

Glucagon-Like Peptide 1 Improves the Ability of the β -Cell to Sense and Respond to Glucose in Subjects With Impaired Glucose Tolerance

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Impaired glucose tolerance (IGT) and NIDDM are both associated with an impaired ability of the β -cell to sense and respond to small changes in plasma glucose concentrations. The aim of this study was to establish if glucagon-like peptide 1 (GLP-1), a natural enteric peptide and potent insulin secretagogue, improves this defect. Two weight-matched groups, one with eight subjects having IGT (2-h glucose, 10.1 ± 0.3 mmol/l) and another with seven subjects with diet-treated NIDDM (2-h glucose, 14.5 ± 0.9 mmol/l), were studied on two occasions during a 12-h oscillatory glucose infusion, a sensitive test of the ability of the β -cell to sense and respond to glucose. Glucose was infused with a mean rate of $4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, amplitude 33% above and below the mean rate, and periodicity of 144 min, with infusion of saline or GLP-1 at $0.4 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 12 h. Mean glucose levels were significantly lower in both groups during the GLP-1 infusion compared with during saline infusion: 9.2 ± 0.4 vs. 6.4 ± 0.1 mmol/l in the IGT subjects ($P < 0.0004$) and 14.6 ± 1.0 vs. 9.3 ± 0.7 mmol/l in NIDDM subjects ($P < 0.0002$). Despite this significant reduction in plasma glucose concentration, insulin secretion rates (ISRs) increased significantly in IGT subjects (513.3 ± 77.6 vs. 583.1 ± 100.7 pmol/min; $P < 0.03$), with a trend toward increasing in NIDDM subjects (561.7 ± 122.16 vs. 642.8 ± 128 pmol/min; $P = 0.1$). These results were compatible with enhanced insulin secretion in the presence of GLP-1. Spectral power was used as a measure of the ability of the β -cell to secrete insulin in response to small changes in the plasma glucose concentration during the oscillatory infusion. Spectral power for ISR increased from 2.1 ± 0.9 during saline infusion to 7.4 ± 1.3 during GLP-1 infusion in IGT subjects ($P < 0.004$), but was unchanged in NIDDM subjects (1.0 ± 0.4 to 1.5 ± 0.6 ; $P = 0.3$). We concluded that low dosage GLP-1 improves the ability of the β -cell to secrete insulin in both IGT and NIDDM subjects, but that the ability to sense and respond to subtle changes in plasma glucose is improved in IGT subjects, with only a variable response in NIDDM subjects.

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AUC, area under the curve; GLP-1, glucagon-like peptide 1; IGT, impaired glucose tolerance; ISR, insulin secretion rate.

β -Cell dysfunction was improved by GLP-1 infusion, suggesting that early GLP-1 therapy may preserve β -cell function in subjects with IGT or mild NIDDM. *Diabetes* 47:1259–1265, 1998

Impaired glucose tolerance (IGT) is common in the U.S. population. The prevalence of IGT increases from 11% in the general population ages 20–74 years to 24% in those ages 40–74 years with a family history of diabetes and a body weight $>120\%$ of normal (1). Subjects with IGT are at high risk for the development of NIDDM in the future (2,3). One strategy to prevent the morbidity and mortality associated with NIDDM is the primary prevention of hyperglycemia in subjects at increased risk for NIDDM. IGT is characterized by the presence of insulin resistance (4–6) and early subtle defects in β -cell function (7–9). These early defects include an impaired ability of the β -cell to sense and respond to small changes in plasma glucose concentrations and a mild shift to the right of the glucose-insulin secretion dose-response curve. The deterioration of glucose control with time is predominantly due to progressive impairment of β -cell function (10).

Glucagon-like peptide 1 (GLP-1), a natural enteric peptide, is secreted from the L-cells of the gut and acts as an incretin hormone that stimulates pancreatic β -cells to secrete insulin in a glucose-dependent manner (11–13). Its therapeutic potential in NIDDM has been previously demonstrated (14–20). Exogenous infusion of pharmacological doses of GLP-1 for 4 h in NIDDM subjects with poorly controlled glycemia normalized fasting plasma glucose concentrations (15); longer infusions for 10 h maintained near-normal plasma glucose concentrations overnight and improved both basal and stimulated β -cell function to nondiabetic levels (18). However, GLP-1 infused overnight in NIDDM subjects did not improve glucose response to meals the next day, suggesting that the GLP-1 priming effect of β -cells in NIDDM subjects was short lived (19). When GLP-1 was infused for 19 h (i.e., overnight) and during three standard meals in NIDDM subjects, plasma glucose levels were reduced, but the impaired postprandial β -cell function was only slightly improved (19). β -Cell responses to prolonged infusion of GLP-1 have not been previously studied in IGT subjects, nor has the effect of GLP-1 on β -cell responses to small increases and decreases in plasma glucose concentration. The present study was undertaken to address these issues, using an oscillatory glucose infusion protocol (21).

TABLE 1
Baseline clinical parameters of IGT and NIDDM subjects

ID	Sex	Age	BMI	Fasting glucose (mmol/l)	2-h glucose (mmol/l)	Fasting insulin (pmol/l)	GHb
IGT							
D01	M	50	25.7	5.78	8.99	54.8	5.8
D02	F	52	26.8	5.94	10.52	42.1	5.7
D03	M	49	32.2	5.73	9.45	66.7	6.3
D04	M	42	30.6	5.99	9.89	35.5	5.9
D05	M	46	38.2	6.14	11.06	103.6	6.5
D11	M	46	27.5	6.15	9.39	27.4	6.6
D12	M	60	22.7	5.57	10.44	20.8	6.2
D13	M	61	31.8	6.87	11.06	46.9	6.2
Mean ± SE		50.9 ± 2.2	29.4 ± 1.7	6.02 ± 0.14	10.1 ± 0.3	49.7 ± 9.3	6.2 ± 0.1
NIDDM							
D06	M	53	26.4	8.81	16.27	24.2	6.7
D07	M	61	27.9	6.87	11.28	87.3	7.2
D08	M	60	34.2	7.66	15.05	30.7	5.9
D09	M	53	27.8	6.86	18.66	37.7	7.7
D10	M	66	23.9	8.34	12.9	28.5	8.1
D14	M	49	41.3	7.31	12.78	413.2	6.2
D15	M	56	35.1	7.64	14.28	30.1	7.3
Mean ± SE		57.8 ± 2.4	30.9 ± 2.3	7.64 ± 0.27	14.5 ± 0.9	93.1 ± 54.0	7.0 ± 0.3
<i>P</i> value		0.08	0.6	<0.0006	<0.0005	0.46	<0.015

P value refers to comparison between IGT and NIDDM.

RESEARCH DESIGN AND METHODS

Subjects. Studies were performed in 15 subjects who were divided into two groups on the basis of their plasma glucose response to an oral glucose tolerance test, using World Health Organization (WHO) criteria (22). Eight subjects had IGT and seven subjects had NIDDM. The sex, age, BMI, fasting glucose, 2-h glucose, fasting insulin, and GHb concentrations for each subject are presented in Table 1. NIDDM subjects were treated with diet alone with the exception of one subject, D07, who had been treated with an oral hypoglycemic agent that was discontinued 4 weeks before the study. None of the diabetic patients had ever received insulin. All subjects were placed on a weight-maintenance diet containing at least 200 g of carbohydrate/day for 2 weeks before the study. All studies were performed in the Clinical Research Center of the University of Marburg. The protocol was approved by the ethics committee, and all subjects gave written informed consent.

Experimental protocol. Each subject was studied on three separate occasions. All studies were performed after a 12-h overnight fast beginning at 7:00 A.M., unless otherwise stated, with subjects in the recumbent position. An intravenous catheter was placed in each forearm, one for blood sampling and one for administration of glucose, saline, or GLP-1, as needed. In all experiments, the arm containing the sampling catheter was maintained in a heating blanket to ensure arterialization of the venous sample.

Oral glucose tolerance test. Blood samples were drawn for the measurement of glucose, C-peptide, insulin, glucagon, and GLP-1 during the baseline and then at 30-min intervals for 120 min after ingestion of 75 g glucose (Boehringer Mannheim, Mannheim, Germany). The glucose concentrations were used to define the degree of glucose intolerance according to WHO criteria (22).

Administration of an oscillatory glucose infusion. It has been previously demonstrated that the peripheral administration of glucose in an oscillatory pattern results in regular oscillations in plasma glucose (21). In normal subjects, the β -cell is able to detect and respond to repetitive increases and decreases in glucose with parallel changes in insulin secretion (21). This adjustment of insulin secretory oscillations to glucose oscillations is termed "entrainment." Lack of entrainment by glucose is an early manifestation of β -cell dysfunction in individuals with IGT and mild NIDDM (8,9). To determine if the β -cell was able to detect and respond to oscillations of glucose, glucose was infused in an oscillatory pattern with a small volume of saline for 12-h, similar to methods previously described using 16-h infusions (8,9,21). The amplitude of the administered oscillations was 33% above and below the mean rate of $4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, and their periodicity was 144 min. To establish the effect of GLP-1 on the ability of the β -cell to respond to oscillations of glucose, glucose was infused in the same manner and GLP-1 was infused at a constant rate of $0.4 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for the entire 12-h period. Each study consisted of an initial 2-h period (7:00–9:00 A.M.) to allow a steady state to

be achieved, followed by a subsequent 10-h period (9:00 A.M. to 7:00 P.M.), during which time blood samples were drawn at 15-min intervals for glucose, insulin, C-peptide, and glucagon and at 60-min intervals for GLP-1.

Assays. Plasma glucose levels were measured by the glucose oxidase technique (1500 G; YSI, Yellow Springs, OH). The coefficient of variation of this method is <2%. Plasma insulin was measured by the Abbott IMx Microparticle Enzyme Immunoassay (Abbott, North Chicago, IL), with the average intra-assay coefficient of variation being 5%. Plasma C-peptide was measured as previously described (23). The lower limit of sensitivity of the assay is 0.02 pmol/ml, with the intra-assay coefficient of variation averaging 6%. Glucagon was measured using a commercially available radioimmunoassay kit (Biermann, Bad Nauheim, Germany), with the intra-assay coefficient of variation averaging 8%. Immunoreactive GLP-1 was measured using the specific polyclonal antibody GA 1178 (Affinity Research, Nottingham, U.K.) (24). It has 100% reactivity with GLP-1(1-36) amide and the truncated GLP-1(7-36) amide. Immunoreactive GLP-1-like material was extracted from plasma samples on C-18 cartridges, using acetonitrile for elution of the samples. The detection limit of the assay was 2 fmol/tube. The antiserum did not cross-react with glucose-dependent insulinotropic polypeptide, pancreatic glucagon, glicentin, oxyntomodulin, or GLP-2. Intra- and interassay coefficients of variation were 3.4 and 10.4%, respectively. GHb was measured by using ion-exchange high-performance liquid chromatography, with an intra-assay coefficient of variation of 4% (Bio-Rad, Hercules, CA). The normal range of this assay is 4.1–6.5%.

Data analysis

Determination of insulin secretion rates. Standard kinetic parameters for C-peptide clearance adjusted for age, sex, and body surface area were used (25) to derive, in each 15-min interval between blood sampling, the insulin secretion rate (ISR) from the plasma C-peptide concentrations by deconvolution, as previously described (26,27).

Oral glucose tolerance tests. Incremental areas under the curve (AUCs) from 0 to 120 min were calculated for glucose, insulin, C-peptide, glucagon, and GLP-1.

Ultradian oscillations in insulin secretion

Spectral analysis. Each individual ISR profile from the oscillatory glucose infusion protocol was submitted to spectral analysis to investigate whether the oscillations were entrainable, as previously reported (21). Each spectrum was normalized, assuming the total variance of each series to be 100%, and was expressed as the normalized spectral power. Each series was detrended with the first difference filter before spectral estimates were calculated using a Tukey window of 24 data points, as described by Jenkins and Watts (28).

Statistical analyses. All results are expressed as means ± SE. Data analysis was performed using the Statistical Analysis System (Version 6; SAS Institute, Cary, NC). The significance of intra-individual differences induced by GLP-1 infusion was determined using paired *t* tests. In the case of a nonstandard deviated data,

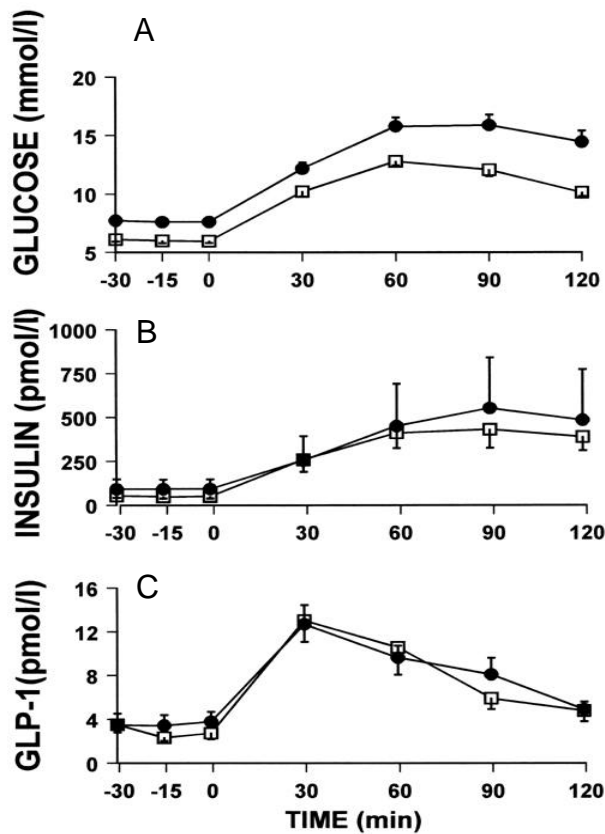


FIG. 1. Mean glucose (A), insulin (B), and GLP-1 (C) responses during oral glucose tolerance testing in eight IGT subjects (□) and seven NIDDM subjects (●).

a Mann-Whitney *U* test was used for comparison. Pearson's correlation coefficient was used to evaluate correlations between pairs of parameters. Differences were considered to be significant at $P < 0.05$.

RESULTS

Basal levels of plasma glucose and insulin. The demographics of the study groups are shown in Table 1. Subjects were matched for age and BMI. Mean fasting glucose, 2-h glucose, and GHb levels were lower in IGT than in NIDDM subjects. Fasting insulin levels did not differ between groups.

Responses to oral glucose. Fasting and 2-h glucose levels were significantly lower in IGT than in NIDDM subjects (Table 1). Figure 1 shows the glucose insulin and GLP-1 responses to 75 g of glucose. The AUC for glucose from 0 to 120 min was lower in the IGT than in the NIDDM group, but the AUC for insulin, C-peptide, glucagon, and GLP-1 did not differ between groups (Table 2).

Effect of GLP-1 on mean 10-h levels of plasma glucose, ISR, insulin, and glucagon. Mean glucose levels were significantly lower in both groups during the GLP-1 infusion compared with during saline infusion, with an average drop of 2.8 ± 0.4 mmol/l in IGT subjects ($P < 0.0004$) and 5.3 ± 0.5 mmol/l in NIDDM subjects ($P < 0.0002$). Despite this significant reduction in plasma glucose concentrations, mean ISRs were significantly increased during GLP-1 infusion compared with during saline infusion in IGT subjects (513.3 ± 77.6 vs. 583.1 ± 100.7 pmol/min; $P < 0.03$), with a trend toward increasing in NIDDM subjects (561.7 ± 122.16 vs. 642.8 ± 128 pmol/min; $P = 0.1$) (Table 3). Mean insulin levels were also

maintained during GLP-1 infusion compared with during saline infusion, increasing 64.4 ± 56.8 pmol/l ($P = 0.29$) in IGT subjects and 73.9 ± 59.1 pmol/l ($P = 0.25$) in NIDDM subjects. Mean glucagon levels also did not differ during GLP-1 infusion compared with during saline infusion, decreasing by 1.97 ± 1.5 pg/ml ($P = 0.23$) in IGT subjects (46.3 ± 5.7 vs. 49.3 ± 6.3 pg/ml) and by 3.9 ± 2.8 pg/ml ($P = 0.2$) in NIDDM subjects (45.5 ± 4.5 vs. 49.4 ± 3.9 pg/ml). GLP-1 levels achieved during GLP-1 infusion were 22.9 ± 3.0 pmol/l vs. 2.1 ± 0.2 pmol/l during saline infusion ($P < 0.0001$). These levels corresponded to postprandial physiological levels.

Relationship between glucose and ISR in individual IGT subjects. In normal subjects, each pulse of glucose is tightly coupled to a pulse in ISR. This coupling previously has been shown to be defective in IGT subjects (8,9). Profiles of glucose and ISR during oscillatory glucose infusion with saline from one representative IGT subject (D02) are shown in Fig. 2A. This example demonstrates that in IGT subjects, there is loss of the tight coupling between glucose and ISR during saline infusion, with many glucose-independent oscillations in ISR. In the presence of physiological postprandial levels of GLP-1 (Fig. 2B), the pattern of insulin secretory responses to glucose was improved in this IGT subject, with each pulse in glucose followed by a pulse in ISR. This adjustment of insulin secretory oscillations to glucose oscillations is termed "entrainment." Hence GLP-1 improved the ability of the β -cell to entrain an exogenous glucose infusion in this IGT subject.

To determine whether insulin secretion was entrained by glucose in individual subjects, the temporal profiles of insulin secretion were analyzed by spectral analysis. This method evaluates the regularity of insulin secretory oscillations at a predetermined frequency. The power spectra for glucose and ISR in subject D02 are shown in Fig. 2C and D. Peaks in the plasma glucose spectra occurred at 144 min, corresponding to the period of exogenous glucose infusion. During saline infusion (Fig. 2C) there was poor entrainment, as the spectral power for ISR at 144 min was 0.6. During GLP-1 infusion (Fig. 2D), the periodicity of the dominant spectral peak in ISR occurred at 144 min, demonstrating that GLP-1 caused entrainment of the β -cell in this subject. Spectral power improved from 0.6 to 8.9. The mean value for normalized spectral power during 16-h infusions in historical control subjects (BMI = 28.3) with normal glucose tolerance has been 7.2 ± 0.6 (9).

Relationship between glucose and ISR in a representative NIDDM subject. Figure 3A and B demonstrates the profile from one representative NIDDM subject (D07). In contrast to IGT subjects, despite the lowering of plasma glucose concentrations and the maintenance of ISR, the pat-

TABLE 2
Responses to oral glucose

2-h AUC	IGT	NIDDM
<i>n</i>	8	7
Glucose (mmol/l · min · l ⁻¹)	1,293 ± 28	1,646 ± 58*
Insulin (pmol · min · l ⁻¹)	39,801 ± 8,689	46,564 ± 24,873
C-peptide (pmol · min · l ⁻¹)	265 ± 29	222.5 ± 50
Glucagon (ng · min · l ⁻¹)	7,470 ± 760	6,856 ± 640
GLP-1 (pmol · min · l ⁻¹)	998 ± 163	1,043 ± 92

* $P < 0.05$ for IGT vs. NIDDM.

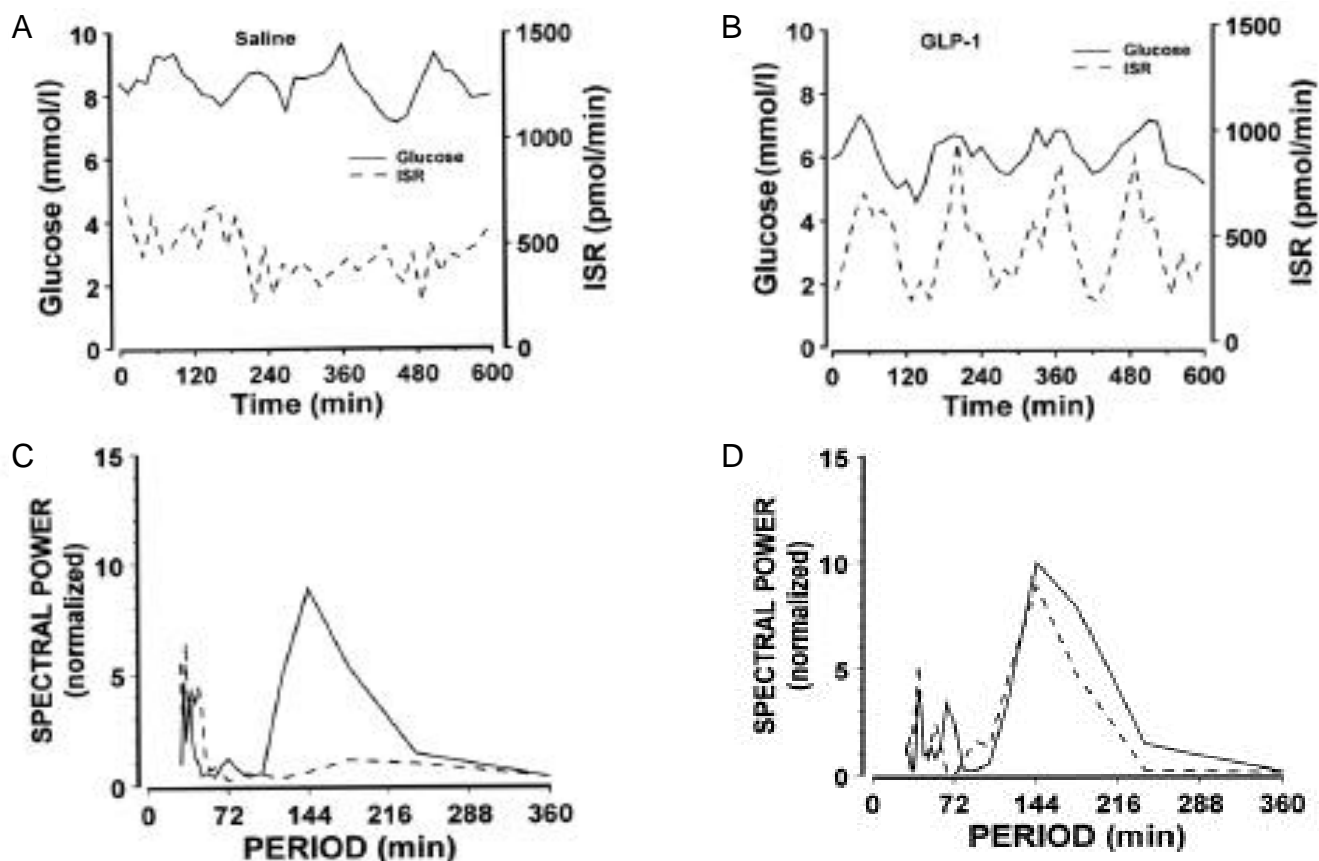


FIG. 2. Profiles of glucose and ISR in one representative IGT subject (D02) during saline (A) and GLP-1 infusion (B). Power spectra of the same subject during saline (C) and GLP-1 infusion (D).

tern of insulin secretory responses to glucose was not improved in this subject during GLP-1 infusion, with many glucose-independent oscillations in ISR persisting. Peaks in plasma glucose spectra occurred at 144 min. During saline infusion, the dominant spectral peak for ISR did not occur at 144 min, and spectral power did not improve greatly with GLP-1 infusion (0.2–1.5) (Fig. 3C and D).

Effect of GLP-1 on spectral power in IGT and NIDDM.

The mean normalized spectral power for glucose in IGT subjects was 11.4 ± 1.0 during saline infusion and 12.4 ± 1.2 during GLP-1 infusion ($P = 0.5$), and in NIDDM subjects was 7.5 ± 2.3 during saline infusion and 9.2 ± 0.8 during GLP-1 infusion ($P = 0.6$). Figure 4 clearly demonstrates that infusion of GLP-1 in IGT subjects enhanced insulin secretory responses to oscillations in plasma glucose, resulting in a greater degree of entrainment of insulin secretion to glucose. This response was variable in NIDDM subjects. The effect was quantified by comparing the normalized spectral power of the insulin secretory profiles. Spectral power for ISR increased from 2.1 ± 1.0 during saline infusion to 7.4 ± 1.3 during GLP-1 infusion ($P < 0.004$), and the mean value was unchanged in NIDDM subjects (1.0 ± 0.4 vs. 1.5 ± 0.6 ; $P = 0.3$).

Relationship between the absolute change in spectral power during infusion of GLP-1 compared with saline and glycemic measures in NIDDM group. There was a significant negative correlation between the absolute change in spectral power and GHb values in the NIDDM group ($r = -0.83$, $P < 0.02$), with no significant correlation between absolute change in spectral power and fasting glucose levels

($r = -0.49$, $P = 0.26$) or between absolute change in spectral power and 2-h glucose values ($r = 0.16$, $P = 0.73$).

DISCUSSION

The results of this study demonstrated that continuous infusion of physiological postprandial levels of GLP-1 reduced plasma glucose concentrations and stimulated insulin secretion in IGT and NIDDM subjects. Most importantly, GLP-1 restored the ability of the β -cell to sense and respond to plasma glucose in all IGT subjects (quantified by normalized spectral power), with a variable response in subjects who had already developed NIDDM.

We used a low-dosage oscillatory glucose infusion protocol as it is a sensitive test of the ability of the β -cell to sense and respond to small changes in plasma glucose concentrations, thereby testing the integrity of the feedback loop linking glucose and insulin secretion. A normal response requires an intact glucose-sensing ability. Spectral power analysis was used to evaluate the presence of tight coupling between oscillations in glucose and oscillations in ISR. This method evaluates the regularity of insulin secretory oscillations at a predetermined frequency. Spectral peaks correspond to the dominant periodicity, and the height of the peaks corresponds to spectral power. Using a similar protocol (16-h infusion), we previously showed that the glucose-sensing ability of the β -cell is lost very early in the course of NIDDM when 2-h glucose levels are minimally elevated (9). In that study, spectral power in control subjects was 7.2 ± 0.6 , and was reduced to 2.3 ± 0.4 in IGT subjects. GLP-1 improved spectral

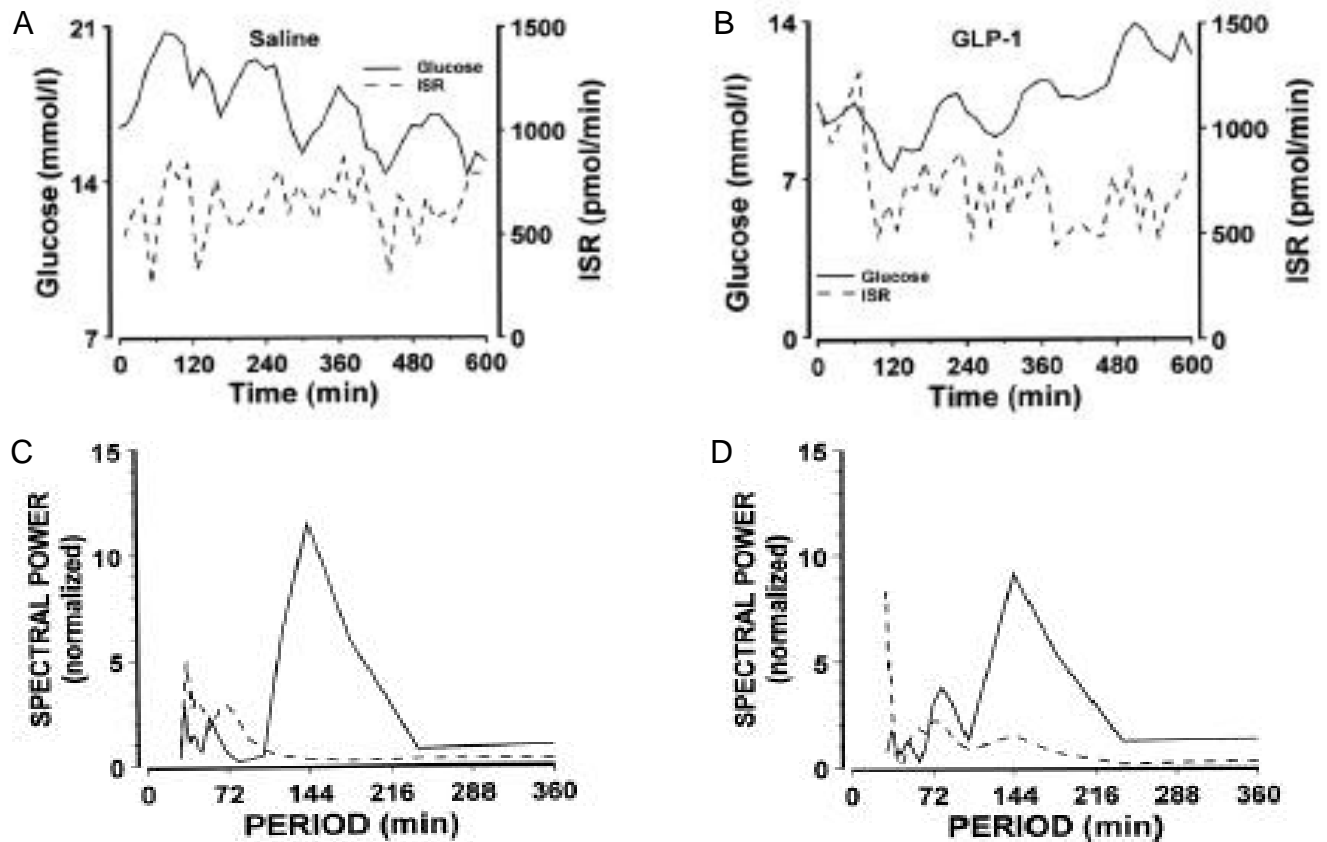


FIG. 3. Profiles of glucose and ISR in one representative NIDDM subject (D07) during saline (A) and GLP-1 infusion (B). Power spectra of the same subject during saline (C) and during GLP-1 infusion (D).

power in our IGT subjects into a more normal range. This improvement in the oscillatory pattern of insulin secretion may be important for the maintenance of normal glucose homeostasis, as insulin infusions that mimic the ultradian oscillations with a 120-min period are more effective than constant infusions of insulin in the reduction of plasma glucose concentrations (29).

GLP-1 has been shown to improve β -cell function in isolated β -cells and animal models. Using patch-clamp techniques on isolated islets, it has been shown that only a subgroup of pancreatic β -cells is sensitive to glucose and that pretreatment of cells with GLP-1 increases the number of glucose-competent β -cells (30). In an animal model of prediabetes, the male Zucker diabetic fatty rat, treatment in the prediabetic phase with subcutaneous GLP-1 via osmotic minipumps for 4 weeks delayed the development of β -cell failure (31).

The possible mechanisms via which β -cell function is improved by GLP-1 include upregulation of glucose-sensing elements, elimination of glucotoxicity, and improvement in insulin resistance. GLP-1 and glucose exert synergistic insulinotropic actions on β -cells, including stimulation of cyclic AMP formation, insulin secretion, insulin biosynthesis, and proinsulin gene expression (12,29,32–35). In a recent study, a 48-h infusion of GLP-1 reversed the age-related decline in glucose tolerance in Wistar rats by not only increasing insulin secretion but also inducing significant changes at the molecular level (36). GLP-1 increased insulin biosynthesis, GLUT2 expression, and glucokinase mRNA and induced β -cells into a secretory mode (36). This would explain the

improvement in glucose-induced insulin secretion. GLP-1 has also been shown to constitute biphasic insulin release in human fetal pancreatic β -cells, possibly as a result of cAMP-mediated priming of the glucose-sensor mechanism (37).

Elimination of glucotoxicity (38) is an unlikely explanation for the improvement in β -cell function seen in our IGT subjects, as these subjects had only minimally elevated glucose levels during the 12-h glucose infusion. Such elevations in plasma glucose concentrations have not been reported to cause glucotoxicity. In fact, a 42-h period of mild hyperglycemia (7.5 mmol/l) in IGT subjects has been previously shown to prime the insulin secretory response to a subsequent glucose stimulus (9). This priming response was reduced or absent in subjects who had already developed NIDDM. This again suggests that glucose sensing and priming are reduced once NIDDM has developed. Other reports have also suggested that mild hyperglycemia potentiates glucose-induced insulin secretion (39,40), but that exposure to high dosages of glucose for prolonged periods may actually induce defects in insulin secretion (41). In the present study, the variable β -cell response in NIDDM subjects may have been due to the different degrees of glycemia in this group, as there was a negative correlation between the absolute change in spectral power and GHb values ($P < 0.02$).

The peripheral effects of GLP-1 are controversial (15,42,43), with recent studies demonstrating that GLP-1 has no effect on insulin sensitivity in healthy or diabetic subjects (44,45). Using intravenous glucose tolerance tests, with somatostatin suppression of insulin secretion to circumvent

TABLE 3
Mean glucose and ISR responses to 12-h saline or GLP-1 infusion

ID	Mean glucose		Mean ISR	
	12-h saline	12-h GLP-1	12-h saline	12-h GLP-1
IGT				
D01	7.49	6.48	376.1	390.9
D02	8.34	6.06	457.9	465.9
D03	10.16	6.46	900.2	1,042.7
D04	7.90	6.36	328.5	365.9
D05	10.06	6.37	798.0	1,005.8
D11	10.56	6.35	428.6	460.3
D12	8.74	6.51	305.0	328.1
D13	10.30	6.47	512.2	605.1
Mean ± SE	9.19 ± 0.43	6.38 ± 0.05*	513.3 ± 77.6	583.1 ± 100.7*
NIDDM				
D06	16.73	11.53	232.3	477.7
D07	17.28	10.51	640.3	715.4
D08	9.94	6.24	615.6	487.7
D09	13.95	8.84	366.5	412.5
D10	15.05	9.90	346.2	448.9
D14	12.97	7.41	1,212.0	1,375.9
D15	16.21	10.85	519.3	581.3
Mean ± SE	14.59 ± 0.97	9.33 ± 0.73*	561.7 ± 122.2	642.8 ± 128.1

*P < 0.05, by paired t test, saline vs. GLP-1 infusion.

the problem of differences in insulin levels, GLP-1 had no effect on glucose-induced glucose uptake in healthy subjects (46). The characteristics of the glucose-insulin feedback loop are such that an improvement in insulin-induced peripheral glucose uptake should have resulted in lower plasma insulin levels, which we did not find in this study. The reduction in glucagon induced by GLP-1 is thought to contribute to its glucose-lowering effects (14,15). We did not observe any reduction in plasma glucagon concentrations during our 10-h sampling period. It is important to note that we did not sample for glucagon during the first 2 h of glucose infusion, and therefore it is possible that glucagon was initially reduced, with the reduction in glucose concentrations after 2 h masking this initial glucagon reduction. Similar results were recently described during an overnight infusion of supraphysiological dosages of GLP-1 in NIDDM subjects (18).

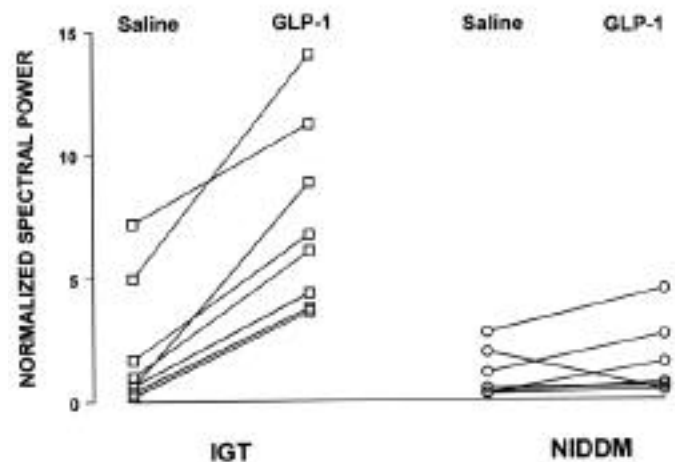


FIG. 4. Comparison of normalized spectral power during saline and GLP-1 infusion in IGT (left) and NIDDM subjects (right).

In conclusion, this study demonstrated that continuous infusion of physiological levels of GLP-1 reduced plasma glucose concentrations and stimulated insulin secretion in IGT and NIDDM subjects. Most importantly, GLP-1 restored the ability of the β-cell to sense and respond to small changes in plasma glucose concentrations in IGT subjects, with only a variable response in NIDDM subjects. In IGT subjects, we observed a significant sixfold increase in spectral power, a measure of β-cell function that does not rely on adjustment for changes in insulin sensitivity. These results suggest that studies should be performed to determine whether GLP-1 therapy may delay or prevent the deterioration of β-cell dysfunction responsible for the progression of IGT to overt NIDDM.

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