Suppression of glucose production by GLP-1 independent of islet hormones: a novel extrapancreatic effect

Ronald L. Prigeon,1,2 Shaista Quddusi,1 Breaey Paty,1 and David A. D’Alessio1,3

1Division of Metabolism, Endocrinology, and Nutrition, University of Washington, 2Veterans Affairs Medical Center/Geriatric Research, Education, and Clinical Center, Baltimore, Maryland 21201; and 3Division of Endocrinology, University of Cincinnati, Cincinnati, Ohio 45267-0547

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Glucagon-like peptide-1 (GLP-1; 7–36 amide) is an intestinal hormone that plays an important role in glucose homeostasis. GLP-1 is a potent insulinotropin that is secreted after oral ingestion, thereby contributing to the incretin effect (the greater insulin release occurring after oral compared with intravenous glucose administration; see Refs. 9, 28, and 35). GLP-1 also decreases glucagon release, either through direct interaction with the α-cell or indirectly via stimulation of insulin and somatostatin secretion (10, 47). Thus the overall effect of GLP-1 on pancreatic islet secretion is to decrease circulating glucose concentrations. In addition to the regulation of islet hormones, GLP-1 slows gastric emptying (49), another action that attenuates the rise in plasma glucose after meal ingestion. This broad range of acute effects on processes governing circulating levels of glucose has stimulated interest in using GLP-1 or GLP-1 analogs for the treatment of diabetes.

Many investigators have also suggested that GLP-1 has effects on glucose metabolism beyond the regulation of pancreatic islet hormone secretion, e.g., extrapancreatic effects. The first report was from Gutniak and colleagues (20) who demonstrated that in C-peptide-negative type 1 diabetic subjects studied with hyperinsulinemic clamps, the glucose infusion rate necessary to maintain euglycemia was increased 15–20% by a concurrent infusion of GLP-1 (20). Subsequently, several groups noted effects of GLP-1 to promote glucose uptake in skeletal muscle, adipocyte, or hepatocyte preparations in vitro (16, 21, 27, 45). Although the initial in vivo study by Gutniak et al. was consistent with the in vitro results, subsequent studies in humans have been divergent, with some studies favoring extrapancreatic effects of GLP-1 (11, 12, 15, 29, 30, 39, 43) and others showing no effect (2, 34, 38, 44). Furthermore, even among the studies that demonstrated an extrapancreatic effect, there has been a disparity in the apparent site of action of the GLP-1, with some investigators suggesting an effect on peripheral tissues (15, 29, 30, 43), whereas others suggested an effect on endogenous glucose production (EGP; see Ref. 39).

Our own studies demonstrated that administration of GLP-1 to healthy humans during intravenous glucose tolerance tests (IVGTT) promoted glucose disappearance not only by stimulating insulin secretion but also by increasing insulin-independent glucose disposition with no effect on insulin sensitivity (11, 12). Because insulin-independent glucose disposition obtained from modeling of glucose and insulin kinetics during an IVGTT gives a measure of the combined effect of glucose disposal and EGP, the changes that
were observed could be the result of an effect of GLP-1 to increase disposal, suppress production, or both. As our initial step to determine whether GLP-1 affects has direct effects on glucose disposal and/or EGP, we performed pilot experiments in which we infused healthy subjects with [3H]glucose tracer during IVGTT performed with and without GLP-1 (37). In these experiments, there was no difference in the disappearance of glucose tracer between the GLP-1 and control studies, whereas overall insulin-independent glucose disposition was augmented. Because alterations in tracer disappearance during an IVGTT reflect only changes in glucose disposal, this suggested to us that the insulin-independent effects of GLP-1 were not the result of augmentation of peripheral glucose uptake and so might be the result of effects of GLP-1 on EGP. The present study reports the results of an experiment designed to directly test this hypothesis. We used a modification of the pancreatic clamp technique with [3H]glucose as a tracer to study healthy, nondiabetic human subjects. The studies were carried out under near-basal conditions in which the EGP rate was high and glucose levels were <5.5 mM to minimize any residual effect of GLP-1 on pancreatic function.

METHODS

Subjects. Nine healthy male subjects aged 24–64 yr, with a mean body weight of 81 ± 11 kg (body mass index 25 ± 1.3), free of chronic medical conditions, taking no medications, and without a family history of diabetes, were recruited for this study. Eight subjects participated in the study of GLP-1 effects on glucose turnover; three of these subjects and the ninth volunteer also participated in a control study without GLP-1. All of the subjects had normal fasting blood glucose values demonstrated on at least two occasions although oral glucose tolerance tests were not performed. Subjects signed an informed consent form approved by the Human Subjects Committee at the University of Washington.

Experimental protocol. Eight subjects participated in this protocol in which GLP-1 was infused while insulin and glucagon levels were clamped (Fig. 1). In the morning after an overnight fast, intravenous cannulas were placed in each forearm for the withdrawal of blood and infusion of hormones and glucose; the arm used for sampling was wrapped in a heating pad to arterialize the blood. After the removal of fasting blood samples, a primed, continuous infusion of [3-3H]glucose (25 μCi followed by 0.25 μCi/min) was initiated and maintained throughout the study. Approximately 20 min thereafter, an infusion of octreotide (30 ng·kg\(^{-1}\)·min\(^{-1}\)) was initiated followed ~30 min later with infusions of insulin (0.1–0.2 mU·kg\(^{-1}\)·min\(^{-1}\)) and glucagon (0.5–0.65 ng·kg\(^{-1}\)·min\(^{-1}\)). The hormone infusion rates were selected based on those used by others to mimic fasting hormone levels (24, 44). Blood was sampled at 5- to 15-min intervals throughout the study, and glucose concentrations were measured at the bedside using a glucose analyzer (Beckman Instruments, Fullerton, CA). Initially, both insulin and glucagon infusion rates were adjusted to achieve and maintain blood glucose in the fasting range. Subsequently, only the glucagon infusion rate was adjusted to avoid the slow response time for insulin rate changes. After sufficient time had elapsed for tracer and hormone equilibrium, and plasma glucose levels were stable, synthetic GLP-1 was administered intravenously at a rate of 30 pmol·kg\(^{-1}\)·h\(^{-1}\) for 60 min. Although the time to achieve glucose stability was variable, a minimum of 200 min of tracer and octreotide infusion, 90 min of a final rate of insulin infusion, and 60 min of a final rate of glucagon infusion were established in each subject before giving GLP-1.

Synthetic GLP-1 was synthesized by solid-state methods at the Peptide Core Laboratory maintained by the Department of Pharmacology at the University of Washington, and purified by HPLC. Purity was confirmed by analytical HPLC and mass spectroscopy, and lyophilized aliquots of the peptide were tested to ensure sterility and absence of pyrogens before use.

Four subjects (three of whom also participated in the GLP-1 study) participated in a protocol to examine the stability of rate of appearance (Ra) and disappearance (Rd) values. These individuals were studied for 5 h using methods identical to those described above except that no GLP-1 was administered.

Assays. Blood samples were placed in tubes containing heparin for determinations of glucose, insulin, and glucose radioactivity, a benzamidine-based antiproteolytic cocktail for glucagon measurement (17), and 50 mM EDTA plus 500 KIU/ml aprotinin for assay of GLP-1 and C-peptide. Blood samples were immediately placed on ice and centrifuged within 1 h, and the plasma was removed and stored at −20°C until assay. Plasma glucose was measured using a glucose oxidase method, and glucose radioactivity was determined in plasma and infused by liquid scintillation counting (36). GLP-1 immunoreactivity (GLP-1-IR) was measured by RIA using antisera 89390 (kindly provided by Dr. Jens Holst, Panum Institute, Copenhagen, Denmark) as described by Orskov et al. (33) from ethanol extracts of plasma. The antisera used in this assay recognizes both the intact hormone GLP-1(7–36)NH\(_2\) and the metabolite GLP-1(9–36)NH\(_2\) and is a reliable index of the active hormone under steady-state conditions (13). Insulin (51), C-peptide (Linco Research, St. Charles, MO), and glucagon (17) concentrations were determined using previously described RIA.

Calculations and data analysis. Glucose Ra and Rd were calculated using Steele’s equations for nonsteady states (40) after smoothing glucose and radioactivity values using generalized cross-validatory spline approximation (50). Fasting levels of glucose and hormones were computed as the means of four samples taken 15 min before the initiation of octreotide. Baseline insulin, C-peptide, glucagon, and glucose Ra and Rd were computed as the mean of the samples taken during the 30 min before initiation of the GLP-1 infusion. Mean values of the same parameters were also calculated for samples drawn during the GLP-1 infusion. Changes in response to GLP-1 were made by comparison of baseline values with the values obtained during GLP-1 infusion using repeated-measures ANOVA with Dunnett’s test for post hoc comparisons. In addition, mean values for the baseline and

![Figure 1: Experimental protocol. GLP, glucagon-like peptide.](http://ajpendo.physiology.org/DownloadedFrom)
GLP-1 periods were compared using paired t-tests. Data are presented as means ± SE.

RESULTS

Eight subjects participated in the protocol in which the effect of GLP-1 on $R_a$ and $R_d$ during a pancreatic clamp was determined. Fasting insulin and glucagon concentrations were 84.6 ± 20.0 pM and 55.5 ± 6.1 ng/l, respectively. Infusion of octreotide for 30 min before replacement of islet hormones resulted in significantly lower insulin [40 ± 7.2 pM ($P < 0.01$ vs. fasting)] and glucagon [42.3 ± 5.7 ng/l ($P < 0.05$ vs. fasting)] levels. With insulin and glucagon replacement, the average rates necessary to achieve glucose stabilization at fasting levels were 0.15 ± 0.01 mU·kg⁻¹·min⁻¹ and 0.64 ± 0.11 ng·kg⁻¹·min⁻¹, respectively. The final baseline insulin and glucagon concentrations achieved during the pancreatic clamp before GLP-1 infusion were 115 ± 14 pM and 64.7 ± 11.5 ng/l, respectively.

Fasting concentrations of GLP-1-IR were 7.4 ± 0.9 pM and decreased slightly to 6.6 ± 1.0 pM during the final 30 min before GLP-1 infusion (Fig. 2A). Initiation of the GLP-1 infusion started a mean of 275 ± 14 min after the start of octreotide. After the initiation of GLP-1 infusion, levels increased promptly to 28.5 ± 0.7 pM.

Fasting concentrations of glucose in the eight men were 5.4 ± 0.2 mM and were stabilized during the pancreatic clamp to a baseline value of 4.8 ± 0.2 mM.

The coefficient of variation for plasma glucose during the 60 min before the GLP-1 infusion was 4.1 ± 0.6%. After the infusion of GLP-1, glucose values decreased in all eight subjects within 20 min ($P < 0.01$) and remained suppressed throughout the 60 min of GLP-1 infusion (Fig. 2B). The glucose nadir of 4.1 ± 0.2 mM after 50 min of GLP-1 represents a decrease of 15% from steady-state levels.

Peripheral insulin (Fig. 3A and Table 1) levels were unchanged during GLP-1 administration compared with the pre-GLP-1 baseline. Similarly, concentrations of C-peptide did not differ in the period after GLP-1 infusion.

Table 1. Mean values for glucose, insulin, C-peptide, glucagon, $R_a$, $R_d$ and glucose clearance before and after GLP-1 infusion

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>GLP-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose, mM</td>
<td>4.81 ± 0.2</td>
<td>4.40 ± 0.2*</td>
</tr>
<tr>
<td>Insulin, pM</td>
<td>115 ± 14</td>
<td>113 ± 11</td>
</tr>
<tr>
<td>C-peptide, nM</td>
<td>0.153 ± 0.029</td>
<td>0.156 ± 0.026</td>
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<tr>
<td>Glucagon, ng/l</td>
<td>64.7 ± 11.5</td>
<td>65.8 ± 13.8</td>
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<tr>
<td>$R_a$, µmol·kg⁻¹·min⁻¹</td>
<td>22.6 ± 2.8</td>
<td>19.1 ± 2.8*</td>
</tr>
<tr>
<td>$R_d$, µmol·kg⁻¹·min⁻¹</td>
<td>22.2 ± 2.7</td>
<td>21.7 ± 2.6</td>
</tr>
<tr>
<td>Glucose clearance, l·min⁻¹·kg⁻¹</td>
<td>3.7 ± 0.4</td>
<td>4.2 ± 0.6</td>
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</table>

Values are means ± SE. $R_a$, rate of appearance; $R_d$, rate of disappearance; GLP, glucagon-like peptide. *Values different from baseline, $P < 0.05$.
administration compared with baseline (Tables 1 and 2). These values indicate that there was no stimulation of the β-cell by GLP-1 at ambient glucose concentrations slightly less than the fasting values. In addition, plasma glucagon levels were stable before and after the GLP-1 infusion (Fig. 3B and Table 1).

Rates of Ra and Rd over the 60 min before and during GLP-1 infusion are shown in Fig. 4. Both the Ra and Rd were stable before infusion of GLP-1. After GLP-1 administration, the mean Ra for the 60 min of peptide infusion decreased in all eight subjects (P = 0.036; Figs. 4A and 5 and Table 1), with a nadir of 16.6 ± 2.2 μmol·kg⁻¹·min⁻¹ 20–30 min after initiation of the infusion representing an ~25% decrease in EGP. There was no significant change in Rd during the GLP-1 infusion (Fig. 4B and Table 1). Because of the decrease in glucose concentration in response to the GLP-1 infusion, a trend toward an increase in glucose clearance was observed (3.7 ± 0.4 vs. 4.2 ± 0.6 l·min⁻¹·kg⁻¹, P = 0.062).

The stability of Ra and Rd under the conditions of our experiment, but without infusion of GLP-1, was assessed in four subjects. In this protocol, pancreatic clamps were performed for 5 h without a superimposed GLP-1 infusion. During the final 2-h period, circulating levels of insulin and glucagon were 82.2 ± 18.6 pM and 73.6 ± 9.8 ng/l, respectively. Plasma glucose averaged 5.1 ± 0.4 mM over this period, with a coefficient of variation of 7.9 ± 2.3%. The mean rates of glucose turnover, 14.2 ± 0.6 μmol·kg⁻¹·min⁻¹, were lower than the baseline rates for the GLP-1 infusion study, likely because of the lower levels of islet hormones achieved in the four subjects studied. However, the mean rates of Ra and Rd over the final 120 min fluctuated only modestly, with coefficients of variation of 11 and 8%. These results demonstrate that Ra and Rd are stable during the pancreatic clamp conditions we used to study GLP-1 effects.

DISCUSSION

The results of the current study demonstrate that GLP-1 suppresses Ra (in this case representing EGP) in healthy humans in an experimental setting where islet hormone levels are fixed. This novel finding indicates that GLP-1 can affect EGP independent of insulin and glucagon and raises the possibility of another physiological role for GLP-1 to promote glucose homeostasis. Although the existence of extrapancreatic effects of GLP-1 has been reported in several previous

Table 2. Plasma C-peptide concentrations in the 8 subjects immediately before and after GLP-1 infusion

<table>
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<tr>
<th>Time, min</th>
<th>Subject No.</th>
<th>Mean ± SE</th>
<th>Subject No.</th>
<th>Mean ± SE</th>
<th>Subject No.</th>
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<td>0.13</td>
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<td>4</td>
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<td>0.07</td>
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<tr>
<td>0</td>
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<td>2</td>
<td>0.20</td>
<td>3</td>
<td>0.20</td>
<td>4</td>
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Fig. 4. Rates of glucose appearance (Ra; A) and glucose disappearance (Rd; B) in 8 healthy men before and during infusion of GLP-1. Data points represent means ± SE. *Difference from baseline, P < 0.05.

Fig. 5. Ra at baseline and during 60 min of GLP-1 infusion in 8 healthy men. *Difference from baseline, P < 0.05.
studies in humans (11, 12, 15, 20, 29, 30, 39, 43), the present report is the first to specifically identify suppression of EGP as a site of islet-independent GLP-1 action.

Hvidberg and coworkers (22) were the first to demonstrate that GLP-1 decreased EGP in fasting humans. However, they did not inhibit islet hormone secretion and observed significant increases in insulin and decreases in glucagon concentrations when GLP-1 was given. Therefore, they attributed the observed effects of GLP-1 on EGP to the changes in the islet hormones. The protocol we used was different from that of Hvidberg et al. (22) in that octreotide was given to inhibit islet hormone secretion. Based on the peripheral concentrations of insulin, glucagon, and C-peptide that did not change in response to the GLP-1 infusion, we were successful in clamping the islet hormones. The decrease in EGP under these conditions indicates that an islet-independent effect of GLP-1 on EGP exists in addition to that mediated by alterations in islet hormone concentrations.

We used the fasting blood glucose concentration for each subject as the glycemic target and adjusted insulin and glucagon infusion rates to achieve this level with the rationale that glucose production is relatively high in the fasting state and that this would be the optimal situation to demonstrate effects of GLP-1 on EGP. We achieved our goal of clamping the blood glucose in the fasting range, but with some discrepancies in matching the baseline levels of insulin and glucagon to fasting concentrations of these hormones; average plasma glucagon and insulin concentrations for the group were 15–20% higher than in the fasting state. The variation between fasting and baseline levels of insulin and glucagon likely accounts for the wide range and higher average rate of steady-state $R_a$ and $R_d$ in our subjects relative to values that are commonly observed for normal fasting subjects (7, 23). In fact, there was a strong correlation between the differences in fasting and clamped insulin and glucagon concentrations and the steady-state glucose $R_a$; the greater the difference in clamped to fasting hormone levels the higher the $R_a$ ($r = 0.59$ for insulin and 0.60 for glucagon). However, despite the variation in antecedent rates of steady-state $R_a$ and $R_d$ among the subjects, GLP-1 suppressed plasma glucose and $R_a$ in each of them (Fig. 5). This demonstrates that the effect of GLP-1 was not only independent of the plasma insulin and glucagon levels but is maintained across a range of EGP rates.

Infusion of GLP-1 decreased plasma glucose levels to an average minimum of 4.1 mM, but to a level as low as 3.3 mM in one subject. Under these conditions, it is possible that counterregulatory factors or the decreased concentration of glucose per se attenuated any further effect of GLP-1 on EGP. Therefore, the magnitude of suppression of $R_a$ under the experimental conditions of this study, −15–25% (Fig. 4), may be a conservative estimate of the capacity of GLP-1 to inhibit EGP. It is plausible that the effect may be greater when glucose levels are clamped or under altered metabolic conditions such as diabetes where $R_a$ is increased.

We were unable to demonstrate that GLP-1 affected $R_d$. However, when we considered that glucose concentrations were lower after GLP-1 infusion, a near-significant increase in glucose clearance was observed. Although it is possible that a significant change could be detected by adding more subjects, it appears that the GLP-1 effect on EGP is more important than the possible effect on glucose clearance under fasting conditions.

Several other groups have studied the effects of GLP-1 on EGP during blockade of islet hormone secretion with results that conflict with ours. However, there were significant methodological differences between these studies and ours that may explain this discordance. For example, Toft-Neilsen et al. (42) and Larsson and colleagues (26) gave GLP-1 during pancreatic clamps in which insulin and glucagon were not replaced. Under these conditions, baseline $R_a$ was substantially decreased (18, 31), and the ability to detect further effects of GLP-1 is muted. Orskov et al. (34) found no effect of GLP-1 on $R_a$ in healthy subjects during pancreatic clamps with glucagon replacement and euglycemic hyperinsulinemia. However, the elevations in plasma insulin in this study were sufficient for near-complete inhibition of EGP. Similarly, Vella et al. (44) found no effect of GLP-1 to suppress EGP in persons with type 2 diabetes, and Egan and coworkers (15) noted a similar lack of effect in obese, insulin-resistant subjects. However, in these studies, infusion of GLP-1 was initiated coincident with increases in plasma levels of insulin, or insulin and glucose, which were sufficient to significantly suppress EGP. Thus the experimental conditions described in these reports were not optimal for testing the effects of GLP-1 on EGP per se. Finally, Shalev et al. (39) found that GLP-1 decreased $R_a$ and increased $R_d$, but they were not successful in completely inhibiting β-cell secretion and so could not separate insulin-dependent from insulin-independent effects (39). Thus we believe that the differences between our findings and those of previous studies (15, 26, 34, 39, 42, 44) can be credibly explained by methodological differences, primarily in that previous studies examined EGP under conditions where it is low or being suppressed by other factors so that effects of GLP-1 on EGP are difficult to detect.

Although we have shown that GLP-1 suppresses EGP at fixed levels of circulating insulin and glucagon, we cannot discern the specific site(s) of action at which this occurs from our current protocol. Because the major sources of glucose production in the fasting state are the liver and the kidney, the results of this study indicate a regulatory role for GLP-1 at one or both of these sites. There is some controversy regarding the distribution of the GLP-1 receptor in mammals. Most (4, 5, 41), but not all (48), investigators have been unable to find evidence of GLP-1 receptor gene expression in hepatic cells. Although most of these analyses have been performed in rat tissues (4, 5, 41, 48), two groups have been unable to find GLP-1 receptor mRNA
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in extracts from human liver (14, 46). Several investigators have demonstrated GLP-1 receptor expression in kidney extracts (5, 48), so it is possible that GLP-1 selectively inhibits renal glucose production. Alternatively, it has been theorized that there may be as yet undiscovered GLP-1 receptor subtypes (5, 14, 15) that could account for GLP-1 regulation of liver glucose metabolism. Yet another possibility is suggested in a paper by Nakabayashi et al. (32) who describe an increase in hepatic vagal afferent impulses after perfusion of GLP-1 through the rat portal vein and suggest that specific neural sensing of gut peptides may take place in the portal bed (32). This hypothesis is supported by the recent findings of Balkan and Li (3) and Burcelin et al. (6) who noted differential effects of intraportal and peripheral GLP-1 infusions. Although each of these possibilities provides a tenable mechanism whereby GLP-1 could inhibit EGP, further work will be needed to clarify this issue.

GLP-1 is secreted rapidly after meal ingestion and peaks at 20–30 min postcibum (25). This pattern of release is consistent with the action of an incretin hormone in that insulin secretion is augmented with the first rise in blood glucose concentrations. During the early phases of nutrient absorption, there is a prompt and dramatic decrease in EGP, as hepatic glucose production is suppressed and the liver begins to store glucose (19). This rapid change in postprandial hepatic glucose flux is regulated by changes in the concentrations of islet hormones perfusing the liver (8), as well as by the rise in portal venous glucose levels (17). The results of the present study raise the possibility that an islet-independent effect of GLP-1 also plays a role in this process. This action is a potential complement to the stimulation of insulin secretion and inhibition of glucagon release that are the principal effects previously attributed to GLP-1. This finding suggests an expanded role for GLP-1 in the regulation of normal glucose metabolism and adds another site where pharmacological application of this peptide could be useful.

We thank Ellen Laschansky and Robin Vogel for careful measurement of glucose and plasma peptides, Karmen Eng for other technical support, and Henry Zebrowski for synthesis and purification of GLP-1. In addition, we acknowledge the valuable encouragement and scientific critique of Drs. Jay Taborsky, John Ensinck, and Daniel Porte, Jr.

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DISCLOSURES

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