Differential Effects of Acute and Extended Infusions of Glucagon-Like Peptide-1 on First- and Second-Phase Insulin Secretion in Diabetic and Nondiabetic Humans

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**OBJECTIVE** — The purpose of this study was to determine whether an extended infusion of the incretin hormone glucagon-like peptide 1 (GLP-1) has a greater effect to promote insulin secretion in type 2 diabetic subjects than acute administration of the peptide.

**RESEARCH DESIGN AND METHODS** — Nine diabetic subjects and nine nondiabetic volunteers of similar age and weight were studied in identical protocols. First-phase insulin release (FPIR, the incremental insulin response in the first 10 min after the intravenous glucose bolus) and second-phase insulin release (SPIR, the incremental insulin response from 10–60 min after intravenous glucose) were measured during three separate intravenous glucose tolerance tests (IVGTTs): 1) without GLP-1 (control); 2) with acute administration of GLP-1 as a square wave starting just before glucose administration; and 3) with an extended infusion of GLP-1 for 3 h before and during the IVGTT.

**RESULTS** — In the subjects with diabetes, FPIR was severely impaired—a defect that was only modestly improved by acute administration of GLP-1 (1,952 ± 512 vs. 8,072 ± 1,664 pmol/l · min, \(P < 0.05\)). In contrast, the 3-h preinfusion of GLP-1 normalized fasting hyperglycemia (7.9 ± 0.5 vs. 5.2 ± 0.6, \(P < 0.05\)), increased FPIR by 5- to 6-fold (197 ± 97 vs. 1,141 ± 409 pmol/l · min, \(P < 0.05\)), and augmented SPIR significantly (1,952 ± 512 vs. 4,026 ± 851 pmol/l · min, \(P < 0.05\)), but to a lesser degree than the acute administration of GLP-1. In addition, only the 3-h GLP-1 preinfusion significantly improved intravenous glucose tolerance (\(K_e\) control 0.61 ± 0.04, acute infusion 0.71 ± 0.04, \(P = \text{NS}\); 3-h infusion 0.92 ± 0.08%/min, \(P < 0.05\)). These findings were also noted in the nondiabetic subjects in whom acute administration of GLP-1 significantly increased SPIR relative to the control IVGTT (9,439 ± 2,885 vs. 31,533 ± 11,660 pmol/l · min, \(P < 0.001\)) with less effect on FPIR (3,221 ± 918 vs. 4,917 ± 1,614 pmol/l · min, \(P = 0.075\)), while the 3-h preinfusion of GLP-1 significantly increased both FPIR (3,221 ± 918 vs. 7,948 ± 2,647 pmol/l · min, \(P < 0.01\)) and SPIR (9,439 ± 2,885 vs. 21,997 ± 9,849 pmol/l · min, \(P < 0.03\)).

**CONCLUSIONS** — Extended administration of GLP-1 not only augments glucose-stimulated insulin secretion, but also shifts the dynamics of the insulin response to earlier release in both diabetic and nondiabetic humans. The restoration of some FPIR in subjects with type 2 diabetes is associated with significantly improved glucose tolerance. These findings demonstrate the benefits of a 3-h infusion of GLP-1 on \(\beta\)-cell function beyond those of an acute insulin secretagogue, and support the development of strategies using continuous or prolonged GLP-1 receptor agonism for treating diabetic patients.
mimic the physiologic role of GLP-1 as an acute insulin secretagogue. In these studies subcutaneous injection raised plasma GLP-1 to supraphysiologic levels, stimulated insulin secretion, and improved glycemic control moderately. However, the results of other recent studies raise the possibility that GLP-1 may be even more effective when administered continuously. Rachman et al. (15,16) normalized β-cell function, relative to a group of matched nondiabetic subjects, and established nearly normal fasting and postprandial glycemia (16) in a group of type 2 diabetic individuals given 18-h infusions of GLP-1 in one of the most impressive demonstrations of the potential of GLP-1 treatment to date. More recently, Zander et al. (17) reported that 6 weeks of continuous subcutaneous infusion of GLP-1 in diabetic patients significantly lowered HbA1c, and improved β-cell function. Interestingly, both the Rachman and Zander studies reported restoration of the first-phase insulin response to glucose in their GLP-1–treated patients, suggesting that one of the prototypical abnormalities of type 2 diabetes is amenable to treatment with this peptide. Taken together, the data on GLP-1 administration in persons with diabetes raise the possibility that continuous administration of GLP-1 may have beneficial effects beyond those seen with acute administration. However, to our knowledge, a direct comparison of the insulinotropic effects of acute versus more extended administration of GLP-1 has not been performed. In the study described herein, we addressed the question of whether an extended infusion of GLP-1 has actions that are distinct from acute administration on glucose-stimulated insulin release in diabetic and nondiabetic subjects.

**RESEARCH DESIGN AND METHODS**— Nine patients with type 2 diabetes (five men and four women) were recruited. These individuals were selected as representative of patients in our clinic with type 2 diabetes. They had a mean age of 57 ± 7 years and had stable body weights, with an average BMI of 31 ± 1.8 kg/m². The mean duration of diabetes was 8 ± 0.6 years. All subjects were taking oral hypoglycemic agents (three taking sulfonylureas, three taking metformin, and three taking both) and their metabolic control was variable with HbA1c values between 6.7 and 8.5% and fasting blood glucose levels from 6.1 to 10.5 mmol/l. Nine healthy subjects (four men and five women) who had no personal or family history of diabetes served as control subjects. They were comparable in age (47 ± 5 years [P = 0.9 vs. diabetic subjects]) and BMI (28 ± 2 kg/m² [P = 0.30 vs. diabetic subjects]), though not tightly matched to the diabetic patients.

Volunteers were admitted to the clinical research centers (CRC) at the University of Washington or the Cincinnati Children’s Hospital on three separate mornings after an overnight fast of 12 h. Diabetic subjects were asked to withhold their medications on the morning of the experiments. After the protocols were explained, each subject signed informed consent forms that had been approved by the local institutional review board for human subjects. Indwelling lines were placed into forearm veins and kept open with a slow drip of normal saline, and the arms were wrapped in heating pads to arterialized venous blood. After collection of fasting blood samples the subjects underwent intravenous glucose tolerance tests (IVGTTs) according to one of three protocols.

1) Control IVGTT: Subjects had a 2- to 3-h observation period during which plasma glucose was monitored as a control for the extended GLP-1 protocol (below). After the removal of baseline blood samples, a bolus of 0.3 g/kg glucose was given over 30 s and blood sampled at 2, 3, 5, 7, 10, 12, 14, 16, 19, 22, 25, 30, 35, 40, and 50 min.

2) GLP-1 acute infusion (GLP-1-A): Subjects had a 2- to 3-h observation period as described above. Starting 1–2 min before the administration of intravenous glucose, synthetic GLP-1 (18) was given as an intravenous bolus (0.9 pmol/kg), followed by a continuous infusion (0.45 pmol · kg · min) for 1 h. The IVGTT was identical to that described above.

3) GLP-1 3-h preinfusion (GLP-1-PI): GLP-1 0.45 pmol · kg · min was infused for 3 h before the intravenous glucose bolus was given and was continued throughout the 60 min of the IVGTT.

The order of the three protocols was balanced within each group of subjects (diabetic and nondiabetic) such that three subjects each started with protocols 1, 2, and 3. The order of the second and third study was varied, but could not be fully balanced because the total number of subjects was nine.

Blood samples were collected in heparinized tubes for insulin and glucose analysis, a benzamidine-based antiproteolytic cocktail for glucagon determination, and heparin (2,000 units/ml)/50 mmol/l EDTA/aprotinin (500 KIU/ml) was used for measurement of GLP-1. After immediate centrifugation, the plasma was stored at −20°C. Glucose was measured by a glucose oxidase method, and insulin and glucagon concentrations were determined by previously described radioimmunoassays (19,20). GLP-1 immunoreactivity (GLP-1-IR) was measured in ethanol extracts of plasma by a radioimmunoassay using antisemur 89390 (kindly donated by Dr. Jens Holst, Paa-num Institute, Copenhagen, Denmark), as described by Willms et al. (21). The antisemur used to measure GLP-1-IR recognizes the COOH-terminal amide of the peptide and has equal avidity for GLP-1 [7–36 amide] and the metabolite GLP-1 [9–36 amide], which is believed to be metabolically inactive (22).

Fasting insulin and glucose levels were designated as the means of two samples taken shortly after the intravenous lines were placed. Basal insulin and glucose levels refer to the mean values obtained on samples drawn from −15 to 0 min before the IVGTT. First-phase insulin release (FPIR) was calculated as the incremental area above basal during the first 10 min after the intravenous glucose bolus using the trapezoidal rule. Second-phase insulin release (SPIR) was calculated similarly as the incremental area above basal from 10–60 min after glucose administration, and total insulin secretion was taken as the insulin area above basal for the entire 60 min of the IVGTT. The glucose disappearance constant (Kg) was determined from the slope of the natural logarithm of the eight glucose values from 10 to 30 min after the intravenous glucose bolus. Changes in glucagon levels in response to the IVGTT were calculated as the area below the basal glucagon concentrations obtained in the 60 min after intravenous glucose. Comparisons of parameters calculated during the three separate experiments in each subject were made using repeated-measures ANOVA with post hoc testing to distinguish spe-
RESULTS

Plasma concentrations of GLP-1-IR

The GLP-1-IR shown in Fig. 1 includes both bioactive GLP-1 as well as the metabolic derivative GLP-1[9-36], which has a longer half-life in circulating plasma and comes to steady-state more slowly. Fasting concentrations of GLP-1-IR in the nondiabetic subjects were similar on the three mornings of study: 7.4 ± 2.6, 8.6 ± 2.0, and 8.2 ± 2.1 pmol/l for control, GLP-1-A, and GLP-1-PI, respectively (P = 0.68). GLP-1-IR did not change significantly over the ensuing 4 h of study in the control experiment (Fig. 1A). During the constant infusion of GLP-1 (GLP-1-PI), GLP-1-IR values increased ~6-fold to a mean value of 48.9 ± 3.7 pmol/l throughout the study. In GLP-1-A, the bolus and infusion of GLP-1 caused plasma levels of GLP-1-IR to stabilize at a plasma level of 50.5 ± 3.8 pmol/l during the IVGTT.

The GLP-1-IR profiles were similar in the diabetic subjects (Fig. 1B). Fasting concentrations on the three mornings of study were 9.7 ± 0.9, 9.8 ± 1.2, and 7.6 ± 0.7 pmol/l for control, GLP-1-A, and GLP-1-PI, respectively (P = 0.22). During the control study, GLP-1-IR levels did not change significantly. During GLP-1-PI, GLP-1-IR concentrations increased to a mean level of 51.2 ± 6.0 pmol/l for the duration of the study. In GLP-1-A protocol, GLP-1-PI levels stabilized at 43.2 ± 4.8 pmol/l, a level not significantly different from those obtained in GLP-1-PI.

Insulin secretion and glucose disappearance in nondiabetic subjects

The nondiabetic volunteers had similar fasting glucose and insulin values on the 3 days of study (5.1 ± 0.2, 5.2 ± 0.2, 5.3 ± 0.2 mmol/l and 106 ± 28, 108 ± 21, 118 ± 31 pmol/l for the control, GLP-1-A, and GLP-1-PI, respectively). Insulin and glucose values did not change over the course of the 2- to 3-h observation period between taking the fasting and basal samples in the control and GLP-1-A studies. In the GLP-1-PI protocol, the 3-h infusion of GLP-1 was associated with a rise in fasting insulin values from 118 ± 31 to a peak of 210 ± 72 pmol/l after 40 min, and then a fall to a mean basal value of 96 ± 21 pmol/l. Coincidentally, blood glucose levels decreased to a nadir of 4.3 ± 0.11 mmol/l 100 min after the initiation of GLP-1, before gradually increasing over the next 80 min to a mean basal level of 4.8 ± 0.1 mmol/l.

Intravenous glucose administration caused plasma glucose concentrations to peak at similar levels for the control, GLP-1-A, and GLP-1-PI studies (15.4 ± 0.8, 14.7 ± 0.7, and 14.6 ± 0.6 mmol/l, respectively; P = 0.81; Fig. 2). Insulin secretion in response to the bolus of glucose alone followed a biphasic pattern with an early peak and a diminished but persistent level of insulin release over the remaining 50 min (Fig. 2). Compared with the control study, SPIR was significantly enhanced by the 3-h preinfusion of GLP-1 (GLP-1-PI) but not by acute administration of GLP-1 (GLP-1-A; Table 1). In contrast, SPIR was greater during both experiments in which GLP-1 was given relative to the control study, and was significantly increased during GLP-1-A compared with GLP-1-PI. Thus, although the integrated insulin levels during the IVGTT were similar among the subjects during the studies with GLP-1 administration (36,470 ± 13,274 and 29,944 ± 12,496 pmol/l • min, respectively, for GLP-1-A and GLP-1-PI [P = 0.33]), infusion of GLP-1 for 3 h before the IVGTT caused a shift in the insulin profile with an increase in the proportion of insulin released in the first 10 min.

Administration of GLP-1 in the GLP-1-A and GLP-1-PI studies was associated with more rapid rates of glucose disappearance than during the control study, as reflected in increased values of Ks (Table 1). The rates of glucose disappearance did...
Acute versus extended GLP-1

Figure 2—Plasma glucose and insulin concentrations before and after IVGTT in nondiabetic subjects (A) and diabetic subjects (B) during the saline control (△), GLP-1-A, acute administration of GLP-1 (■), and GLP-1-PI, prolonged administration of GLP-1 (●). Note the different scales for insulin data in the diabetic and nondiabetic subjects. Data are presented as means ± SE.

not differ between the acute and prolonged GLP-1 infusions. Calculation of $K_p$ using the glucose values for the entire 60 min of the IVGTT were similar to those derived from the conventional 30-min computation.

Insulin and glucagon secretion and glucose disappearance in diabetic subjects

The diabetic subjects had similar fasting glucose and insulin values on the 3 days of study (7.9 ± 0.5, 7.6 ± 0.5, 7.9 ± 0.7 mmol/l and 12± 18, 12± 16, 13± 20 pmol/l for the control, GLP-1-A, and GLP-1-PI studies, respectively). During the 3-h administration of GLP-1 preceding the IVGTT in GLP-1-PI, there was a marked and continuous decline in plasma glucose to a mean level that was similar to the nondiabetic subjects, 5.2 ± 0.6 mmol/l (Fig. 3A). Seven of the nine diabetic volunteers normalized (<6 mmol/l) their fasting glucose concentrations during the 3-h infusion of GLP-1, and all reached levels <7 mmol/l. Insulin levels tended to increase in the diabetic subjects during the 3-h preinfusion in the GLP-1-PI study (Fig. 3B), but the response was variable and did not reach statistical significance for the group overall ($P = 0.08$). There was also a trend toward decreasing fasting plasma glucagon levels with GLP-1 administration during GLP-1-PI (Fig. 3C), but no values at any of the time points from −180 to 0 were significantly lower than the fasting levels ($P = 0.07$).

After receiving an intravenous bolus of glucose there was a prompt increase in plasma glycemia to a peak at 2−3 min (Fig. 2). Peak values were similar in the control and GLP-1-A studies, 15.8 ± 0.6 and 15.6 ± 0.5 mmol/l, respectively, and greater than the peak achieved in GLP-1-PI, 13.0 ± 0.7 ($P < 0.05$). However, the mean incremental rise in plasma glucose from the pre-IVGTT basal value was similar in all three studies (7.9 ± 0.5, 8.0 ± 0.3, and 7.8 ± 0.4 mmol/l for control, GLP-1-A, and GLP-1-PI, respectively).

Plasma insulin levels in response to intravenous glucose in the control study demonstrated the markedly abnormal pattern typical of type 2 diabetes, with a minimal early response and a slowly increasing and meager second phase of insulin secretion. Administration of GLP-1 significantly increased insulin concentrations in both the GLP-1-A and GLP-1-PI studies (Fig. 2). GLP-1 given immediately before the intravenous glucose bolus caused both a small but significant increase in FPIR and a marked increase in SPIR compared with the control study (Table 1). In GLP-1-PI, the 3-h preinfusion of GLP-1 also augmented insulin secretion, but with a strikingly different pattern. Preinfusion of GLP-1 had a relatively greater effect on FPIR, which was significantly increased relative to that obtained in both the control and GLP-1-A studies (Table 1). In contrast, in GLP-1-PI there was a proportionately smaller increase in SPIR relative to the control study, and this increase was significantly lower than that seen in GLP-1-A. The effects of GLP-1 on the phases of insulin secretion were not dependent on the basal insulin level since the differences among the three protocols were not altered when the data were normalized for the basal insulin concentrations (data not shown). Thus, in diabetic subjects, similar to the nondiabetic control subjects, the effect of a 3-h pretreatment with GLP-1 was to shift the plasma concentrations.

<table>
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<tr>
<th>Table 1—Islet hormone secretion and glucose disappearance in diabetic and nondiabetic subjects during IVGTT with and without GLP-1</th>
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<tr>
<td><strong>Nondiabetic Subjects</strong></td>
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<tr>
<td><strong>Total IR (pmol/l · min)</strong></td>
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<tr>
<td>12,761 ± 3,769</td>
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<tr>
<td>3,321 ± 918</td>
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<td>9,439 ± 2,885</td>
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<td>1.28 ± 0.16</td>
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<td><strong>Glucagon (ng/ml · min)</strong></td>
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<td>−487 ± 114</td>
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Data are means ± SE. *$P < 0.05$ vs. control study; ††$P < 0.05$ for comparisons of GLP-1-A and GLP-1-PI. Total IR, total insulin release.
insulin profile during the IVGTT toward more immediate release. This occurred despite lower absolute glucose levels over the course of the study.

Plasma glucagon concentrations decreased in the diabetic subjects following the administration of glucose in all three studies. There was no difference in the glucagon decrement below basal during the three IVGTTs \((P = 0.58)\), suggesting that administration of GLP-1, either acutely or as a 3-h pretreatment, did not augment the effect of hyperglycemia to suppress \(\alpha\)-cell secretion in this group of diabetic men and women.

Glucose disappearance was impaired in the diabetic subjects during each of the three studies (Table 1). However, in GLP-1-PI, the 3-h infusion of GLP-1 caused a significant increase in \(K_g\) compared with the other two studies. This increase in the rate of glucose disappearance was significantly greater in GLP-1-PI compared with GLP-1-A, despite the total insulin response being greater in the latter experiment. There was no suggestion of differing insulin, glucagon, or glycemic responses to GLP-1 among the subjects on metformin, sulfonylurea, or combination therapy (data not shown).

**CONCLUSIONS** — Several previous studies have demonstrated that pharmacologic doses of GLP-1 dramatically increase insulin secretion in persons with type 2 diabetes \((7–9,15,16,23)\). In this study we sought to determine specifically whether the time of exposure to GLP-1 affected its stimulatory effect on circulating insulin levels. Our results indicate that in both diabetic and nondiabetic humans, there are differential effects of GLP-1 to alter the insulin profile that are dependent on the timing of GLP-1 administration. When subjects received GLP-1 for 3 h before a glucose challenge, there was a disproportionate increase in FPIR relative to SPIR; in this paradigm a degree of FPIR was restituted in the subjects with diabetes and glucose tolerance was significantly improved. Acute administration of GLP-1, immediately before the glucose challenge, augmented total insulin release in diabetic subjects, but without the major change in FPIR that was seen in GLP-1-PI and without a significant improvement in intravenous glucose tolerance. These findings suggest that there are insulinotropic actions of GLP-1 that accrue with extended exposure to the peptide, and have clear implications for the use of GLP-1 in the treatment of diabetes.

We designed this study to examine the insulin response to both an acute administration of GLP-1, similar to the postprandial setting in that both plasma glucose and GLP-1 are rising concurrently, and after a 3-h period of GLP-1 pretreatment. Based on the work of Nauck et al. \((8)\) we anticipated that intravenous GLP-1 would decrease fasting plasma glucose and increase insulin levels in hyperglycemic diabetic subjects. Therefore, we selected 3 h for our pretreatment period so as to initiate the IVGTT at a point of relatively stable plasma glucose and insulin concentration, a condition that was achieved in the GLP-1-PI protocol. In addition, we administered GLP-1 almost simultaneously with intravenous glucose in the GLP-1-A protocol in order to evaluate insulin secretion from a stable baseline. We used phasic insulin secretion as an index of effectiveness since this is an almost universal abnormality in patients with diabetes that has been shown to be responsive to GLP-1 \((15,17)\). While plasma insulin concentrations are a function of insulin clearance in addition to \(\beta\)-cell secretion, recent studies have demonstrated that

![Figure 3](https://example.com/figure3.png)  
**Figure 3**—Fasting concentrations of glucose (A), insulin (B), and glucagon (C) in diabetic subjects before and during 3 h of GLP-1 infusion. Data are presented as means ± SE.
GLP-1 given intravenously for several hours does not alter insulin clearance (24). Therefore, it seems likely that plasma insulin levels accurately reflect insulin secretion during our studies.

GLP-1 is metabolized to the truncated congener GLP-1[9–36] following release into the blood, and because the latter has a longer half-life, steady-state levels of GLP-1-IR after a GLP-1 infusion are comprised of an ~1:4 ratio of GLP-1[7–36]amide and GLP-1[9–36]amide (25). Based on this information, we assume that plasma GLP-1-IR in the GLP-1-A and GLP-1-PI studies (Fig. 1) approximates this mixture of peptides after 15–20 min of GLP-1 administration when steady-state is reached. For the acute study we gave a priming bolus of GLP-1 in order to rapidly raise plasma concentrations and achieve a square wave of insulinotropic GLP-1[7–36]amide (25). The kinetics of GLP-1 metabolism in the plasma, with a half-life for conversion of GLP-1[7–36] to GLP-1[9–36] of ~1 min (1), achievement of steady-state would be expected within 5 min. Although we did not measure intact GLP-1[7–36]amide in this study, we have subsequently measured this peptide specifically in healthy humans treated with a bolus and infusion identical to what we used in protocol GLP-1-A and found values to be >80% of steady-state levels within 3 min (T.V., R.P., and D.D., unpublished observations). Therefore, we believe that the circulating, active GLP-1[7–36] levels during the IVGTT are matched between the two studies. In both infusion studies, the plasma levels of GLP-1-IR were 40–70 pmol/l, a level that is supraphysiologic since maximal postprandial concentrations have typically been reported to be in the 10–40 pmol/l range (21,26–28).

It is well established that GLP-1 augments insulin secretion during intravenous glucose administration in healthy humans (1), and we have previously observed that GLP-1 infused for 30 min before and during an IVGTT increases the acute insulin response to glucose (18). Therefore, it was surprising to note the impact of the timing of GLP-1 administration on insulin secretory dynamics in the nondiabetic control group in the current study. Over the first 30 min of the experiments, the insulin profiles in the nondiabetic subjects were almost mirror images in the GLP-1-A and GLP-1-PI studies, despite nearly identical plasma glucose and GLP-1-IR concentrations. Insulin secretion following the 3-h preinfusion of GLP-1 followed a pattern that was similar, albeit magnified, to the control experiment with ~25–30% of the insulin response in the first 10 min after glucose infusion. In contrast, when GLP-1 was given as a square wave with the bolus of intravenous glucose, the most prominent portion of the insulin response was delayed and occurred from 10–30 min, even in the face of declining plasma glucose concentrations. These data demonstrate that in healthy humans, a pre-infusion of GLP-1 has differential effects on the dynamics of insulin secretion that are distinct from the acute effects as an insulin secretagogue.

The most important finding in the current study was that the extended infusion of GLP-1 restored a glucose-stimulated FPIR in the diabetic subjects in whom it was absent in the control studies and only minimally increased when GLP-1 was raised to similar levels acutely. Despite this return of biphasic insulin secretion in the diabetic subjects, the magnitude of their FPIR was still considerably less than that of the control subjects. Given that defective FPIR is a uniform finding in type 2 diabetes (29,30), and is a core characteristic of this condition (31), our findings amplify those of Rachman et al. (15,16) as to the potential benefit of GLP-1 on insulin secretion. Previous work, both in vitro and in diabetic and nondiabetic humans, suggested that GLP-1 improves the sensitivity of the β-cell to glucose (15,32–34). Administration of GLP-1, concurrent with glucose, resulted in a small but significant increment of FPIR in diabetic subjects. However, given the minimal FPIR in most of the diabetic subjects, the overall effect of acute GLP-1 on the dynamic pattern of insulin secretion was trivial, and early insulin secretion was ~6% of total insulin release. In contrast, 3 h of GLP-1 changed the insulin secretory profile such that the FPIR was 22% of the total insulin released over 60 min, similar to the 26% observed in the nondiabetic subjects. Therefore, it appears that 3 h of treatment with pharmacologic amounts of GLP-1 can substantially improve one of the basic pathologic processes in type 2 diabetes. Importantly, this correction of the dynamics of insulin secretion was associated with a significant improvement in intravenous glucose tolerance.

During the 3-h preinfusion with GLP-1 there was a steady decline in the fasting hyperglycemia in all the diabetic subjects. We considered the possibility that this correction of blood glucose levels may have contributed to the change in insulin secretory dynamics in GLP-1-PI. While previous studies have shown that normalization of hyperglycemia improves insulin secretion in type 2 diabetes (35,36), we do not attribute the improvement in FPIR during the long infusion of GLP-1 to the changes in baseline glycemia for several reasons. First, 3 h of GLP-1 also increased FPIR in our nondiabetic subjects in whom fasting glucose changed only minimally. Second, in previously published studies in which FPIR was restored in diabetic subjects rendered euglycemic, the duration of blood glucose lowering required was 1–2 days (35,36). Our subjects had nondiabetic glucose levels for only 1–2 h, a much shorter period than those shown to have benefits on β-cell function. Support for this contention is a previously published comparison of overnight treatment of type 2 diabetic subjects with GLP-1 and insulin (15). In this study, normal fasting glucose levels were achieved with both treatments, but there was no improvement in the blunted FPIR of the diabetic volunteers after 10 h of insulin-induced euglycemia, while overnight treatment with GLP-1 restored the acute insulin response to glucose (15). Finally, among our group of diabetic volunteers who were receiving chronic glucose-lowering medications, fasting blood glucose values varied widely, from near normal (6.1 mmol/l) to moderately hyperglycemic (10.6 mmol/l), but FPIR during the control IVGTT was absent or profoundly impaired in all of them. This suggests that in this group of subjects, an impaired FPIR is an inherent part of their type 2 diabetes independent of their chronic level of hyperglycemia. Therefore, we believe that the augmentation of FPIR in our diabetic subjects during the GLP-1-PI study was primarily an effect of GLP-1.

The diabetic subjects in our study were reflective of a large subset of persons with type 2 diabetes in that they were middle-aged, moderately obese, free of chronic diabetic complications, treated with oral agents, and in moderate to good glycemic control. We withheld anti-
diabetic medications on the morning of the studies so as not to have a worsening of glycemic control, and because each subject served as their own control, medication effects were balanced. Because of the small sample size of this study we cannot comment on the relative effects of GLP-1 when combined with sulfonylurea compared with metformin. However, previous studies suggest that the effects of GLP-1 in combination with these drugs are additive (37,38). It is possible that there were some residual effects of the oral agents. However, given the paired design of the study, these effects would be expected to cancel out. Based on their insulin response to intravenous glucose alone, this group of patients had defects in insulin secretion that typify type 2 diabetics. It seems reasonable that the therapeutic application of GLP-1, or other GLP-1 receptor agonists, would include this group of patients. The major clinical corollary of this study is that methods that provide extended administration of GLP-1 will be more efficacious than acute, bolus dosing. The present results indicate that 3 h of treatment with GLP-1 confers a significant benefit on the dynamics of insulin secretion and glucose disappearance. Whether shorter periods of infusion are equally efficacious will require further study to determine.

In summary, the major findings in the present study are that GLP-1 has differential effects on the dynamics of insulin secretion that are dependent on the time course of peptide administration in both healthy and type 2 diabetic humans. FPIR is restored in diabetic subjects given a 3-h infusion of GLP-1, and this improves intravenous glucose tolerance relative to a more pronounced SPIR induced by acute infusion of GLP-1. The present findings indicate that GLP-1 has insulinotropic effects when administered for several hours that are beyond those of an acute secretagogue. These results add to the growing collection of information indicating the therapeutic potential of GLP-1 in patients with type 2 diabetes, and suggest that modalities employing prolonged or continuous administration of hormone are likely to be most efficacious.

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