

Effects of the Long-Acting Human Glucagon-Like Peptide-1 Analog Liraglutide on β -Cell Function in Normal Living Conditions

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Liraglutide is a long-acting glucagon-like peptide (GLP)-1 analog, which exerts its glucose-lowering action through multiple mechanisms (1). One important feature of liraglutide is its ability to enhance β -cell function. The effects on β -cell function have been demonstrated using standardized β -cell function tests based on intravenous glucose administration (2–4). However, these studies may not reflect the modes of action of liraglutide during normal living. To assess the effects of liraglutide on β -cell function in normal living, we have used a validated β -cell model to analyze 24-h triple-meal experiments.

RESEARCH DESIGN AND METHODS

— This study includes data used for a different analysis in a previous publication (3), where the experimental protocol, approved by the local ethics committee and performed in accordance with the Helsinki Declaration, was described in detail.

Thirteen type 2 diabetic patients (five women and eight men) were examined. Their mean \pm SD age was 56.4 ± 9.2 years, BMI was 31.2 ± 3.6 kg/m², last measured A1C before inclusion was $7.3 \pm 0.4\%$ (normal range $<6.4\%$), and the duration of diabetes was 3.0 ± 2.6 years.

The study is a randomized, double-blind, placebo-controlled, crossover

trial, with a washout period of 6–7 weeks between treatments. After inclusion, the patients discontinued their oral hypoglycemic agents (sulfonylurea and metformin) for 2 weeks before the study. Liraglutide (6 μ g/kg body wt) or placebo was injected subcutaneously into the abdomen once daily (at ~ 0745 h) for 9 days. After 7 days of treatment, the patients were hospitalized at 2200 h. On the next day, while continuing treatment, three standard meals were served at 0800, 1200, and 1800 h. Breakfast contained 2,660 kJ (protein 14%, carbohydrate 55%, and fat 31%), lunch 2,865 kJ (protein 16%, carbohydrate 50%, and fat 34%), and dinner 3,397 kJ (protein 28%, carbohydrate 53%, and fat 19%). Blood was collected at varying intervals for determination of glucose, insulin, and C-peptide, which were measured as previously described (3).

β -Cell function

β -Cell function was assessed using a model that describes the relationship between insulin secretion (ISR) and glucose concentration (5,6). The model expresses ISR (in picomoles per minute per squared meter of body surface area) as the sum of two components. The first component represents the dependence of ISR on absolute glucose concentration and is characterized by a dose-response function

relating the two variables. Characteristic parameters of the dose response are the mean slope within the observed glucose range, denoted as β -cell glucose sensitivity, and ISR at a fixed reference glucose value of 9 mmol/l (approximately the mean basal glucose value in the whole group). The dose response is modulated by a potentiation factor, which accounts for several potentiating mechanisms (prolonged exposure to hyperglycemia, non-glucose substrates, gastrointestinal hormones, neurotransmitters, and liraglutide). The potentiation factor is set to be a positive function of time and is constrained to average unity during the experiment; thus, it expresses the relative potentiation of the secretory response to glucose. Changes in the potentiation factor were evaluated as the fold change over a given time interval. The second ISR component represents the dependence of ISR on the rate of change of glucose concentration and is expressed by a single parameter, denoted as rate sensitivity, which is related to early insulin release (5,6). The model parameters were estimated from glucose and C-peptide concentration by regularized least squares, as previously described (5,6).

Statistical analysis

Data and results are presented as means \pm SD or as median (interquartile range) for non-normally distributed ISR parameters. Differences between liraglutide and placebo were tested using the Wilcoxon's signed-rank test (significance level $P < 0.05$). Associations were tested by standard linear regression.

RESULTS — Liraglutide decreased mean and nocturnal (2300–0800 h) plasma glucose levels (from 9.7 ± 3.3 to 7.8 ± 2.1 and from 8.3 ± 2.7 to 6.8 ± 1.5 mmol/l, respectively, $P < 0.01$) (Fig. 1A), whereas the decrease in fasting glucose did not reach statistical significance (9.6 ± 2.8 vs. 8.6 ± 2.4 , $P = 0.15$). Mean plasma insulin (173 ± 132 vs. 161 ± 87 pmol/l) and C-peptide (1.6 ± 0.8 vs.

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Abbreviations: GLP, glucagon-like peptide; ISR, insulin secretion.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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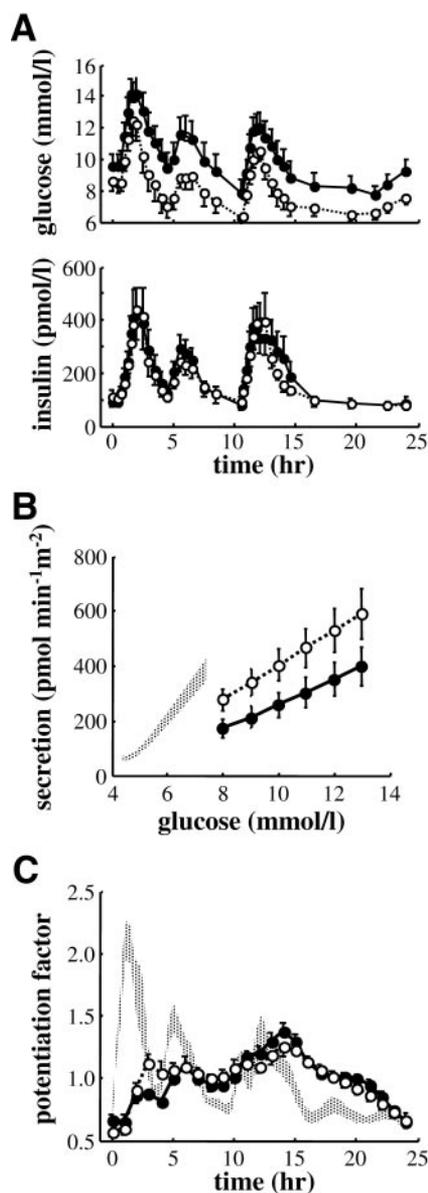


Figure 1—A: Plasma glucose and insulin concentrations during placebo (solid line and ●) and liraglutide (broken line and ○). Time is relative to the beginning of the test (0800 h). Data are means \pm SE. B: Dose response with placebo (solid line and ●) and liraglutide (broken line and ○). The dose responses are plotted over a glucose range corresponding approximately to the observed glucose excursions. The slope of the dose response is glucose sensitivity. C: Potentiation factor during placebo (solid line and ●) and liraglutide (broken line and ○). Data are means \pm SE. The dashed areas represent the dose response (B) and the potentiation factor (C) in normal subjects, redrawn from ref. 6.

1.6 ± 0.6 nmol/l) concentrations and total insulin secretion (median 274 [interquartile range 126] vs. 304 nmol/m² [92])

did not change; in contrast, modeling analysis predicted a marked effect on the β -cell dose response (Fig. 1B). In particular, the β -cell dose response was shifted upwards and steeper, as reflected by a significant increase in glucose sensitivity (from 38 [51] to 54 pmol/min per m² per mmol/l [59], $P < 0.01$) and in insulin secretion at 9 mmol/l glucose (from 189 [225] to 322 pmol/min per m² [265], $P < 0.0005$). Liraglutide also significantly increased the fold rise of potentiation factor induced by breakfast (from 0800 to 1100 h), from 1.2 (interquartile range 0.7) to 2.1-fold (1.2), $P < 0.002$ (Fig. 1C). The change in rate sensitivity was not significant (0.5 [0.4] vs. 0.1 nmol/m² per mmol/l [0.5]).

In a multivariate regression model, the treatment-induced changes in insulin secretion at 9 mmol/l glucose and glucose sensitivity (log transformed) were independent predictors of the corresponding changes in mean glucose levels (standardized correlation coefficients -0.49 for insulin secretion at 9 mmol/l glucose and -0.49 for glucose sensitivity, explained variance 65%, $P < 0.005$).

CONCLUSIONS— The novel finding is that liraglutide treatment significantly enhances β -cell function evaluated under conditions of normal living and that the β -cell function improvement is related to the improvement in glucose levels.

The modes of β -cell function improvement are similar to those observed after a single liraglutide dose with the use of the graded glucose infusion test (2), i.e., an upward shift and a steeper slope of the β -cell dose-response curve. In addition, the current data show that liraglutide also improved potentiation of insulin secretion during the first meal by restoring, in part, the potentiation peak, which is markedly blunted in diabetes (5). This phenomenon is similar to what has been observed with exenatide (7) and is suggestive of a potentiating effect mediated by analogous mechanisms, possibly by direct stimulation of the GLP-1 receptor.

However, in comparison with a group of normal subjects in which β -cell function was assessed with similar experimental and data analysis methods (6), in our diabetic patients neither the β -cell dose response nor potentiation were normalized (Fig. 1), in contrast with previous

observations based on an intravenous test (2). In fact, glucose sensitivity with liraglutide was still well below normal (median 54 [interquartile range 59] vs. 84 pmol/min per m² per mmol/l [41] in ref. 6, $P < 0.05$), and the initial potentiation peak remained considerably blunted. Although these abnormalities might have been overestimated due to the younger age of the control group, the finding stresses the importance of assessing β -cell function under physiological conditions of β -cell stress.

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