0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(4):1249–1255

doi: 10.1210/jc.2006-1882

The Dipeptidyl Peptidase IV Inhibitor Vildagliptin Suppresses Endogenous Glucose Production and Enhances Islet Function after Single-Dose Administration in Type 2 Diabetic Patients

Bogdan Balas, Muhammad R. Baig, Catherine Watson, Beth E. Dunning, Monica Ligueros-Saylan, Yibin Wang, Yan-Ling He, Celia Darland, Jens J. Holst, Carolyn F. Deacon, Kenneth Cusi, Andrea Mari, James E. Foley, and Ralph A. DeFronzo

Division of Diabetes (B.B., M.R.B., C.D., K.C., R.A.D.), Department of Medicine, University of Texas Health Science Center at San Antonio, San Antonio, Texas 78229; Novartis Institutes for Biomedical Research (C.W., Y.-L.H.), Cambridge, Massachusetts 02139; PharmaWrite, L.L.C. (B.E.D.), Princeton, New Jersey 08540; Novartis Pharmaceuticals Corp. (M.L.-S., Y.W., J.E.F.), East Hanover, New Jersey 07054; Panum Institute (J.J.H., C.F.D.), University of Copenhagen, DK-2400 Copenhagen, Denmark; and Institute of Biomedical Engineering (A.M.), National Research Council, 35127 Padova, Italy

Aims/Hypothesis: Vildagliptin is a selective dipeptidyl peptidase IV inhibitor that augments meal-stimulated levels of biologically active glucagon-like peptide-1. Chronic vildagliptin treatment decreases postprandial glucose levels and reduces hemoglobin A_{1c} in type 2 diabetic patients. However, little is known about the mechanism(s) by which vildagliptin promotes reduction in plasma glucose concentration.

Methods: Sixteen patients with type 2 diabetes (age, 48 ± 3 yr; body mass index, 34.4 ± 1.7 kg/m^2; hemoglobin A_{1c}, 9.0 ± 0.3%) participated in a randomized, double-blind, placebo-controlled trial. On separate days patients received 100 mg vildagliptin or placebo at 1730 h followed 30 min later by a meal tolerance test (MTT) performed with double tracer technique (3-^{3}H-glucose iv and 1-^{14}C-glucose orally).

Results: After vildagliptin, suppression of endogenous glucose production (EGP) during 6-h MTT was greater than with placebo (1.02 ± 0.06 *vs.* 0.74 ± 0.06 mg·kg^{-1}·min^{-1}; $P = 0.004$), and insulin secretion rate increased by 21% ($P = 0.003$) despite significant reduction in mean plasma glucose (213 ± 4 *vs.* 230 ± 4 mg/dl; $P = 0.006$). Consequently, insulin secretion rate (area under the curve) divided by plasma glucose (area under the curve) increased by 29% ($P = 0.01$). Suppression of plasma glucagon during MTT was 5-fold greater with vildagliptin ($P < 0.02$). The decline in EGP was positively correlated ($r = 0.55$; $P < 0.03$) with the decrease in fasting plasma glucose (change = −14 mg/dl).

Conclusions: During MTT, vildagliptin augments insulin secretion and inhibits glucagon release, leading to enhanced suppression of EGP. During the postprandial period, a single dose of vildagliptin reduced plasma glucose levels by enhancing suppression of EGP. **(*J Clin Endocrinol Metab* 92: 1249–1255, 2007)**

VILDAGLIPTIN IS AN orally effective, selective inhibitor of dipeptidyl peptidase IV (DPP-4) that augments meal-stimulated levels of biologically active glucagon-like peptide-1 (GLP-1) and improves glucose tolerance in animal models of diabetes (1, 2) and patients with type 2 diabetes mellitus (T2DM) (3). Clinical trials to date have confirmed that chronic treatment with vildagliptin monotherapy reduces postprandial glucose levels and produces a clinically meaningful reduction in hemoglobin A_{1c} in patients with T2DM without causing hypoglycemia (4). GLP-1 has been shown to increase insulin secretion (5) and suppress glucagon release (6) in a glucose-dependent manner. Based on these observations, *i.e.* increased insulin to glucagon ratio, one would predict that DPP-4 inhibition would lead to the postprandial suppression of hepatic glucose production. However, no previous study has examined glucose kinetics after a meal.

Whether DPP-4 inhibitors promote glycemic control solely by increasing plasma GLP-1 levels remain controversial because previous studies demonstrated that the rise in endogenous GLP-1 concentration after DPP-4 inhibition is modest, and these drugs have a delayed effect (weeks) to improve glucose homeostasis (7, 8). Variable effects of vildagliptin on plasma insulin levels also have been reported. After a meal tolerance test, DPP-4 inhibitors (including vildagliptin) have been shown to either have no effect or increase insulin levels in the face of a decrease in plasma glucose concentration (3, 9). However, other studies have observed a reduction in plasma insulin concentration, as well as insulin secretory rate, after short-term treatment with vildagliptin (10). During long-term vildagliptin administration, improved insulin sensitivity has been demonstrated in both animals (11) and humans (9, 10) with type 2 diabetes.

First Published Online January 23, 2007

Abbreviations: AUC, Area under the curve; DPP-4, dipeptidyl peptidase IV; EGP, endogenous glucose production; FFA, free fatty acid; FPG, fasting plasma glucose; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide-1; ISR, insulin secretory rate; T2DM, type 2 diabetes mellitus.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

Clinical studies have shown not only the expected reduction in postprandial glucose levels but an unexpected decrease in the fasting glucose concentration as well (4). The latter might be expected in chronic studies in which the improved metabolic state may contribute to the reduction in fasting plasma glucose. However, in an acute study with vildagliptin, there was a clear suggestion that fasting glucose levels already were reduced after first day of treatment (10). This suggests that the effect of vildagliptin to increase GLP-1 and glucose-dependent insulinotropic peptide (GIP) levels may extend into the postmeal period, thereby increasing the insulin to glucagon ratio and thus inhibiting postmeal hepatic glucose production.

In the present study we investigated the mechanisms by which the DPP-4 inhibitor vildagliptin reduces postmeal plasma glucose concentrations in type 2 diabetic patients using a double-tracer technique. We chose to examine the response to a single dose of vildagliptin in diabetic patients not previously exposed to a DPP-4 inhibitor to avoid the confounding effects of metabolic changes associated with chronic drug administration.

Subjects and Methods

Subjects

Sixteen patients with T2DM were studied: 10 males and six nonfertile females, aged 48 ± 3 yr, body mass index 34.4 ± 1.7 kg/m^2, hemoglobin A_{1c} 9.0 ± 0.3%, diabetes duration 3.5 ± 0.6 yr with no detectable anti-glutamate decarboxylase antibodies or diabetes complications. All subjects were in good health as determined by medical history, physical examination, screening blood tests, urinalysis, and electrocardiogram. Diabetes was controlled by diet and exercise alone (n = 4) or a stable dosage (≥6 months) of metformin (n = 3), sulfonylurea (n = 4), or both (n = 5). No subject was taking any other medication known to affect glucose or lipid metabolism. Body weight was stable (± 3 pounds) in all participants for 6 months before study. No subject participated in a heavy exercise program.

All studies were carried out at the Clinical Research Center of the University of Texas Health Science Center at San Antonio. The study was approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio, and informed written consent was obtained from each patient before participation.

Study design

The study used a double-blind, randomized, placebo-controlled, two-period crossover design. At screening all subjects received dietary guidance and remained on a weight-maintaining diet (50% carbohydrates, 20% protein, and 30% fat) from screening to the end of study. Patients continued to take their regular antidiabetic medication throughout the studies.

Meal tolerance test with double tracer

The first meal tolerance test was done 7–21 d after the screening visit. Subjects were admitted to the General Clinical Research Center at 0700 h on the morning of the day of study after a 10-h overnight fast. At 0800 h, they were fed a standardized breakfast (one fifth of daily caloric allotment) and at 1200 h, they were fed a standardized lunch (two fifths of daily caloric allotment). At 1430 h, a catheter was inserted into an antecubital vein and a prime [20 μCi × fasting plasma glucose (FPG)/100]-continuous (0.20 μCi/min) infusion of [3-^{3}H]glucose was started and maintained until 0800 h on the next day. A second catheter was placed in the antecubital vein of the opposite arm for blood withdrawal. At 1730 h subjects ingested 100 mg vildagliptin or placebo (assigned in random fashion) with 200 ml water. At 1800 h (time 0), subjects ingested a standardized mixed meal (75 g of glucose, 19 g of protein, and 22 g of lipid in a total of 535 calories). The glucose in the meal was labeled with 75 μCi of [1-^{14}C]glucose. Patients consumed their dinner within 30 min and were not allowed to eat or drink anything else except water until 0800 h on the following morning.

Plasma samples for 3-^{3}H-glucose activity were drawn at −30, −20, −15, −10, − 5, and 0 min before ingestion of the meal, every 15 min from 1800 to 2400 h and every 30 min thereafter until 0800 h. Plasma 1-^{14}C-glucose-specific activity was obtained at time 0, every 15 min from 1800 to 2400 h, and every 30 min thereafter. Samples for plasma insulin, C-peptide, glucagon, GLP-1, and free fatty acids (FFAs) concentrations and DPP-4 activity were obtained at −30, −15, and 0 min before the meal and every 15–30 min thereafter until 0800 h on the following morning. Urine was collected from 1800 to 2200 h (period 1) and 2200 to 0800 h (period 2) for determination of urinary glucose concentration. Approximately 14 d later, all subjects returned to the General Clinical Research Center for a repeat procedure that was identical with first study. Whether subjects received vildagliptin or placebo during the first or second study was randomly determined.

Analytical determinations

The plasma glucose concentration was determined by the glucose oxidase method with a Beckman Glucose Analyzer II (Beckman Instruments Inc., Fullerton, CA). Plasma insulin, C-peptide, and glucagon concentrations were determined by RIA (Diagnostics Products, Los Angeles, CA). Plasma FFA concentration was measured by standard colorimetric methods (Wako Diagnostics, Neuss, Germany). Plasma ^{3}H-glucose and ^{14}C-glucose radioactivity was determined on barium hydroxide/zinc sulfate precipitated plasma extracts as previously described (12). Plasma DPP-4 activity was measured by an enzymatic assay (1). Plasma intact GLP-1 concentration was measured by ELISA using an N-terminal-specific antibody (Linco Research, St. Charles, MO) in the laboratory of Novartis. Plasma intact GIP concentration was measured by RIA with an antibody specific for the N terminus in the laboratory of Carolyn Deacon (13).

Calculations

Basal rates of appearance in the systemic circulation were measured as the ratio of the [3-^{3}H]glucose infusion rate to the steady-state plasma [3-^{3}H]glucose-specific activity. After glucose ingestion, total rates of glucose appearance and glucose disappearance from the peripheral circulation were computed from the [3-^{3}H]glucose data using a two-compartment model for the glucose system. Calculations were based on a total glucose distribution volume of 250 ml/kg, an initial glucose distribution volume of 65 ml/kg, and a clearance rate of glucose from the first compartment of 29 ml/kg·min. Urinary glucose loss was subtracted from the rate of total glucose disappearance that was integrated over the two time periods (0–480 and 480–840 min) to obtain total tissue glucose disposal during the entire test. The [1-^{14}C]glucose data were used to calculate the appearance of oral glucose. The [1-^{14}C]glucose plasma radioactivity was divided by the specific activity of the glucose drink to calculate the plasma oral glucose concentrations, *i.e.* the levels that glucose would attain in the systemic circulation if the sole source of glucose were the oral load. These calculated oral glucose concentration and the [3-^{3}H]glucose data were then used to compute the appearance of oral glucose in peripheral plasma. The rate of appearance of endogenous glucose was subsequently obtained as the difference between total and oral rates of glucose appearance (14, 15).

Insulin secretory rate (ISR) was estimated from plasma C-peptide levels (16) using ISEC, a program that uses a regularized method of deconvolution constrained to nonnegative values to carry out the calculations (17). An index of β-cell function was calculated as the ratio of the ISR [area under the curve (AUC)] to the plasma glucose (AUC) levels for specified time intervals.

We also examined the effect of vildagliptin on β-cell function using the Mari model (18, 19), which provides four indices of insulin secretion: 1) insulin secretion at a fixed, near basal plasma glucose concentration of approximately 140 mg/dl, which provides an index of basal secretory tone; (2) a dynamic component that represents the dependence of insulin secretion on the plasma glucose concentration and represents β-cell sensitivity to glucose; 3) the rate sensitivity or ability of the β-cell to respond to the rate of change in plasma glucose concentration; and 4)

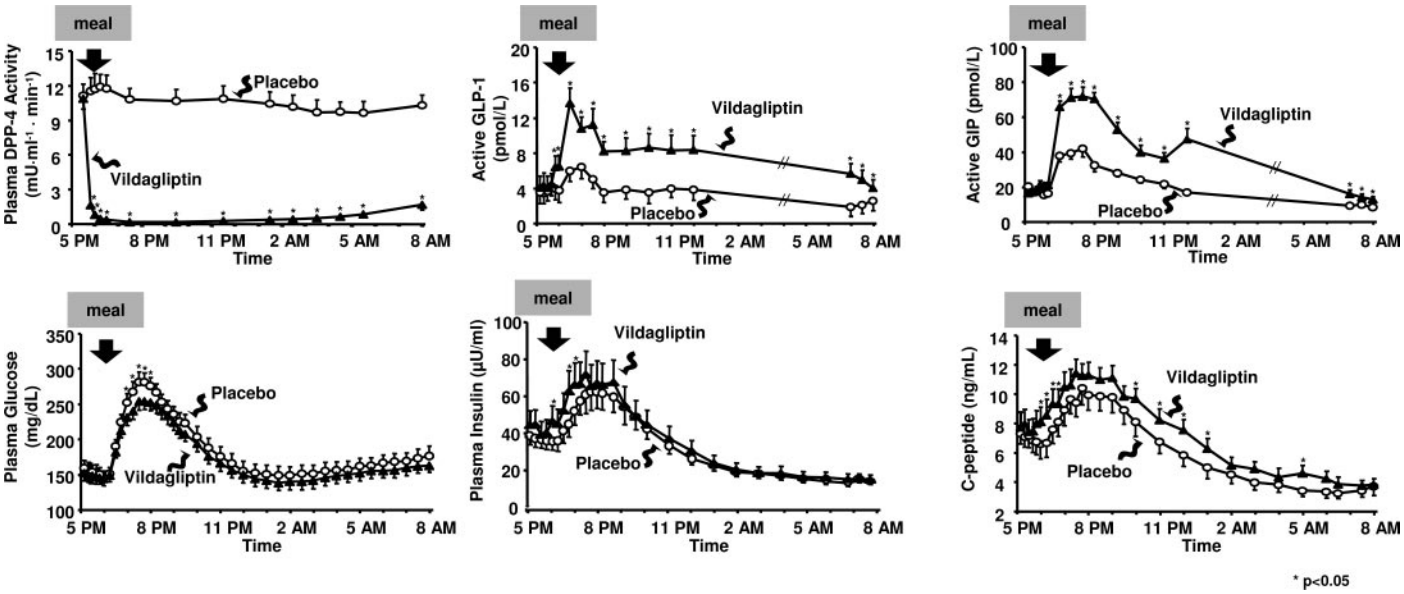

FIG. 1. Plasma DPP-4 activity and plasma GLP-1, GIP, glucose, insulin, and C-peptide concentrations during the meal tolerance test after ingestion of vildagliptin and placebo. Data are the mean ± SE.

a time-dependent potentiation factor that accounts for a number of modulators of insulin secretion.

The absolute and incremental/decremental AUCs for specified time intervals were calculated for each parameter using the trapezoidal method.

Statistical methods

Each of the derived pharmacodynamic end points was summarized by treatment. ANOVA was performed for treatment comparisons. The sources of variation in the ANOVA model were sequence, period, and treatment as fixed effects and subject (sequence) as a random effect. The least squares mean treatment difference and associated *P* value were derived from the comparison between vildagliptin and placebo within the ANOVA. Correlation coefficients (r) were derived and used as a measure of association.

Results

Plasma DPP-4 activity and plasma glucose and hormone levels

After the administration of 100 mg of vildagliptin at 1730 h, there was a prompt and virtually complete suppression of plasma DPP-4 activity, which persisted until 0800 h on the following morning (Fig. 1). DPP-4 inhibition was associated with significant postmeal increases in both plasma GLP-1 and GIP concentrations, which did not return to basal levels until 0800 (Fig. 1). After vildagliptin, meal-stimulated plasma insulin and C-peptide concentrations increased significantly, whereas plasma glucagon decreased significantly (Figs. 1 and 2 and Table 1). These changes in plasma insulin and glucagon concentrations were associated with a significant reduction in postmeal plasma glucose concentration (Fig. 1 and Table 1), which persisted throughout the overnight period, and there was a 14 mg/dl decrease in the FPG on the morning after the administration of vildagliptin, although the decrease in FPG did not reach statistical significance. After vildagliptin there was a tendency for the postmeal plasma FFA concentration to decrease and remain decreased throughout the sleeping hours, but the decline did not reach statistical significance when compared with placebo (data not shown).

The insulin secretory rate (deconvolution of the plasma C-peptide concentration curve) increased significantly within 30 min after ingestion of vildagliptin (Fig. 3) and remained elevated during the postmeal period and throughout the sleeping hours (Fig. 3). Because the primary stimulus for insulin secretion is the rise in plasma glucose concentration, the ISR (AUC)/glucose (AUC) represents an index of β-cell function. During all time periods after vildagliptin, ISR (AUC)/glucose (AUC) was increased (Fig. 3). Using the Mari model (18, 19), after a single dose of vildagliptin, the β-cell dose-response curve was shifted upward so that insulin secretion at 150 mg/dl glucose (approximate basal glucose concentration) was significantly increased (5.2 ± 0.7 *vs.* 4.4 ± 0.7 pmol·kg^{-1}·min^{-1}, $P < 0.04$). The slope of the curve re-

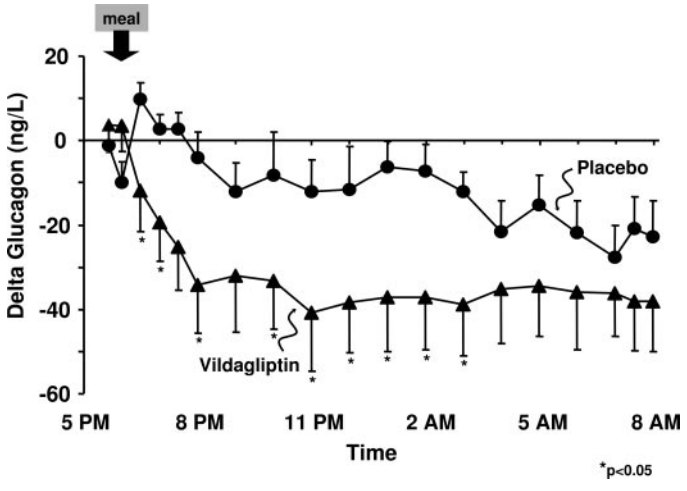

FIG. 2. Change from baseline in plasma glucagon concentration during the meal tolerance test and during the postabsorptive period after ingestion of vildagliptin and placebo. Data are the mean ± SE.

TABLE 1. Effect of vildagliptin and placebo on the plasma glucose and insulin concentrations during the meal tolerance test and postabsorptive period

Parameter	Vildagliptin	Placebo	Mean difference	*P* value
Plasma glucose, time 0 (mg/dl)	144 ± 10	146 ± 9	−2	NS
Mean plasma glucose, 0–120 min (mg/dl)	215 ± 10	233 ± 10	−18	0.001
Mean plasma glucose, 0–240 min (mg/dl)	207 ± 10	222 ± 9	−15	0.001
Plasma glucose at 840 min (mg/dl)	163 ± 10	177 ± 14	−14	NS
Plasma insulin, time 0 (μU/ml)	45 ± 10	36 ± 7	9	0.05
Mean plasma insulin, 0–120 min (μU/ml)	63 ± 14	54 ± 11	9	0.05
Mean plasma insulin, 0–840 min (μU/ml)	33 ± 6	30 ± 6	3	0.04

NS, Not significant.

lating insulin secretion rate to the plasma glucose concentration, *i.e.* glucose sensitivity, tended to increase (0.050 ± 0.007 *vs.* 0.039 ± 0.006 pmol·kg^{-1}·min^{-1}·mg^{-1}·dl, $P = 0.28$), but the difference did not reach statistical significance (Fig. 4). The change in insulin secretion at 150 mg/dl glucose was inversely related to the change in mean plasma glucose concentration during the mixed meal ($r = -0.66$, $P < 0.002$). Vildagliptin did not significantly change the potentiation factor.

Glucose kinetics

During the 6-h period after ingestion of the meal (1800–2400 h), the rate of appearance of oral glucose was similar in the vildagliptin and placebo studies (1.72 ± 0.14 *vs.* 1.61 ± 0.14 mg·kg^{-1}·min^{-1}) and it would be calculated that 66.6 ± 0.9 and 67 ± 0.9 grams of the ingested glucose load was absorbed. The total rate of glucose appearance (oral plus endogenous) in the systemic circulation during the 6 h after ingestion of the meal was similar in both groups (2.84 ± 0.25 *vs.* 2.77 ± 0.21 mg·kg^{-1}·min^{-1}, $P = 0.78$). The difference the rate of total systemic glucose appearance and oral glucose appearance provides the rate of endogenous glucose production (EGP), which primarily reflects the liver, with a small contribution from the kidney. The time course of change in EGP is displayed in Fig. 5. In both the vildagliptin and placebo groups, there was a prompt suppression of EGP after the meal. However, within 60 min after ingestion of the meal, suppression of EGP was greater with vildagliptin and the inhibition of EGP was significantly greater during all time periods from 2000 to 0800 h on the following morning (Fig. 5). From 0 to 240, 0 to 480, and 0 to 840 min, the suppression of EGP was 25, 34, and 59% greater (all $P \leq 0.01$) after vildagliptin *vs.* placebo. The decrement in overnight EGP after vildagliptin was correlated with the decrement in fasting plasma glucose concentration ($r = 0.55$, $P < 0.03$). Both the increments in plasma insulin concentration (C-peptide, ISR) and the decrement in plasma glucagon concentration were correlated with decrement in EGP ($r = 0.51$, $P < 0.05$ and $r = -0.49$, $P < 0.05$, respectively). The increment in insulin to glucagon ratio correlated with the enhanced suppression of EGP ($r = 0.79$, $P < 0.001$). No significant differences were noticed in the glucose disappearance rate or the glucose metabolic clearance rate (Fig. 6) during the vildagliptin *vs.* placebo studies. Urinary excretion of glucose was significantly reduced by vildagliptin during the first 4 h after the ingestion of the mixed meal (757 ± 207 *vs.* 1617 ± 381 mg/dl, $P < 0.02$).

Discussion

To the best of our knowledge, this represents the first study to examine the mechanisms via which vildagliptin acutely reduces the plasma glucose concentration in type 2 diabetic patients. We chose to examine the acute effects of vildagliptin to avoid effects that would be secondary to alterations in the metabolic milieu, *i.e.* reversal of glucotoxic, lipotoxicity, and other as-yet-unrecognized changes. Our results demonstrated that 100 mg vildagliptin reduce the postprandial glucose excursion after ingestion of mixed meal, augment β-cell function, and suppress inappropriate glucagon secretion (therefore improving α-cell function). A single dose of 100 mg vildagliptin at +1730 h caused a greater than 90% suppression of DPP-4 activity that was maintained until 0800 h on the following morning. This inhibition of DPP-4 activity was associated with significant increases on both meal-stimulated plasma active GLP-1 and GIP levels, which remained elevated throughout the evening and sleeping hours and did not return toward basal levels until 0800 h on the following morning. These results suggest that DPP-4 inhibitors can exert effects that persist well beyond the postmeal period.

Consistent with previous publications (3, 9), our results

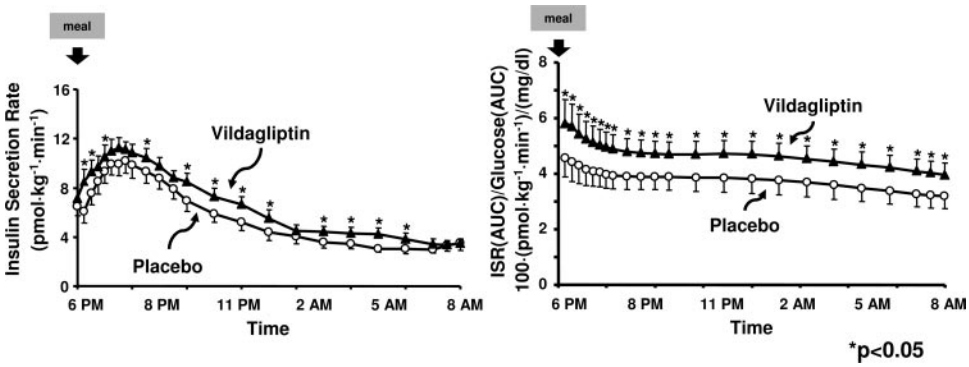

FIG. 3. ISR and ISR (AUC)/plasma glucose (AUC) during the meal tolerance test after ingestion of vildagliptin and placebo. Data are the mean ± SE.

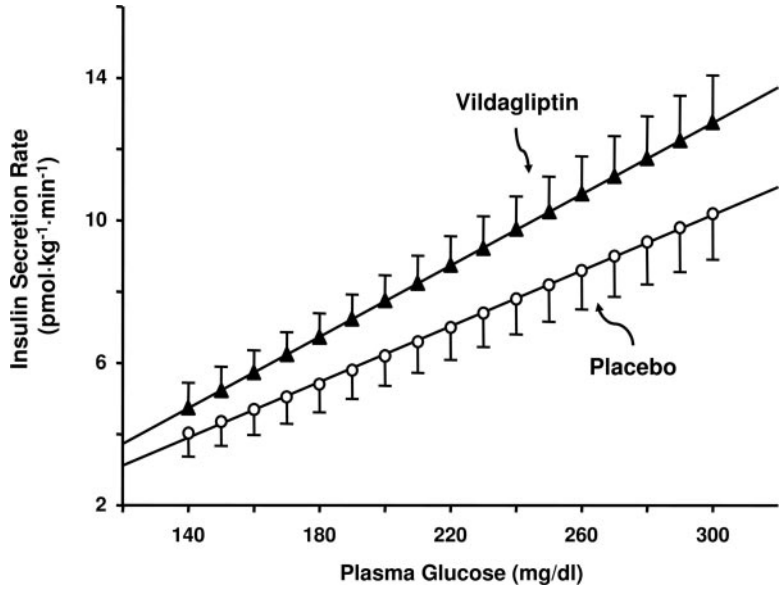

FIG. 4. Effect of vildagliptin and placebo on glucose sensitivity of insulin secretion from the Mari model (18, 19). Data are the mean ± SE.

demonstrate that even a single dose of vildagliptin can augment insulin secretion in T2DM patients (Fig. 3). However, unlike most previous studies, our results demonstrate that both plasma insulin and C-peptide concentrations were increased in absolute terms, whereas previous studies demonstrated reduced or unchanged plasma insulin C-peptide levels which, in the essence of a reduction in plasma glucose concentration, led to an increase in ISR (AUC)/glucose (AUC). This difference between our present and prior studies may be explained by the fact that we measured the plasma insulin response after the evening meal, whereas previous studies evaluated insulin secretion in the morning after an overnight fast. Because the plasma insulin concentration provides only an indirect measure of insulin secretion, we also measured the plasma C-peptide concentration and, by deconvolution analysis (16, 17), calculated the ISR. In each subject we observe an increase in ISR (AUC)/glucose (AUC) (Fig. 3), which did not return to values observed in the placebo-treated group until 0600 h on the following morning, *i.e.* approximately 12 h after the vildagliptin was ingested. We also examined the effect of vildagliptin on β-cell function using the Mari model (18, 19). Consistent with previous results in which vildagliptin was administered to T2DM subjects for 28 d, there was an upward shift of the β-cell dose-response curve such that insulin secretion at 150 mg/dl glucose, *i.e.* about the plasma glucose concentration at the start of the mixed meal, increased significantly. There also was a modest increase in the slope of the dose-response curve relating the insulin secretory rate of the plasma glucose concentration (Fig. 4). Collectively, these results demonstrate that a single dose of vildagliptin is capable of improving β-cell function. Neither the rate sensitivity nor the potentiation factor changed significantly after vildagliptin.

No previous study has examined the effect of DPP-4 inhibition on glucose kinetic after ingestion of a mixed meal in T2DM individuals. Vildagliptin administration 30 min before meal ingestion significantly reduced the postprandial plasma glucose excursion. This could not be explained by an alteration in glucose appearance or enhanced splanchnic glucose uptake because the rate of appearance of ingested ^{14}C-glucose was virtually identical in the vildagliptin and placebo studies. Rather, the rate of endogenous (primarily reflecting hepatic) glucose production was significantly reduced after vildagliptin. Although a small amount of EGP has been shown to be derived from the kidney, we believe that the enhanced suppression of EGP after vildagliptin primarily reflects an effect on the liver because previous studies (20) have shown that ingestion of a mixed meal has no effect on renal glucose production in type 2 diabetic patients. This reduction in EGP is most likely explained by two factors: 1) an increase in insulin secretion, leading to enhanced portal delivery of insulin to the liver, and 2) enhanced suppression of plasma glucagon concentration (Fig. 2). However, an effect on the liver independent of insulin and glucagon, possibly mediated by GLP-1 (21), cannot be excluded. During the 6-h period after meal ingestion, vildagliptin caused a 1.3-fold greater reduction in EGP than placebo. Both the increments (increases) in plasma insulin concentration (C-peptide, ISR) and the decrement (decrease) in plasma glucagon concen-

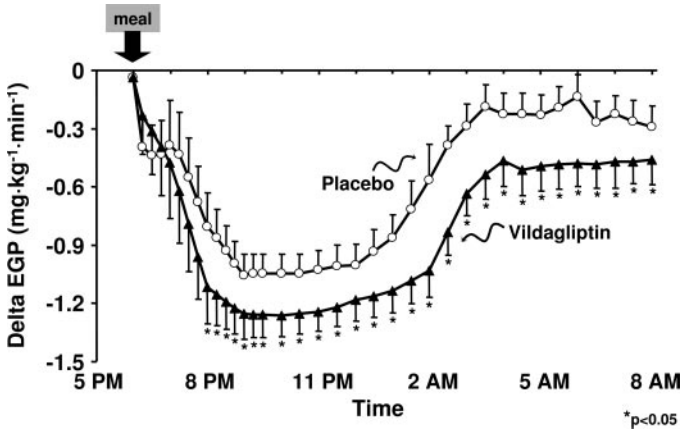

FIG. 5. Change from baseline in the rate of EGP during the meal tolerance test and postabsorptive period after ingestion of vildagliptin and placebo. Data are the mean ± SE.

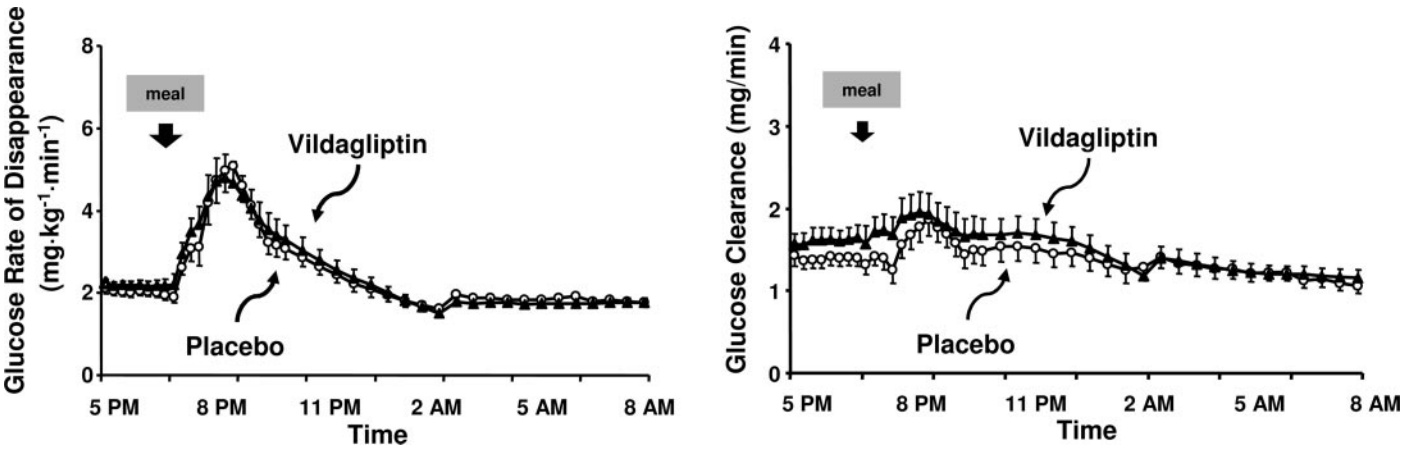

FIG. 6. Total body rate of glucose disappearance and glucose clearance during the meal tolerance test and during the postabsorptive period after ingestion of vildagliptin and placebo. Data are the mean ± SE.

tration were correlated with decrement (decrease) in EGP. Not surprisingly, the increment (increase) in insulin to glucagon ratio, which is the primary determinant of hepatic glucose production, was strongly correlated with the enhanced suppression of EGP ($r = 0.79$). It is noteworthy that the reduction in fasting plasma glucose concentration and EGP, after vildagliptin persisted long after the meal was completely absorbed and persisted until 0800 h on the following morning. During this overnight period, the reduction in EGP was correlated with the decrease in FPG concentration ($r = 0.55$). The observation is consistent with previous studies that have demonstrated that the rate of basal EGP is the primary determinant of the fasting plasma glucose concentration (22).

Two previous studies (9, 10) demonstrated an improvement in insulin sensitivity in T2DM subjects after chronic vildagliptin administration. In the present study, we failed to observe any increase in either the rate of glucose disappearance or the metabolic clearance rate of glucose after the mixed meal in vildagliptin-treated subjects. The difference between the present and previous studies may reflect the duration of treatment: one dose *vs.* 28 d (10) and 1 yr (9). It is noteworthy that there was a tendency for the plasma FFA concentration to decline in the present study. It is possible that more chronic DPP-4 inhibition would have resulted in a more substantial decline in plasma FFA and increase in insulin-stimulated glucose disposal. The most likely explanation for the downward trend in plasma FFAs after meal ingestion is the increase in plasma insulin level with resultant inhibition of lipolysis.

Lastly, vildagliptin therapy was associated with a significant reduction in urinary glucose excretion after meal ingestion. This simply could be explained by the reduction in postprandial plasma glucose excursion. However, it remains to be determined whether the increases in GLP-1 and/or GIP either directly or indirectly influence renal glucose handling. With respect to this possibility, acute GLP-1 administration has been shown to reduce glomerular hyperfiltration in T2DM patients (23).

In summary, a single dose of 100 mg of vildagliptin administered before the evening meal: 1) causes a sustained inhibition of plasma DPP-4 activity and increase meal/post meal levels of GLP-1 and GIP; 2) improves β-cell function as manifested by an increase in ISR(AUC)/glucose(AUC) and by modeling; 3) augments meal/postprandial plasma insulin levels and reduces plasma glucagon concentration; 4) improves meal glucose tolerance primarily related to enhanced suppression of EGP; and 5) decreases overnight plasma glucose levels, which are correlated with a significant reduction in endogenous glucose production.

Acknowledgments

Received August 28, 2006. Accepted January 17, 2007.

Address all correspondence and requests for reprints to: Bogdan Balas, M.D., Diabetes Division, University of Texas Health Science Center at San Antonio, 7703 Floyd Drive, MC 7886, San Antonio, Texas 78229. E-mail: balas@uthscsa.edu.

Disclosure Statement: B.B., M.R.B., and C.D. have nothing to disclose. C.W., M.L.-S., Y.-L.H., and J.E.F. are employed and have equity interest in Novartis. B.E.D. has equity interest in Novartis and Merck. Y.W. is employed by Novartis. J.J.H. has grant support from Novartis and consults for Merck and Novo-Nordisk. C.F.D. consults for BMS and Takeda. K.C. consults for Abbott, Pfizer, Novartis, Merck, and Lilly. A.M. has grant support from Novartis. R.A.D. consults for Novartis, Eli Lilly, Bristol Myers Squibb, Roche, Amylin, and Takeda and has grant support from Bristol Myers Squibb, Novartis, and Eli Lilly.

References

1. **Villhauer EB, Brinkman JA, Naderi GB, Burkey BF, Dunning BE, Prasad K, Mangold BL, Russell ME, Hughes TE** 2003 1-[[(3-Hydroxy-1-adamantyl)amino]acetyl]2-cyano-(S)-pyrrolidine: a potent, selective, and orally bioavailable dipeptidyl peptidase IV inhibitor with antihyperglycemic properties. J Med Chem 46:2774–2789
2. **Dardik B, Valentin M, Schwartzkopf C, Gutierrez C, Stevens D, Russel M, Villhauer E, Hughes T** 2003 NVP-LAF237, a dipeptidyl peptidase IV inhibitor, improves glucose tolerance and delays gastric emptying in obese insulin resistant cynomolgus monkeys. Diabetes 52(Suppl 1):A322
3. **Ahren B, Landin-Olsson M, Jansson PA, Svensson M, Holmes D, Schweizer A** 2004 Inhibition of dipeptidyl peptidase-4 reduces glycemia, sustains insulin levels, and reduces glucagon levels in type 2 diabetes. J Clin Endocrinol Metab 89:2078–2084
4. **Ahren B, Gomis R, Standl E, Mills D, Schweizer A** 2004 Twelve- and 52-week efficacy of the dipeptidyl peptidase IV inhibitor LAF237 in metformin-treated patients with type 2 diabetes. Diabetes Care 27:2874–2880
5. **Kreymann B, Williams G, Ghatei MA, Bloom SR** 1987 Glucagon-like peptide-1 7–36: a physiological incretin in man. Lancet 2:1300–1304
6. **Nauck MA, Heimesaat MM, Behle K, Holst JJ, Nauck MS, Ritzel R, Hufner M, Schmiegel WH** 2002 Effects of glucagon-like peptide 1 on counterregulatory hormone responses, cognitive functions, and insulin secretion during hyperinsulinemic, stepped hypoglycemic clamp experiments in healthy volunteers. J Clin Endocrinol Metab 87:1239–1246

7. **Nauck MA, El-Ouaghlidi A** 2005 The therapeutic actions of DPP-IV inhibition are not mediated by glucagon-like peptide-1. Diabetologia 48:608–611
8. **Holst JJ, Deacon CF** 2005 Glucagon-like peptide-1 mediates the therapeutic actions of DPP-IV inhibitors. Diabetologia 48:612–615
9. **Ahren B, Pacini G, Foley JE, Schweizer A** 2005 Improved meal-related β-cell function and insulin sensitivity by the dipeptidyl peptidase-IV inhibitor vildagliptin in metformin-treated patients with type 2 diabetes over 1 year. Diabetes Care 28:1936–1940
10. **Mari A, Sallas WM, He YL, Watson C, Ligueros-Saylan M, Dunning BE, Deacon CF, Holst JJ, Foley JE** 2005 Vildagliptin, a dipeptidyl peptidase-IV inhibitor, improves model-assessed β-cell function in patients with type 2 diabetes. J Clin Endocrinol Metab 90:4888–4894
11. **Burkey BF, Li X, Bolognese L, Balkan B, Mone M, Russell M, Hughes TE, Wang PR** 2005 Acute and chronic effects of the incretin enhancer vildagliptin in insulin-resistant rats. J Pharmacol Exp Ther 315:688–695
12. **Groop LC, Bonadonna RC, DelPrato S, Ratheiser K, Zyck K, Ferrannini E, DeFronzo RA** 1989 Glucose and free fatty acid metabolism in non-insulin-dependent diabetes mellitus. evidence for multiple sites of insulin resistance. J Clin Invest 84:205–213
13. **Deacon CF, Nauck MA, Meier J, Hucking K, Holst JJ** 2000 Degradation of endogenous and exogenous gastric inhibitory polypeptide in healthy and in type 2 diabetic subjects as revealed using a new assay for the intact peptide. J Clin Endocrinol Metab 85:3575–3581
14. **Radziuk J, Norwich KH, Vranic M** 1978 Experimental validation of measurements of glucose turnover in nonsteady state. Am J Physiol 234:E84–E93
15. **Ferrannini E, Simonson DC, Katz LD, Reichard Jr G, Bevilacqua S, Barrett EJ, Olsson M, DeFronzo RA** 1988 The disposal of an oral glucose load in patients with non-insulin-dependent diabetes. Metabolism 37:79–85
16. **Van Cauter E, Mestrez F, Sturis J, Polonsky KS** 1992 Estimation of insulin secretion rates from C-peptide levels. Comparison of individual and standard kinetic parameters for C-peptide clearance. Diabetes 41:368–377
17. **Hovorka R, Soons PA, Young MA** 1996 ISEC: a program to calculate insulin secretion. Comput Methods Programs Biomed 50:253–264
18. **Mari A, Schmitz O, Gastaldelli A, Oestergaard T, Nyholm B, Ferrannini E** 2002 Meal and oral glucose tests for assessment of β-cell function: modeling analysis in normal subjects. Am J Physiol Endocrinol Metab 283:E1159–E1166
19. **Mari A, Tura A, Gastaldelli A, Ferrannini E** 2002 Assessing insulin secretion by modeling in multiple-meal tests: role of potentiation. Diabetes 51(Suppl 1):S221–S226
20. **Meyer C, Woerle HJ, Dostou JM, Welle SL, Gerich JE** 2004 Abnormal renal, hepatic, and muscle glucose metabolism following glucose ingestion in type 2 diabetes. Am J Physiol Endocrinol Metab 287:E1049–E1056
21. **Prigeon RL, Quddusi S, Paty B, D'Alessio DA** 2003 Suppression of glucose production by GLP-1 independent of islet hormones: a novel extrapancreatic effect. Am J Physiol Endocrinol Metab 285:E701–E707
22. **DeFronzo RA, Ferrannini E, Simonson DC** 1989 Fasting hyperglycemia in non-insulin-dependent diabetes mellitus: contributions of excessive hepatic glucose production and impaired tissue glucose uptake. Metabolism 38:387–395
23. **Gutzwiller JP, Tschopp S, Bock A, Zehnder CE, Huber AR, Kreyenbuehl M, Gutmann H, Drewe J, Henzen C, Goeke B, Beglinger C** 2004 Glucagon-like peptide 1 induces natriuresis in healthy subjects and in insulin-resistant obese men. J Clin Endocrinol Metab 89:3055–3061

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.