A model of GLP-1 action on insulin secretion in nondiabetic subjects

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Submitted 30 November 2009; accepted in final form 19 February 2010

Dalla Man C, Micheletto F, Sathananthan A, Rizza RA, Vella A, Cobelli C. A model of GLP-1 action on insulin secretion in nondiabetic subjects. Am J Physiol Endocrinol Metab 298: E1115–E1121, 2010. First published February 23, 2010; doi:10.1152/ajpendo.00705.2009.—Glucagon-like peptide-1 (GLP-1)-based therapies for diabetes have aroused interest because of their effects on insulin secretion and glycemic control. However, a mechanistic model enabling quantitation of pancreatic response to GLP-1 has never been developed. To develop such a model we studied 88 healthy individuals (age 26.3 ± 0.6 yr, BMI 24.9 ± 0.4 kg/m²) by use of a hyperglycemic clamp. A variable infusion maintained glucose concentrations at 150 mg/dl for 240 min. At 120 min, an intravenous infusion of GLP-1 was started (0.75 pmol·kg⁻¹·min⁻¹ from 120–180 min, 1.5 pmol·kg⁻¹·min⁻¹ from 181–240 min). Consequently, plasma C-peptide concentration rose from 1,852.0 ± 62.8 pmol/l at 120 min to 4,272.2 ± 176.4 pmol/l at 180 min and to 6,995.8 ± 323.5 pmol/l at 240 min. Four models of GLP-1 action on insulin secretion were considered. All models share the common assumption that insulin secretion is made up of two components, one proportional to glucose rate of change through dynamic responsivity, Φd, and one proportional to glucose through static responsivity, Φs, but differing by modality of GLP-1 control. The model that best fit C-peptide data assumes that above-basal insulin secretion depends linearly on GLP-1 concentration and its rate of change. An index (I) measuring the percentage increase of secretion due to GLP-1 is derived. Before GLP-1 infusion, Φd = 245.7 ± 15.6 10⁻⁹ and Φs = 25.2 ± 1.4 10⁻⁹ min⁻¹. Under GLP-1 stimulus, I = 12.6 ± 0.71% per pmol/l, meaning that an increase of 5 pmol/l in peripheral GLP-1 concentrations induces an ~60% increase in basal insulin secretion.

GLUCAGON-LIKE PEPTIDE-1 (GLP-1) is produced by the enteroendocrine L cells of the intestinal mucosa and is released into the portal circulation in response to meal ingestion (2). It arises from the posttranslational processing of proglucagon by prohormone convertase-1 (PC-1) in the enteroendocrine L cells of the intestinal mucosa (16). GLP-1 enhances insulin secretion and inhibits glucagon release in a glucose-dependent manner (17), prompting the development of GLP-1-based therapies for the treatment of diabetes (11). However, infused GLP-1 is rapidly inactivated by the widely distributed enzyme dipeptidyl peptidase-4 (DPP-4), which removes the two NH₂-terminal amino acids, consequently requiring constant infusion to maintain its effects on insulin secretion. GLP-1-based therapy for type 2 diabetes has required the development of GLP-1 receptor agonists that resist the action of DPP-4 (21) or compounds that inhibit DPP-4, thereby raising endogenous concentrations of active GLP-1 (10). It has previously been suggested that genetic differences may explain some of the variation to GLP-1 response in prior studies (25).

Several studies are available on GLP-1 action on insulin secretion both at the cellular (13, 14, 18) and at the whole body levels (1, 2, 10, 15, 17, 19); however, none of them has ever aimed to mechanistically model GLP-1 action on insulin secretion. In fact, quantitating the effect of GLP-1 on insulin secretion is not straightforward, given that GLP-1 delays gastric emptying (26) and is a glucose-dependent secretagogue. Consequently, measuring the response to an oral meal challenge has required the use of modeling techniques to account for changes in insulin secretion in response to changing glucose concentrations. Changes in gastric emptying alter the rate of portal appearance of meal-derived glucose and consequently need to be accounted for in such situations. These considerations have often led to the use of a hyperglycemic clamp to quantitate response to GLP-1 infusion. However, peripheral insulin concentrations do not represent insulin secretion but rather the sum of pancreatic insulin secretion, hepatic insulin extraction, and distribution into the circulating compartment. Thus, more accurate measurements of insulin secretion are based on deconvolution (12, 24–27) from C-peptide concentrations, given that both are secreted in an equimolar fashion and C-peptide is not extracted by the liver. However, to mechanistically describe pancreatic insulin secretion and derive indexes of β-cell function, one can use the C-peptide minimal model (4), which allows exploration of the influence of glucose concentrations on insulin secretion, after a glucose perturbation. Furthermore, infusion of GLP-1 adds a second secretagogue that influences insulin secretion in concert with hyperglycemia. Developing a modification of the C-peptide minimal model that allows quantitation of the effect of hyperglycemia and GLP-1 on β-cell secretion would therefore be an important tool with which to explore the basis for interindividual differences in insulin secretion in response to GLP-1.

We therefore studied a group of healthy subjects by use of a hyperglycemic clamp and two infusion rates of GLP-1 (half-maximal and maximal). We subsequently used glucose, GLP-1, and C-peptide data to develop a model to describe these data and quantitate the percentage increase of secretion due to GLP-1.

RESEARCH DESIGN AND METHODS

Subjects

After approval from the Mayo Institutional Review Board, 88 subjects with an overnight fasting glucose <5.3 mmol/l gave written informed consent to participate in the study. All subjects were in good health, were at a stable weight, and did not engage in regular vigorous exercise. Subjects (52 females and 36 males) were <40 yr of age (average 26.3 ± 0.6 yr) at the time of participation and had no history...
of impaired fasting glucose or diabetes or of prior therapy with anti-diabetic medication. Subjects had a BMI between 19 and 40 kg/m² (average 24.9 ± 0.4 kg/m²) and no history of chronic disease or prior abdominal surgery. All subjects were instructed to follow a weight maintenance diet containing ∼55% carbohydrate, 30% fat, and 15% protein for the period of study. Body composition was measured using dual-energy X-ray absorptiometry (DPX scanner; Lunar, Madison, WI).

Experimental Design

Subjects were admitted to the CRU at 1700 on the evening prior to the study. Subsequently, they consumed a standard 10 cal/kg meal (55% carbohydrate, 30% fat, and 15% protein), after which they fasted overnight. At 0600 (−60 min) a forearm vein was cannulated with an 18-gauge needle to allow infusions to be performed. An 18-gauge cannula was inserted retrogradely into a vein of the dorsum of the contralateral hand. This was placed in a heated Plexiglas box maintained at 55°C to allow sampling of arterialized venous blood. At time 0 min a primed (0.1 g/kg over 4 min), continuous infusion of 50% dextrose was initiated. The dextrose infusion rate was varied to maintain peripheral glucose concentrations at ∼150 mg/dl (Fig. 1). At 120 min, GLP-1(7–36) amide (Bachem, San Diego, CA) was infused (15 pmol/kg lean body mass over 10 min and then at a rate of 0.75 pmol·kg⁻¹·min⁻¹). At 180 min, the infusion rate was increased to 1.5 pmol·kg⁻¹·min⁻¹. Prior experience with infusion of GLP-1 at a fixed rate (1.2 pmol·kg⁻¹·min⁻¹) has suggested that such an infusion requires 20–30 min to reach adequate concentrations of GLP-1 (32). Given the short duration of infusion, we used a higher infusion rate for the first 10 min to rapidly achieve elevated GLP-1 concentrations. We did not use a GLP-1 bolus over 2–3 min, in order to avoid potential nausea and vomiting associated with a rapid, sudden rise of GLP-1.

Measurements

Fig. 1. Average glucose infusion rate used to maintain glucose level at 150 mg/dl, despite change in GLP-1 induced C-peptide concentrations. Error bars represent standard error.

C-peptide Minimal Model

The model used to describe C-peptide secretion before GLP-1 infusion is the C-peptide minimal model originally proposed in Ref. 28 for graded up-and-down glucose infusion and then employed also during an oral test (4). Briefly, the pancreatic secretion (SR) is linked to plasma C-peptide concentration by the two-compartment model of C-peptide kinetics originally proposed by Eaton et al. (12):

\[
\left\{
\begin{aligned}
\dot{C}P_1(t) &= -[k_{01} + k_{21}] \cdot CP_1(t) + k_{12} \cdot CP_2(t) + SR(t) \\
\dot{C}P_2(t) &= k_{21} \cdot CP_1(t) - k_{12} \cdot CP_2(t)
\end{aligned}
\]

where CP₁ and CP₂ (pmol/l) are C-peptide concentrations in the accessible and peripheral compartments, respectively, and k₀₁, k₁₂, and k₂₁ (min⁻¹) are C-peptide kinetic parameters fixed to standard values (30) to ensure numerical identification of the overall model. The model also assumes that SR is made up of a basal (SRₐ), a static (SRₛ), and a dynamic (SRₜ) component:

\[
SR(t) = SRₐ(t) + SRₛ(t) + SRₜ(t)
\]

SRₛ is assumed equal to the provision of releasable insulin to β-cells, controlled by glucose concentration above a threshold h:

\[
SRₛ(t) = -\alpha \cdot \{SR(t) - \Phiₐ \cdot (G(t) - h)\}
\]

Basiclly, the static secretion component is proportional, through parameter Φₛ, to delayed glucose concentration above a threshold h, with a time delay equal to 1/α. Φₛ is the static β-cell responsivity to glucose and measures the ability of glucose rate of change to stimulate SRₛ.

SRₜ represents the secretion of insulin from the promptly releasable pool and is proportional to the rate of increase of glucose:

\[
SRₜ(t) = \begin{cases} 
\Phiₜ \cdot \frac{dG(t)}{dt} & \text{if } \frac{dG(t)}{dt} > 0 \text{ and } G(t) > G_b \\
0 & \text{otherwise}
\end{cases}
\]

Glp-1 Minimal Models

Since several reports in the literature indicate that GLP-1 acts only on above-basal insulin secretion while it has no effect on basal secretion, (2, 13, 17), we assumed that GLP-1 potentiates only above-basal insulin secretion. Four models of increasing complexity of GLP-1 action have been tested.

Model 1. Model 1 assumes a proportional action of GLP-1 on above-basal insulin secretion:

\[
\Delta SR_{GLP-1} = \Delta SR(t) \cdot [a \cdot GLP-1(t) + 1]
\]

with ∆SR(t) the glucose-dependent secretion rate before GLP-1 infusion, ∆SR_{GLP-1} the glucose-dependent secretion rate after GLP-1 infusion, GLP-1(t) the over-basal hormone concentration, and a model parameter.

Model 2. Model 2 assumes a proportional plus derivative action of GLP-1 on ∆SR:

\[
\Delta SR_{GLP-1} = \Delta SR(t) \cdot [a \cdot GLP-1(t) + b \cdot GLP-1(t) \cdot \frac{dGLP-1(t)}{dt}]
\]

with ∆SR(t) the glucose-dependent secretion rate before GLP-1 infusion, ∆SR_{GLP-1} the glucose-dependent secretion rate after GLP-1 infusion, GLP-1(t) the over-basal hormone concentration, and model parameters.
with AUC denoting the area under the curve and GLP1_{max} the peak C-peptide concentrations is likely to be nonlinear (see RESULTS, Plasma C-peptide and GLP-1 concentration). Thus, model 3 is proposed, which assumes a nonlinear (Michaelis-Menten) action of GLP-1 on ΔSR:

\[
\Delta SR^{GLP1}(t) = \left\{ \begin{array}{ll}
\Delta SR(t) \cdot \left[ 1 + \frac{c \cdot GLP1(t)}{d + GLP1(t)} \right] & \text{if } \frac{dGLP1(t)}{dt} > 0 \\
\Delta SR(t) \cdot \left[ 1 + \frac{c \cdot GLP1(t)}{d + GLP1(t)} + 1 \right] & \text{otherwise}
\end{array} \right.
\]

with a and b model parameters representing the percentage increase of ΔSR due to the GLP-1 and GLP-1 rate of change, respectively.

Model 3. Our data show that the relationship between GLP-1 and C-peptide concentrations is likely to be nonlinear (see RESULTS, Plasma C-peptide and GLP-1 concentration). Thus, model 3 is proposed, which assumes a nonlinear (Michaelis-Menten) action of GLP-1 on ΔSR:

\[
\Delta SR^{GLP1}(t) = \Delta SR(t) \cdot \left[ 1 + \frac{c \cdot GLP1(t)}{d + GLP1(t)} \right]
\]

with c and d model parameters representing, respectively, the maximum percentage increase of ΔSR due to GLP-1 and the value of the above-basal GLP-1 concentration at which the half-maximum percentage increase is obtained.

Model 4. Finally, model 4 assumes a nonlinear and derivative action of GLP-1 on ΔSR:

\[
\Delta SR^{GLP1}(t) = \left\{ \begin{array}{ll}
\Delta SR(t) \cdot \left[ 1 + \frac{c \cdot GLP1(t)}{d + GLP1(t)} \right] & \text{if } \frac{dGLP1(t)}{dt} > 0 \\
\Delta SR(t) \cdot \left[ 1 + \frac{c \cdot GLP1(t)}{d + GLP1(t)} \right] & \text{otherwise}
\end{array} \right.
\]

with b, c, and d defined as above.

The GLP-1 Potentiation Index

It is useful to quantify the ability of GLP-1 to control insulin secretion through a potentiation index (Π). The index is defined as the ratio between the average percent increase in over-basal insulin secretion and average GLP-1 plasma concentration. With this definition, Π (% per pmol/l) can be derived for all the above models. However, since model 2 was selected as the most parsimonious (see RESULTS), we report the derivation of Π only for model 2:

\[
\Pi = \int_{0}^{\infty} \frac{\Delta SR^{GLP1}(t) - \Delta SR(t)}{\Delta SR(t)} \cdot \frac{dGLP1(t)}{dt} \cdot \frac{dGLP1(t)}{dt} \cdot \frac{100}{\Delta SR(t) \cdot dGLP1(t)} \cdot \frac{dGLP1(t)}{dt} \cdot \frac{100}{\Delta SR(t) \cdot dGLP1(t)}
\]

with AUC denoting the area under the curve and GLP1_{max} the peak value of over-basal GLP-1 concentration.

Parameter Estimation and Model Comparison

The GLP-1 models have been incorporated into the C-peptide model to describe SR as function of glucose and GLP-1 concentrations. All models were numerically identified on C-peptide data by nonlinear least squares (6, 7), as implemented in SAAM II [Simulation Analysis and modelling software (3)]. Error of C-peptide data was assumed to be independent, Gaussian, and with zero mean and known variance (29).

Statistical Analysis

Data are presented as means ± SE, if not differently indicated. Two-sample comparisons were done by Wilcoxon signed rank test (significance level set to 5%). Pearson’s correlation was used to evaluate univariate correlation.

RESULTS

Plasma C-Peptide and GLP-1 Concentration

Basal plasma C-peptide concentration was 578.3 ± 23.1 pmol/l; at 120 min, before the intravenous infusion of GLP-1 was started, C-peptide concentration was 1.852.0 ± 62.8 pmol/l, due to the rise in glucose concentration, and plasma GLP-1 was 4.4 ± 0.8 pmol/l. After the GLP-1 infusion, plasma GLP-1 concentration increased to 23.9 ± 1.6 pmol/l at 180 min and to 42.2 ± 2.1 pmol/l at 240 min (all differences were statistically significant, P < 0.0001), and consequently C-peptide concentration rose to 4,272.2 ± 176.4 and 6,995.8 ± 323.5 at 180 and 240 min, respectively (all differences were statistically significant, P < 0.0001) (Fig. 2). The ratios between above-basal C-peptide and above-basal GLP-1 concentrations were 266.4 ± 19.8 and 196.6 ± 11.1 at 180 and 240 min, respectively, and the difference was statistically significant (P < 0.0001). As already mentioned, this result supports the hypothesis that GLP-1 acts nonlinearily on C-peptide secretion.

Model Comparison

Table 1 shows the criteria used for model selection. All the tested models fit the data well as confirmed by the Run Test, which supported randomness of residuals in 70% of the subjects. Time courses of weighted residuals obtained with the four models are shown in Fig. 3. Model 4 provided, on average, the best fit. As expected, increasing the complexity of the model (and the number of parameters), worsens the precision of parameter estimates (increased CV), but the parsimony criterion indicates model 4 as the most parsimonious (lowest AIC). On the other hand, model 4 collapsed into simpler models in most cases: e.g., to model 3 in 11 subjects, since parameter b was zero, to model 2 in 43 subjects, since parameter d was very high, and even to model 1 in 17 subjects, since both changes in parameters b and d occurred. Even if in the remaining 21 subjects model 4 was superior to the other models, we are inclined to select model 2 as the best model,
since it is the most parsimonious to adequately fit the data in most cases. In addition (see below), it provides estimates of the potentiation index only modestly different from that of model 4, which is the most complex among the proposed models.

**Model Indexes**

Model parameters are reported in Table 2 together with their precision.

Before GLP-1 infusion, β-cell responsivity indexes were: $\Phi_b = 25.2 \pm 1.4 \times 10^{-9} \text{ min}^{-1}$ and $\Phi_d = 245.7 \pm 15.6 \times 10^{-9}$. Under GLP-1 stimulus, the potentiation index estimated with model 2 was $12.6 \pm 0.7\%$ per pmol/l. This means that, if peripheral active GLP-1 concentration increases of 5 pmol/l, as occurs after a meal, over-basal insulin secretion is increased by $\sim 60\%$.

Note that if potentiation index were estimated with more complex models, similar results would have been obtained; e.g., with model 4, $\Pi = 15.5 \pm 1.1\%$ per pmol/l (correlation with model 2 index: $R = 0.95 \ P < 0.001$). This confirms that model 2, despite being less accurate than model 4 in some cases, still provides good estimates of the efficiency of the GLP-1 control on over-basal insulin secretion.

**DISCUSSION**

GLP-1 is a potent insulin secretagogue that stimulates insulin secretion in a glucose-dependent manner. When infused in supraphysiological concentrations, it delays gastric emptying and promotes satiety (8), leading to weight loss (33). Since these actions are useful in the treatment of type 2 diabetes, GLP-1-based therapy for type 2 diabetes has been developed for clinical use in humans. The role of such therapies in the treatment algorithm for type 2 diabetes is as yet uncertain; consequently, neither DPP-4 inhibitors nor GLP-1 receptor agonists are used as first-line therapy.

However, there has been some suggestion that there is interindividual heterogeneity in response to GLP-1, raising the possibility that some individuals may benefit more from such therapy than others earlier in the disease (25, 31). Given the potential expense and side effects from such intervention, it would be reasonable to develop a quantitative measure of GLP-1-induced insulin secretion that can be used to examine differences in individual response to this hormone. Several studies are available on GLP-1 action on insulin secretion (1, 2, 10, 13–15, 17–19), however, to the best of our knowledge, none of them has ever aimed to mechanistically model GLP-1

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**Table 1. Comparison of GLP-1 action models**

<table>
<thead>
<tr>
<th>Model</th>
<th>Residual Independence (%)</th>
<th>Data Fit (WRSS)</th>
<th>Precision (CV)</th>
<th>Parsimony Criterion (AIC)</th>
<th>No. Parameters</th>
<th>%Nonzero Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>68%</td>
<td>192</td>
<td>7%</td>
<td>194</td>
<td>1</td>
<td>100%</td>
</tr>
<tr>
<td>Model 2</td>
<td>75%</td>
<td>145</td>
<td>13%</td>
<td>149</td>
<td>2</td>
<td>77%</td>
</tr>
<tr>
<td>Model 3</td>
<td>70%</td>
<td>163</td>
<td>28%</td>
<td>167</td>
<td>2</td>
<td>44%</td>
</tr>
<tr>
<td>Model 4</td>
<td>71%</td>
<td>109</td>
<td>28%</td>
<td>115</td>
<td>3</td>
<td>19%</td>
</tr>
</tbody>
</table>
action on β-cells. For instance, other investigators have previously utilized a hyperglycemic clamp to measure insulin secretion from deconvoluted C-peptide data. However, such a methodology does not take into account potential changes in glucose concentration during the hyperglycemic clamp or the changing GLP-1 concentrations prevailing during the experiment. The only model that indirectly accounts for a potentiation due to incretin is the one proposed by Mari et al. (20). It introduced a potentiating factor, which modulates the dose-response relation between insulin secretion and plasma glucose to better fit the C-peptide data, but it did not explicitly describe the incretin effect. Other studies (e.g., Ref. 1) also found a correlation between GLP-1 and the potentiating factor or utilized the model to assess different hormone responses in the morning vs. the afternoon (19). Another method used to assess incretin potentiation was that employed in Ref. 5. There the β-cell responsivities to glucose, Φₘ, and Φ₄ were calculated for both oral and intravenous matched glucose infusions, using the C-peptide minimal model originally proposed by Toffolo et al. for graded up-and-down glucose infusion (28) and then em-

![Fig. 3. Average weighted residuals obtained with models 1, 2, 3, and 4. Error bars represent standard deviation.](image)

Table 2. Estimates of model parameters

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>α [min⁻¹]</td>
<td>0.036 ± 0.002</td>
<td>0.042 ± 0.002</td>
<td>0.038 ± 0.002</td>
<td>0.043 ± 0.002</td>
</tr>
<tr>
<td>h [mg/dl]</td>
<td>90.15 ± 1.20</td>
<td>90.25 ± 1.11</td>
<td>93.25 ± 1.17</td>
<td>91.84 ± 1.07</td>
</tr>
<tr>
<td>Φ₄ [10⁻⁹]</td>
<td>249.51 ± 16.18</td>
<td>245.7 ± 15.6</td>
<td>253.35 ± 16.28</td>
<td>246.72 ± 15.60</td>
</tr>
<tr>
<td>Φₘ [10⁻⁹·min⁻¹]</td>
<td>29.9 ± 2.00</td>
<td>25.25 ± 1.4</td>
<td>29.75 ± 1.87</td>
<td>25.77 ± 1.50</td>
</tr>
<tr>
<td>a [l/pmol]</td>
<td>0.11 ± 0.01</td>
<td>0.12 ± 0.01</td>
<td>0.12 ± 0.01</td>
<td>0.56 ± 0.06</td>
</tr>
<tr>
<td>b [l·min/pmol]</td>
<td>0.62 ± 0.06</td>
<td>0.62 ± 0.06</td>
<td>6.40 ± 0.93</td>
<td>4.09 ± 0.86</td>
</tr>
<tr>
<td>c [dimensionless]</td>
<td>60.73 ± 9.89</td>
<td>60.73 ± 9.89</td>
<td>60.73 ± 9.89</td>
<td>54.75 ± 10.76</td>
</tr>
<tr>
<td>d [pmol/l]</td>
<td></td>
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Values are means ± SE. Numbers in parentheses represent CV%.
plied during an oral test (4). The difference between oral and intravenous indexes provided an indirect measure of the incretin effect; there was an -60% difference between the two indexes, implying that the incretin effect is responsible for such potentiation.

However, in none of the above studies was there an attempt to mechanistically describe GLP-1 action on insulin secretion. The novelty of the present study is thus the development and validation against experimental data of a model of GLP-1 action on insulin secretion that, in contrast to other methods, allows simultaneous estimation of both β-cell responsibility to glucose and of the ability of GLP-1 to enhance secretion. This model is a potential tool to quantitate between-subject variation in response to GLP-1. To this end, 88 healthy individuals were studied. They underwent a hyperglycemic clamp with an exogenous infusion of GLP-1 (Fig. 1), which brought hormone concentration first to physiological and then to supraphysiological concentrations (Fig. 2).

Four models have been tested. All of them are based on the common assumption that insulin secretion is made up of a basal component; a dynamic component, proportional to glucose rate of change through the dynamic responsibility index \( \Phi_d \) \( (10^{-7}) \); and a static index, proportional to glucose through the static responsibility \( \Phi_s \) \( (10^{-9} \text{ min}^{-1}) \) (4). Moreover, since it is known that GLP-1 enhances insulin secretion in a glucose-dependent manner (2, 13, 17), all of the tested models assume that GLP-1 concentration modulates the above-basal insulin secretion. Models differ in the modalities with which GLP-1 controls insulin secretion, e.g., linear or nonlinear, static or derivative control.

We found that model 2 was the most parsimonious (Table 1). In fact, it better fit the C-peptide data and provided precise parameter estimates in the largest number of subjects. It provides a potentiation index, \( \Pi = 12.6 \pm 0.7\% \) per pmol/l, measuring the ability of GLP-1 to promote above-basal insulin secretion. To appreciate the meaning of this index, consider that, during hyperglycemic conditions \((\sim 150 \text{ mg/dl})\), an increase of 5 pmol/l in peripheral GLP-1 concentrations, similar to that occurring after a meal, is predicted to induce a 63% increase in glucose-stimulated insulin secretion. This finding is comparable with the results reported in Ref. 5 for an OGTT, although the levels of GLP-1 were not reported. Furthermore, we also identified the original C-peptide model separately in the intervals 0 –120 min (no incretin stimulation) and 120 –240 min (incretin stimulation) and estimated two different \( \Phi_s \), i.e., \( \Phi_s^{0–120} \) and \( \Phi_s^{120–240} \), where \( \Phi_s^{120–240} \) was 326% higher on average than \( \Phi_s^{0–120} \), due to an average increase in GLP-1 of 29 pmol/l. This is in agreement with Ref. 5 if one assumes that an average 5 pmol/l increase of GLP-1 is likely to occur during an oral test.

As observed in RESULTS, model selection criteria would have indicated model 4 as the most parsimonious. However, model 4 reduces to model 3 in 11 subjects, since parameter b was zero, to model 2 in 43 subjects, since parameter d was very high, and to model 1 in 17 subjects, since both changes in parameters b and d occurred. One can thus speculate that model 4 is the most general model that is able to predict the C-peptide concentration in very challenging conditions, such as during a hyperglycemic clamp with GLP-1 at physiological and supraphysiological concentration, whereas in most subjects or different experimental conditions, e.g., during a meal, a simpler model (but derived from model 4) may be sufficient; e.g., model 2 is a better candidate when plasma GLP-1 excursions are smaller; thus, the use of a nonlinear model may be not necessary. Of note, the potentiation index provided by model 2 is virtually identical to that obtained with model 4 \( \Pi = 12.6 \pm 0.7\% \) vs. 15.5 \( \pm 1.1\% \) per pmol/l, \( R = 0.95, P < 0.001 \). This supports that, even though simpler, model 2 is robust enough to adequately quantify the action of GLP-1 on glucose-dependent insulin secretion.

Finally, it is interesting to note that the model describing the glucose-dependent insulin secretion \((4, 28)\) is linear in both \( \Phi_d \) and \( \Phi_s \); i.e., doubling \( \Phi_d \) or \( \Phi_s \) results in doubling \( \text{SR}_d \) or \( \text{SR}_s \), respectively. Therefore, all the models described in the section GLP-1 Minimal Models can be rewritten in terms of GLP-1 action of β-cell responsibility indexes; i.e., \( \Pi \) can be defined as the percentage increase of \( \Phi_d \) and \( \Phi_s \) due to GLP-1. This means that GLP-1 produces the same potentiation on both the dynamic and the static phases. The assumption that both \( \Phi_d \) and \( \Phi_s \) are similarly modulated by GLP-1 relies on the evidence provided in Ref. 5, where the percentage increases of \( \Phi_d \) and \( \Phi_s \) due to incretins were similar (58 and 63%, respectively). The adopted protocol design does not allow us to verify this assumption. In fact, when GLP-1 is infused, i.e., from \( t = 120 \) to 240 min, glucose is approximately constant and the dynamic phase of insulin secretion is virtually absent. This makes it impossible to separately assess GLP-1 potentiation on the dynamic phase \( \Phi_d \). As a matter of fact, four additional models, similar in structure to models 1, 2 3 and 4, respectively, but assuming GLP-1 action on static phase \( \Phi_s \) only, performed similarly to their counterparts. However, we believe that, in light of the applicability of the model to different protocols, the GLP-1 action on dynamic insulin secretion has to be included in the model.

In conclusion, a model of GLP-1 action of insulin secretion in nondiabetic subjects has been proposed. The model has been tested on data obtained from a hyperglycemic clamp with exogenous infusion of GLP-1. Further studies are needed to assess its validity during different protocols, e.g., meal or OGTT, and its applicability in type 2 diabetic patients.

GRANTS

We acknowledge the support of the Mayo Clinic CTSA Grant RR-24150 and Minnesota Obesity Center Grant DK-50456. A. Vella and C. Cobelli are supported by DK-78646 and R. A. Rizza by DK-29953.

DISCLOSURES

One or more authors is employed by and/or has a total financial interest worth more than $10,000 (from consultancy honoraria/expert testimony/corporate grants/patents pending/royalties/other) and/or has a 5% equity in an entity related to the subject matter discussed in the paper. A. Vella has received research grants from Merck and has consulted for Sanofi Aventis and CPEX Pharmaceuticals.

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