

At time (t) = −60 min, subjects ingested 50 mg vildagliptin (Novartis Pharmaceuticals), or a matched placebo tablet, with 100 ml water (Fig. 1). At t = 0 min, an intraduodenal infusion of lipid [10% Intralipid 2 kcal/min, rate: 1.8 ml/min] was commenced at t = 0 min and maintained for 120 min. Blood samples were collected, and visual analog scale (VAS) questionnaires, assessing appetite and gastrointestinal sensations, were completed at the time points indicated. At t = 120 min, the infusion was discontinued, and participants were offered a cold buffet-style meal (t = 120–150 min) from which energy intake was quantified (11).

Fig. 1. Schematic representation of the study protocol. A catheter was positioned with an infusion port in the duodenum. Participants ingested a 50-mg vildagliptin, or a matched placebo, tablet with 100 ml water at time (t) = −60 min. Resting energy expenditure (REE) and respiratory quotient (RQ) were assessed between t = −90 and −60 min, t = −30 and 0 min, t = 15 and 45 min, and t = 90 and 120 min using indirect calorimetry. Intraduodenal infusion of lipid (10% Intralipid 2 kcal/min, rate: 1.8 ml/min) was commenced at t = 0 min and maintained for 120 min. Blood samples were collected, and visual analog scale (VAS) questionnaires, assessing appetite and gastrointestinal sensations, were completed at the time points indicated. At t = 120 min, the infusion was discontinued, and participants were offered a cold buffet-style meal (t = 120–150 min) from which energy intake was quantified (11).
Intralipid at 1.8 ml/min (2 kcal/min)] was commenced and maintained for 120 min. Blood samples were collected and 100-mm visual analog scale (VAS) questionnaires assessing appetite and gastrointestinal sensations were completed, at intervals from \( t = -60 \) to 180 min. REE and RQ were assessed between \( t = -30 \) and 0 min, \( t = 15 \) and 45 min, and \( t = 90 \) and 120 min. At \( t = 120 \) min, the catheter and the ventilated hood were removed, and participants were offered a cold buffet-style meal from which they were instructed to eat until comfortably full (\( t = 120–150 \) min) (11). At \( t = 180 \) min, the intravenous cannula was removed, and the participant left the laboratory.

**Measurements**

**Blood glucose and hormone concentrations.** Venous blood samples (10 ml) were collected in ice-chilled EDTA-treated tubes containing 100 \( \mu \)l DPP-IV inhibitor (DPP4–010; EMD Millipore, Billerica, MA) for analysis of insulin, glucagon, GLP-1 (total and active), GIP (total and active), and PYY [total and PYY-(3–36)]. Blood samples (5 ml) were collected in serum tubes and fluoride oxalate-treated tubes for measurement of serum triglycerides and plasma free fatty acid concentrations, respectively. Venous blood glucose concentrations (mmol/l) were determined by glucometer (Medisense Precision QID; Abbott Laboratories, Bedford, MA). Plasma/serum was obtained by centrifugation (3,200 rpm, 15 min, 4°C) and stored at 80°C.

Total GLP-1 concentrations were measured using a radioimmunoassay (RIA) (antiserum: 89390) specific for the amidated COOH-terminal end of the GLP-1 molecule that reacts equally with intact GLP-1 and the primary metabolite, whereas intact GLP-1 levels were measured using an in-house two-site (sandwich) assay (ELISA) (43). Total GIP was measured using the COOH-terminally directed antisera [code 80867 (22)] that reacts fully with intact GIP and the NH2-terminally truncated metabolite. Intact GIP was measured using an antisera (no. 98171) that is specific for the intact NH2-terminus of GIP (43). Plasma insulin concentrations were measured using ElectroChemiluminescence ImmunoAssay. Plasma glucagon was measured by RIA using a COOH-terminally directed antisera (no. 4305) that recognizes fully processed pancreatic glucagon (43). The RIA (total GLP-1, intact and total GIP, and glucagon) have intra-assay coefficients of variation (CVs) of <6% and interassay CVs of <15%. The ELISA for intact GLP-1 has an intra-assay CV of 2% and an interassay CV of 5%. Total PYY (1–36 + 3–36) and PYY-(3–36) (metabolite) were measured using commercially available RIA kits from Linco [catalog no. PYY-66HK and PYY-(3–36)-67HK; Millipore, St. Charles, MO]. The RIA for total PYY has intra-assay CVs of 9.4, 2.9, and 3.6% and interassay CVs of 8.5, 7.1, and 5.5% for concentrations of 82, 111, and 542 pg/ml, respectively. The RIA for PYY-(3–36) has intra-assay CVs of 11 and 6.4% and interassay CVs of 15 and 7% for concentrations of 84 and 217 pg/ml, respectively. Serum triglyceride and plasma free fatty acid concentrations were assayed in commercial laboratories by SA Pathology (Adelaide, SA, Australia).

**Appetite perceptions and energy intake.** The use of 100-mm VAS questionnaires to evaluate appetite and gastrointestinal sensations has been described previously (32). Food consumption at the buffet meal was determined by weighing meal items before and after presentation to the participant and analyzed using commercially available software (Foodworks 3.01; Xyris Software, Highgate Hill, Queensland, Australia) (11).

REE, RQ, and thermic effect of feeding. The first 10 min of data from each period \( t = -90 \) to -60 [baseline (BL)], \( t = -30 \) to 0, 15–45, and 90–120 min] were discarded to ensure that participants had reached equilibrium, and the remaining values were averaged to provide REE and RQ at BL, and during the lipid infusion (average of values between \( t = 15–45 \) and 90–120 min) (24). REE and RQ did not differ between \( t = -90 \) to -60 and \( t = -30 \) to 0 min so the mean of values obtained between \( t = -90 \) and -60 were used as baseline data. RQ was determined as the ratio of \( V_{CO2}/V_{O2} \). A value of 0.7 is indicative of fat oxidation, whereas a value of 0.8–1.0 is indicative of mixed oxidation of nutrients (e.g., protein and carbohydrate) (24). The thermic effect of feeding (TEF) was determined by subtracting baseline REE from the mean REE values during the intraduodenal fat infusion and is expressed as percent energy consumed during the intraduodenal fat infusion.

**Data and Statistical Analysis**

VAS scores and serum triglyceride concentrations are presented as changes from baseline (\( t = -60 \) min) values; all other data are presented as raw values. Data assessed over time were analyzed by repeated-measures ANOVA, with time and treatment as factors. Changes over time within a treatment were analyzed by repeated-measures ANOVA with time as a factor. Post hoc comparisons, adjusted for multiple comparisons by Bonferroni’s correction, were performed if ANOVAs revealed significant effects. Energy intake (amount and energy consumed and macronutrient distribution), REE, RQ, and TEF were analyzed by paired t-tests. Results are presented as means ± SE, and significance was accepted at \( P < 0.05 \).

**RESULTS**

The study was generally well tolerated. Some subjects experienced mild nausea (placebo: \( n = 7 \), vildagliptin: \( n = 6 \)), mild abdominal cramps (placebo: \( n = 3 \)), and diarrhea (placebo: \( n = 2 \)) during the intraduodenal lipid infusion. Because of technical problems during indirect calorimetry, total data for REE, RQ, and TEF were not available for three participants.

**Blood Glucose**

There was a treatment \( \times \) time interaction for blood glucose concentrations (\( P = 0.000 \)) (Fig. 2A) so that glucose was less between \( t = 60 \) and 105 min following vildagliptin compared with placebo (\( P < 0.05 \)). During the lipid infusion, blood glucose concentrations decreased relative to baseline (\( t = 0 \) min) between \( t = 45 \) and 105 min following vildagliptin (\( P < 0.05 \)), whereas there was no change over time following placebo. After the buffet meal, blood glucose concentrations increased on both days but were markedly lower following vildagliptin compared with placebo (\( P < 0.05 \)).

**Insulin**

There was a treatment \( \times \) time interaction for plasma insulin concentrations (\( P = 0.04 \)) (Fig. 2B) so that concentrations were slightly greater between \( t = 30 \) and 75 min following vildagliptin compared with placebo (\( P < 0.05 \)). During the lipid infusion, plasma insulin concentrations increased relative to baseline (\( t = 0 \) min) between \( t = 30 \) and 120 min following vildagliptin (\( P < 0.05 \)), whereas there was no change over time following placebo. After the buffet meal, plasma insulin concentrations were markedly increased on both days, with no difference between treatments.

**Glucagon**

There was an effect of treatment on plasma glucagon concentrations, with glucagon being lower after treatment with vildagliptin compared with placebo (\( P = 0.000 \)) (Fig. 2C). During the lipid infusion, plasma glucagon concentrations increased relative to baseline (\( t = 0 \) min) between \( t = 45 \) and 120 min following vildagliptin (\( P < 0.05 \)) and between \( t = 15 \) and 180 min following placebo (\( P < 0.05 \)).
and 120 min following placebo. After the buffet meal, plasma glucagon concentrations decreased on both days \((P < 0.05)\).

**Total and Active GLP-1**

There was a treatment \(\times\) time interaction for total plasma GLP-1 concentrations \((P = 0.000)\). Plasma total GLP-1 concentrations increased in response to the intraduodenal lipid infusion on both study days but were lower at \(t = 30, 45, 90, \text{ and } 120\) min and after ingestion of the buffet meal (between \(t = 150\) and \(180\) min) following vildagliptin compared with placebo \((P < 0.05)\) (Fig. 3A).

There was a treatment \(\times\) time interaction for plasma active GLP-1 concentrations \((P = 0.000)\). Plasma active GLP-1 concentrations increased in response to the intraduodenal lipid infusion on both study days but were greater between \(t = 30\) and 180 min following vildagliptin compared with placebo \((P < 0.05)\) (Fig. 3B).

**Total and Active GIP**

There was a treatment effect for plasma total GIP concentrations \((P = 0.02)\). Plasma total GIP concentrations increased in response to the intraduodenal lipid infusion on both study days, but total GIP was lower following vildagliptin compared with placebo (Fig. 3C).

There was a treatment \(\times\) time interaction for plasma active GIP concentrations \((P = 0.0001)\). Plasma active GIP concentrations increased in response to the intraduodenal lipid infusion on both study days but were greater at \(t = 0\) and between \(t = 30\) and 180 min following vildagliptin compared with placebo \((P < 0.05)\) (Fig. 3D).

**Total PYY and PYY-(3–36)**

There was a treatment \(\times\) time interaction for total plasma PYY concentrations \((P = 0.000)\). Plasma total PYY concentrations were lower between \(t = 15\) and 180 min following vildagliptin compared with placebo \((P < 0.05)\) (Fig. 3E).

There was a treatment \(\times\) time interaction for plasma PYY-(3–36) concentrations \((P = 0.000)\). Plasma PYY-(3–36) was lower between \(t = 0\) and 180 min following vildagliptin compared with placebo \((P < 0.05)\) (Fig. 3F).

**Triglycerides and Free Fatty Acids**

There was a treatment \(\times\) time interaction for serum triglyceride concentrations \((P = 0.000)\). During the lipid infusion, serum triglyceride concentrations did not increase relative to baseline on either day. After the buffet meal, serum triglyceride concentrations were increased on both days. Serum triglyceride concentrations were lower after the buffet meal at \(t = 165–180\) min following vildagliptin compared with placebo \((P < 0.05)\) (Fig. 4).

There was no effect of treatment on circulating concentrations of free fatty acids \((P = 0.998)\) (data not shown). During the lipid infusion and after the buffet meal, there was no change in plasma free fatty acids relative to baseline on both days.

**REE, RQ, and TEF**

There was no difference in baseline REE or RQ between study days. On both days, REE increased during the intraduodenal lipid infusion compared with baseline \((P < 0.01)\); however, during the lipid infusion, REE was greater following vildagliptin compared with placebo \((P = 0.01)\) (Fig. 5A).

On both days, RQ decreased during the intraduodenal lipid infusion compared with baseline, indicative of a shift toward lipid oxidation \((P < 0.01)\); however, there was no effect of vildagliptin on RQ (Fig. 5B). There was an effect of treatment on the thermic effect of food such that vildagliptin increased the thermic effect of food compared with placebo \((P = 0.049)\) (Fig. 5C).

**Appetite and Gastrointestinal Symptom Perceptions and Energy Intake at Subsequent Buffet Meal**

There was no effect of treatment on appetite perceptions or ratings of nausea or fullness (data not shown). There was no
effect of treatment on the amount (g), energy (kJ), or macronutrient composition of the food consumed at the buffet meal (Table 1).

DISCUSSION

This study shows that acute administration of the DPP-IV inhibitor vildagliptin during euglycemia modulates the effects of an intraduodenal fat infusion in healthy males to enhance active GLP-1, active GIP, and insulin and suppresses glucagon, glycemia, and postprandial triglycerides. Vildagliptin also reduced total PYY, and PYY-(3–36), and was associated with an increase in REE during intraduodenal fat infusion but had no effect on ad libitum energy intake.

We have confirmed that fat is a potent stimulus for GIP and GLP-1 release in health and that these effects are augmented by DPP-IV inhibition (i.e., enhanced plasma active GIP and GLP-1). Furthermore, the total curves for GLP-1 and PYY followed a comparable pattern, with total GLP-1 and PYY concentrations being lower following treatment with vildagliptin. We regard total values as an estimate of secretion, i.e., we interpret the lower responses after DPP-IV inhibition as reflecting a feedback inhibition of the elevated intact levels on L cell secretion (40). Whereas we assayed both total and intact [GLP-1(7–36)] concentrations, for PYY, total and metabolite concentrations [i.e., PYY-(3–36)] were measured. Here, as expected based on the activity of the DPP-IV inhibitor to block degradation of intact PYY, decreased levels of PYY-(3–36) were observed. Similar effects have been reported following 12 wk of treatment with sitagliptin (1). Our results are consistent with those of Ohlsson et al., who observed potentiated re-
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Fig. 5. REE (A), RQ (B), and thermic effect of lipid (TEF, C) following id lipid infusion following administration of the DPP-IV inhibitor vildagliptin or matched placebo in healthy lean males. Data are means ± SE, n = 13. •Fasting vs. lipid, P < 0.05. •Placebo vs. vildagliptin, P < 0.05.

The postprandial triglyceride response was decreased following vildagliptin, whereas free fatty acids did not change. It is unlikely that the former reflected differences in intake at the buffet meal given that participants consumed the same macronutrient composition on both days. These observations are consistent with reports that vildagliptin lowers postprandial triglyceride concentrations following a high-fat meal, after 4 wk of treatment in patients with type 2 diabetes (28). While the mechanisms underlying this effect are poorly defined, the increases in active GIP and GLP-1 are likely to be relevant. In animal studies, GLP-1 reduces intestinal triglyceride absorption and apolipoprotein production (20, 34), and the GLP-1 receptor has been demonstrated to be essential for intestinal lipoprotein synthesis and secretion (20). Furthermore, GIP reduces postprandial triglyceride levels, which may be mediated by effects on both intestinal triglyceride absorption and peripheral tissue uptake (10).

DPP-IV inhibition increased REE during the Intralipid infusion, which may be attributable to the increase in the thermic effect of intraduodenal lipid. If maintained during prolonged treatment, this could contribute to weight neutrality, and perhaps even weight loss, depending on the macronutrient composition of the diet, an issue that clearly warrants further evaluation. In support of this, data from recent animal studies using the DPP-IV inhibitor teneligliptin indicate that chronic DPP-IV inhibition is able to attenuate the effects of a high-fat diet on body weight by an increase in energy expenditure (13). We observed a decrease in the RQ in response to intraduodenal lipid, indicative of increased fat oxidation. In contrast to previous reports (5), this was not augmented by vildagliptin, but this may reflect the fact that only a single dose was administered. This metabolic response to DPP-IV inhibition may be mediated through GLP-1 receptor-mediated activation of the sympathetic nervous system (5), as evidenced by an increase in plasma norepinephrine (5). Increased insulin secretion may contribute to this effect through effects on lipid metabolism. It is also possible that DPP-IV inhibition exerts its effects through modulation of other hormones that we did not measure. For example, DPP-IV inhibition augments the antilipolytic effect of neuropeptide Y in human adipose tissue (21).

Table 1. Energy (kJ), amount (g), and macronutrient distribution (percentage of energy derived from fat, carbohydrate, or protein) of food consumed at the buffet meal following intraduodenal lipid infusion paired with administration of the DPP-IV inhibitor vildagliptin or matched placebo in healthy lean males

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Vildagliptin</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy intake, kJ</td>
<td>4,647 ± 374</td>
<td>4,497 ± 374</td>
<td>0.4</td>
</tr>
<tr>
<td>Amount consumed, g</td>
<td>1,156 ± 74</td>
<td>1,077 ± 80</td>
<td>0.2</td>
</tr>
<tr>
<td>Protein, %</td>
<td>20 ± 1</td>
<td>20 ± 1</td>
<td>0.5</td>
</tr>
<tr>
<td>Carbohydrate, %</td>
<td>52 ± 2</td>
<td>51 ± 2</td>
<td>0.4</td>
</tr>
<tr>
<td>Fat, %</td>
<td>28 ± 1</td>
<td>29 ± 1</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Data are presented as mean values ± SE; n = 16 subjects. DPP-IV, dipeptidyl peptidase IV.
Administration of exogenous GLP-1-(7–36) (42) or PYY-(3–36) (4) potently suppresses food intake in humans. In the current study, vildagliptin had no effect on ratings of hunger or fullness nor energy intake at the buffet meal. This may be because of the elevation of active GLP-1 being counterbalanced by a concomitant reduction in total PYY and inhibition of conversion of PYY-(1–36) (which has orexigenic effects) to its metabolite PYY-(3–36) (which has anorexigenic effects), and is consistent with the weight-neutral effect of DPP-IV inhibitors observed in trials in type 2 diabetes (12), as opposed to the weight loss observed consistently with GLP-1 receptor agonists (17). The latter are associated with much higher levels of receptor stimulation compared with endogenous stimulation with DPP-IV inhibition.

This study had a number of limitations. First, only a single dose of vildagliptin was administered; effects may potentially differ with prolonged therapy. Fat was administered intraduodenally to exclude the confounding effects of variations in gastric emptying between individuals, which would per se also be likely to impact on the efficacy of DPP-IV inhibition on glyceremia (37). While fat may enhance the response to DPP-IV inhibition, direct comparison with other nutrients and examination of the effects of mixed-nutrient meals consumed orally on glyceremic profiles are warranted. Finally, this study was limited to healthy subjects in whom GIP has substantial insulinotropic effects; it will be important to determine whether DPP-IV inhibitors have comparable effects following fat ingestion in patients with type 2 diabetes.

In conclusion, in healthy males, acute administration of the DPP-IV inhibitor vildagliptin has significant effects on the glycemic, triglyceride, and energy expenditure responses to intraduodenal fat. These observations may have implications for the development of dietary strategies to enhance the efficacy of DPP-IV inhibition.

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DISCLOSURES

MH has participated in Advisory boards and/or symposia for Novo Nordisk, Sanofi-Aventis, Eli-Lilly, MSD, Boehringer Ingelheim, Satogen and Astra Zeneca/BMS, and received honoraria for this activity. CFD has received consultancy and/or speaker fees from Boehringer-Ingelheim, Lilly, Merck/ MSD, Novartis and Novo Nordisk.

AUTHOR CONTRIBUTIONS


REFERENCES


