Assessing Insulin Secretion by Modeling in Multiple-Meal Tests

Role of Potentiation

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We developed a mathematical model of the glucose control of insulin secretion capable of quantifying β-cell function from a physiological meal test. The model includes a static control, i.e., a secretion component that is a function of plasma glucose concentration (the dose-response function), and a dynamic control, i.e., a secretion component that is proportional to the positive values of the glucose concentration derivative. Furthermore, the dose-response function is assumed to be modulated by a time-varying potentiation factor. To test the model, nine nondiabetic control subjects and nine type 2 diabetic patients received three standardized mixed meals over a period of 14–15 h. Blood samples were drawn for the measurement of glucose, insulin, and C-peptide concentration. The dose-response function, the parameter of the dynamic control, and the potentiation factor were determined by fitting the model to glucose and C-peptide concentrations. In diabetic patients, the dose-response function was shifted to the right (glucose concentration at a reference insulin secretion of 300 pmol · min^{-1} · m^{-2} was 11.7 ± 1.1 vs. 7.2 ± 0.7 mmol/l; $P < 0.05$), and decreased in slope (53 ± 15 vs. 148 ± 38 pmol · min^{-1} · m^{-2} · mmol^{-1} · l; $P < 0.05$) and the parameter of the dynamic control was decreased (220 ± 67 vs. 908 ± 276 pmol · m^{-2} · mmol^{-1} · l; $P < 0.05$) compared with the nondiabetic control subjects. Furthermore, potentiation was markedly blunted and delayed: maximum potentiation was observed at the first meal in normal subjects and at the second meal (about 4 h later) in diabetic subjects; the mean time for the potentiation factor was higher (7.1 ± 0.2 vs. 5.9 ± 0.2 h; $P < 0.01$), and the size of potentiation was reduced (2.6 ± 0.5 vs. 7.2 ± 1.5 fold increase; $P < 0.005$). In conclusion, our model of insulin secretion extracts multiple indexes of β-cell function from a physiological meal test. Use of the model in patients with type 2 diabetes retrieves known defects in insulin secretion but also uncovers new facets of β-cell dysfunction.
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The study of insulin secretion by modeling received considerable attention in the 1970s, when sophisticated experiments and models were developed (1–3). The application of modeling to clinical research has since been slow, the intravenous glucose test with ad hoc simplified models being the most widely used approach (4).

A new impulse to in vivo modeling of insulin secretion has come from the C-peptide–based methods (5,6), which have overcome the problem of first-pass hepatic insulin extraction, a potentially confounding factor. The most recent approaches are based on the C-peptide method, in particular those in which a meal or a meal-like test is used to assess β-cell function (7–9). In these approaches, however, little of the original model complexity remains, mainly because of the difficulty of estimating complex models from clinical data.

One of the physiological aspects lost to simplified models is potentiation of insulin secretion by repeated glucose stimulation, which is part of the phenomenon known as the Staub-Traugott effect (10,11). Potentiation is known to have remarkable importance, and has been considered with great attention in early modeling (1,3). In a recent study in which we modeled insulin secretion during a whole day of free living (12), we recognized that some form of potentiation is necessary to explain the experimental data. We have therefore developed a model of the glucose control of insulin secretion that incorporates the potentiation phenomenon. We have used this model to analyze the role of potentiation in multiple-meal tests in lean subjects and in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Subjects. Nine healthy male subjects (age 24 ± 1 years, BMI 22 ± 0.5 kg/m^2) and nine type 2 diabetic patients (five men and four women, age 58 ± 2 years, BMI 33 ± 1 kg/m^2) participated in the study. Diabetes duration was 7 ± 1 years, and HbA_{1c} averaged 9.0 ± 0.5%. Eight patients were treated with oral hypoglycemic agents, one with diet; all medications were discontinued 3 weeks before the study. The subjects were admitted to the hospital 1 or 2 days before the study and consumed their last meal at 7:00 P.M. on the day before the study. On the study day, three meals were served (2,200 kcal in healthy subjects and 1,700 kcal in diabetic patients), of which 25–30% were given as breakfast and the remaining equally divided between the two other meals. Meal composition was 50% carbohydrate, 20% protein, and 30% fat. Breakfast was consumed between 8:00 and 9:00 A.M., lunch 4 h later, and dinner 12 h (healthy subjects) or 10 h (diabetic patients) after breakfast. Blood sampling started before the first meal (time 0) and continued for 14–15 h, for the measurement of plasma glucose, insulin, and C-peptide concentrations. Writ-

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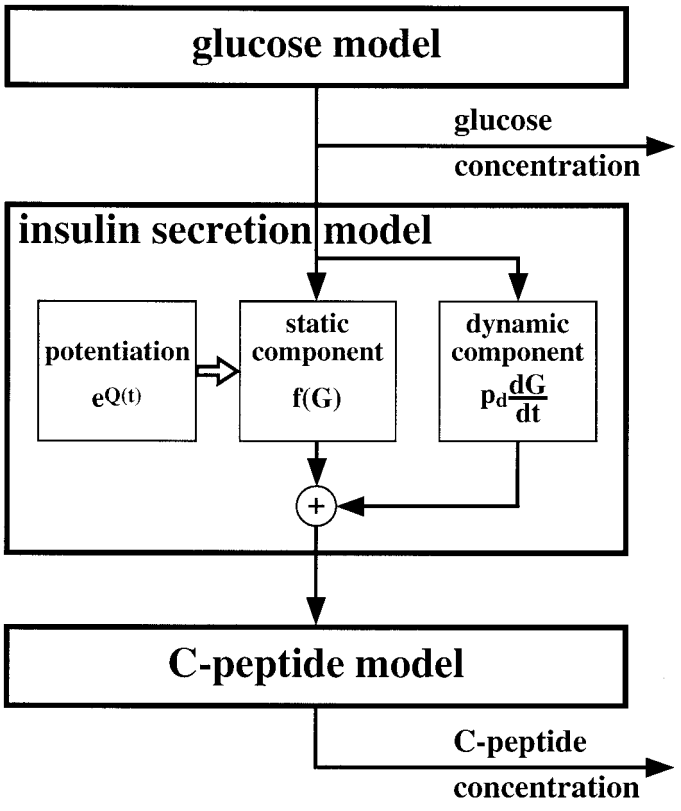

FIG. 1. Model of β-cell function.

ten informed consent was obtained from all subjects, and the protocol was approved by the local ethics committee.

Modeling. The model (Fig. 1) consists of three subunits: a model for fitting the glucose concentration profile, a model describing the relationship between glucose concentration and insulin (or C-peptide) secretion, and a model of C-peptide kinetics.

The purpose of the glucose model is to smooth and interpolate glucose concentrations. It is described by the differential equation

$$\frac{dG(t)}{dt} = -kG(t) + R(t) \quad (1)$$

where $G(t)$ (expressed in mmol/l) is the venous plasma glucose concentration, $k = 0.012$ min^{-1} is an assigned constant, and $R(t)$ is a function of time, represented in discrete form as a piece-wise linear function over 5-min intervals. Equation 1 yields a glucose concentration profile continuous in time and its time derivative. Formally, Eq. 1 is a single-compartment model of glucose kinetics, although in this context it is only used as a method for smoothing glucose concentration.

In the insulin secretion model, insulin secretion [$S(t)$, in pmol/min] is represented as the sum of two components. The first component [$S_g(t)$] expresses a static relationship between insulin secretion and glucose concentration, i.e., it embodies a β-cell dose-response function. This dose-response function is not time-invariant, however, but is modulated by a time-varying factor, expressing a potentiation effect upon insulin secretion:

$$S_g(t) = e^{Q(t)} f(G) \quad (2)$$

where $Q(t)$ is a function of time, represented in discrete form as a piece-wise linear function as $R(t)$ with zero mean over the experimental time period, and $f(G)$ is the dose-response function. The factor $P(t) = e^{Q(t)}$ is denoted as potentiation factor: it is greater than 1 if $Q(t)$ is above average, and less than 1 if $Q(t)$ is below average.

The β-cell dose-response function $f(G)$ has a formally complex expression (Appendix A) but is characterized by the following simple properties: *1*) $f(G)$ is positive for $G > 0$; *2*) $f(G)$ is quasi-linear for G below or above a given glucose threshold; *3*) the transition between the two quasi-linear portions can be both smooth or sharp. $f(G)$ is determined by four parameters: the initial and final slopes (p_3 and p_4, see Appendix A), the threshold glucose level at which the change in slope occurs (p_2), and a parameter determining the smoothness of the change (p_1). This dose-response function has been designed on the basis of our previous analysis (12), in which we have shown that a linear dose-response function is generally sufficient, but in some subjects a change in slope, more or less gradual, must be incorporated. The present dose-response function overcomes the problem of negative $f(G)$ values of the previous formulation, although it still has the drawback that some parameters (curvature and threshold) are not well identified when the actual dose-response function is virtually linear in the range of the observed glucose concentrations. Even in this case, however, the dose-response function is well-defined, as curvature and threshold have little influence on $f(G)$ when $f(G)$ is quasi-linear.

The dose-response function is modified during the experiment by the potentiation factor $P(t)$ (Eq. 2). We define the average dose-response as that corresponding to the average $P(t)$ in the entire experiment (which is close to 1, as $Q(t)$ is 0 on average).

The second insulin secretion component [$S_d(t)$] represents a dynamic dependence of insulin secretion on the rate of change of glucose concentration. $S_d(t)$ is proportional to the derivative of glucose concentration when the derivative is positive, and is 0 otherwise:

$$S_d(t) = \begin{cases} p_d \dfrac{dG(t)}{dt}, \dfrac{dG(t)}{dt} > 0 \\ 0, \dfrac{dG(t)}{dt} \le 0 \end{cases} \quad (3)$$

Total insulin secretion is the sum of the two components described above:

$$S(t) = S_g(t) + S_d(t) \quad (4)$$

Total insulin secretion is calculated every 5 min. Total insulin secretion is not dependent on the specific model presented here, because it is equivalent to insulin secretion as calculated by the C-peptide deconvolution method of Van Cauter et al. (6).

The model for C-peptide kinetics is the two-exponential model proposed by Van Cauter et al. (6), in which the model parameters are determined in each individual on the basis of the subject's sex, weight, height, and age. Plasma C-peptide concentration [$C(t)$] is the convolution product of the individualized, two-exponential C-peptide impulse response $h(t)$ and C-peptide secretion, $S(t)$ (Eq. 4):

$$\mathrm{C(t)} = \mathrm{h(t)} \otimes \mathrm{S(t)} \quad (5)$$

where $\otimes$ denotes convolution.

The model resulting from the combination of Eqs. 1–5 embodies three differential equations (Eq. 1 for glucose and two differential equations for the C-peptide model). The model predicts glucose and C-peptide concentration once the parameters of $f(G)$ and p_d, $R(t)$ (Eq. 1), and $Q(t)$ (Eq. 2) are known. Conversely, the parameters of $f(G)$, p_d, $R(t)$, and $Q(t)$ can be estimated using least-squares techniques from the glucose and C-peptide data. For this purpose, it is necessary to introduce regularization constraints on $R(t)$ and $Q(t)$, as done in deconvolution schemes. The regularization method used adds penalty terms for $R(t)$ and $Q(t)$ to the standard sum of squares term, which eliminate the spurious oscillations that $R(t)$ and $Q(t)$ would otherwise exhibit. The function that the least-squares algorithm actually minimizes is

$$\sum w_G(t)^2[G(t) - \hat{G}(t)]^2 + \sum w_C(t)^2[C(t) - \hat{C}(t)]^2 + \sum[\mathrm{w_R(t)\,R''(t)}]^2 + \sum[\mathrm{w_Q(t)Q''(t)}]^2 + \sum[\mathrm{w_o(t)Q(t)}]^2 \quad (6)$$

where the sums are over all time points, the hat denotes the model prediction, the double quote is the second derivative with respect to time, and the w's are weights. In Eq. 6, the first two terms are the standard weighted sums of squares for glucose and C-peptide, the third and fourth term are the regularization terms based on the second derivatives of $R(t)$ and $Q(t)$, which are normally employed in deconvolution algorithms, and the last term is the sum of $Q(t)$ squared.

The weights of the first two standard least-squares terms, $w_G(t)$ and $w_C(t)$, were set to the inverse of the expected standard deviation of the measurement error for glucose and C-peptide concentration. For glucose, the standard deviation was assumed to be constant and equal to 2% of the mean glucose concentration for each individual experiment. For C-peptide, the measurement error was experimentally found to be concentration dependent and was estimated for each point with the formula: SD = $0.0214 \times C + 10$, where SD and C are in pmol/l. The weights w_R and w_Q determine the degree of smoothness of $R(t)$ and $Q(t)$: high weights give smoother $R(t)$ and $Q(t)$. The weight w_0 constrains $Q(t)$ to be small in a least-square sense. This additional constraint has little importance when the secretion rate is clearly correlated with the glycemic excursions. When this correlation is weaker, it may happen that the changes in insulin secretion are accounted for by the potentiation factor $P(t)$ rather than the dose response $f(G)$. In these situations, the last

term of Eq. 6 helps to explain as much as possible the secretion changes with glycemic excursions rather than with the potentiation factor $P(t)$. These weights were iteratively selected so that the standard deviation of glucose and C-peptide concentrations calculated from the difference between the observed and the model-predicted values are close to the values expected from the measurement error. Model simulation and parameter estimation by minimization of Eq. 6 was performed using the language of technical computing, Matlab.

To illustrate the role of the various secretion components, total insulin secretion is split into three terms according to Eqs. 2 and 4:

$$S(t) = S_d(t) + \bar{P}f(G) + [P(t) - \bar{P}]f(G) = S_d(t) + S_s(t) + S_p(t) \quad (7)$$

where $\bar{P}$ is the mean value of $P(t)$ during the experiment. In Eq. 7, the first component $S_d(t)$ is the dynamic component, the second component $S_s(t)$ is a static component obtained from the average dose-response function (i.e., without potentiation), and the third component $S_p(t)$ is the potentiation component. $S_p(t)$ is a fictitious component expressing the deviation of the actual secretion $S(t)$ from that predicted by $S_d(t)$ and $S_s(t)$ and can be either positive or negative.

Insulin secretion parameters were normalized to body surface area. From the estimated model parameters, other parameters describing β-cell function were calculated. From the dose-response function, the insulin secretion value corresponding to a fixed reference glucose concentration value (e.g., 5 mmol/l) was calculated. The slope of the dose-response function at this glucose concentration was also determined. This parameter quantifies β-cell sensitivity to glucose concentration changes in the vicinity of the reference glucose value. In the present series of subjects, comparison of insulin secretion at a fixed glucose concentration between control and diabetic subjects is not reliable because the two groups had very different glucose levels. Comparison was thus made between the glucose levels corresponding to a fixed (300 pmol · min^{-1} · m^{-2}) insulin secretion.

To quantify the excursion and the time distribution of the potentiation factor, the ratio between its maximum and minimum value and its mean time were calculated. The mean time is the integral over the first 14 h of the product between time and the potentiation factor, divided by the integral of the potentiation factor during the same period. The mean time is the center of gravity of the potentiation factor curve.

Statistical analysis. Data and results are presented as mean ± SE. The statistical significance of differences between groups was assessed with the Mann-Whitney U test.

RESULTS

Glucose and C-peptide concentrations are shown in Fig. 2 together with the model fit. The existence of potentiation is evident from the data of Fig. 2: in the diabetic subjects, for instance, the second C-peptide peak is similar to the first in the face of a lower glucose peak.

Figure 3 shows the components of insulin secretion as calculated by Eq. 7. The figure clearly shows that, in both groups, insulin secretion is not accurately predicted from the glucose changes when using only the static and the dynamic control. For instance, in control subjects, total insulin secretion is underestimated during the first glucose peak and overestimated during the third glucose peak by the static secretion component. With the inclusion of potentiation, total insulin secretion is accurately predicted. Figure 3 also shows that the static component is the largest, whereas the dynamic and the potentiation components are smaller.

Figure 4 shows the dose-response functions, calculated for plasma glucose values in the range of those experimentally observed; Table 1 gives the dose-response parameters. The dose-response function was virtually linear in 14 of 18 subjects. The slope of the dose-response function was higher in control than in diabetic subjects. Furthermore, the parameter of the dynamic control (p_d) was lower in diabetic subjects.

Figure 5 shows the time course of the potentiation factor. The differences in pattern are remarkable. Whereas

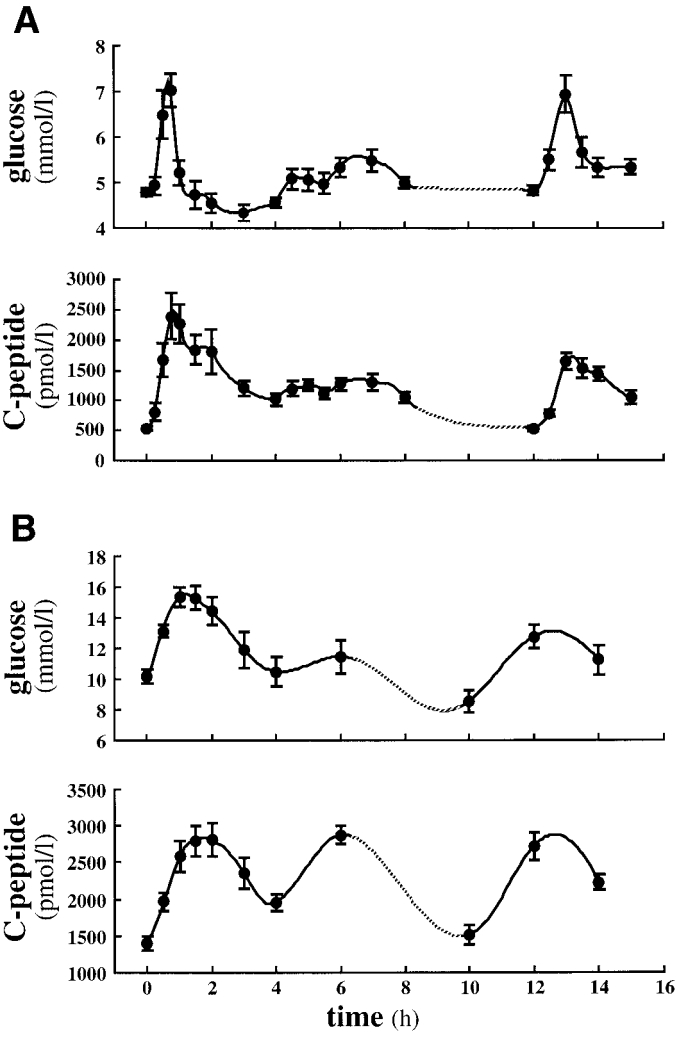

FIG. 2. Glucose and C-peptide concentrations in control subjects (*A*) and type 2 diabetic subjects (*B*). The continuous line represents the model fit; the hatched portion refers to the 4-h period with no data.

in control subjects potentiation rises during the first glucose peak and is responsible for the higher secretory response to the first meal, in diabetic subjects potentiation is much delayed and sustains the secretory response during the second meal. The mean time for the potentiation factor is in fact significantly higher in diabetic subjects (Table 1). Furthermore, in diabetic subjects, the potentiation factor excursion is reduced more than twofold in comparison with nondiabetic subjects (Table 1). Of interest is also that, in control subjects, potentiation follows the first glucose peak, whereas after the third glucose peak, which is comparable to the first in height, potentiation changes only slightly.

DISCUSSION

For a critical evaluation of the results of this work, it is important to review the model characteristics. Building on long-standing concepts of glucose control of insulin secretion and on our own previous experience (12), we modeled a secretion component that is a quasi-linear function of plasma glucose concentration and another component that depends on the derivative of glucose concentration. The need for these components has emerged from more

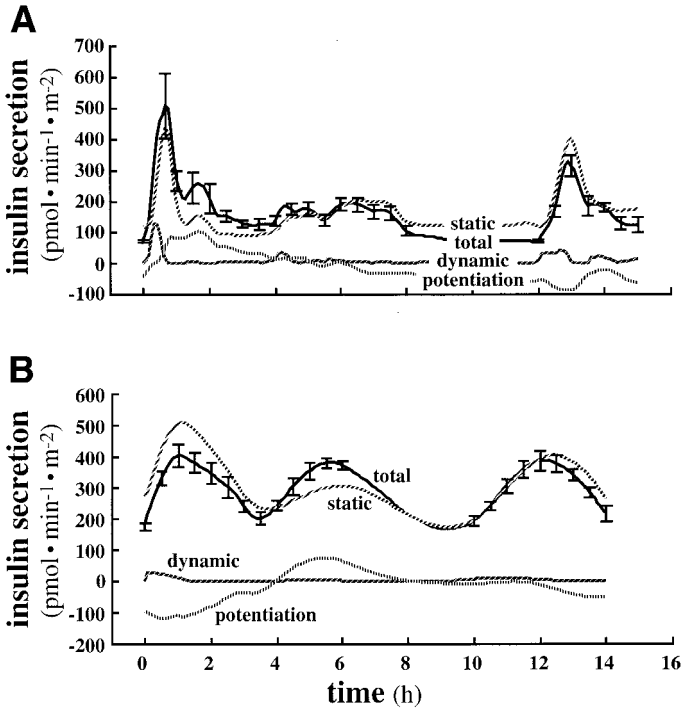

FIG. 3. Insulin secretion components in control subjects (*A*) and type 2 diabetic subjects (*B*). For clarity, error bars are drawn every 30 min for total insulin secretion only.

recent work using meals or meal-like tests (7–9). In our previous work (12) and in the present analysis, we found that these model characteristics are not sufficient to explain the data of repeated meal tests. In particular, an invariant dose-response function is not compatible with the observed data. As the experimental data show clear evidence of potentiation of insulin secretion—a well-known phenomenon—we have featured potentiation in the model.

Because it is not likely that in a repeated meal test potentiation is as simple as described in the mechanistic model of Cerasi et al. (3) or the one by Bergman and Urquhart (1), we have chosen a different approach. We have represented the interplay between the static response of the β-cells to glucose (the dose-response function) and potentiation in a form derived from Cerasi et al. (3), i.e., as the product of the dose-response function and the exponential function of a variable [$Q(t)$ in our notation] representing potentiation. However, in the model of Cerasi et al., potentiation is related to glucose concentration by a set of differential equations, whereas in our model $Q(t)$ is an estimated function of time, constrained to be smooth but with no a priori determined relationship with glucose. Although this choice has some limitations (see below), it has the essential advantage of being independent of specific assumptions on the mechanisms of potentiation. In fact, in our analysis, the potentiation pattern turns out to be not as simply related to glucose concentration as presupposed by the model of Cerasi et al. This is evident, for instance, in control subjects. The model of Cerasi et al. could explain the onset of potentiation during the first meal. However, because potentiation in the last meal is totally different from that in the first meal despite similar glucose excursions, the same model could not explain both meals.

During the first meal, the potentiation pattern is such that it determines an increase in total insulin secretion

TABLE 1
β-Cell function parameters

	Control subjects	Type 2 diabetic subjects
Secretion at 5 mmol/l glucose ($pmol \cdot min^{-1} \cdot m^{-2}$)	136 ± 10	279 ± 24*†
Slope at 5 mmol/l glucose ($pmol \cdot min \cdot {}^{-1}m^{-2}\ mM^{-1}$)	119 ± 30‡	54 ± 15*
Slope ($pmol \cdot min^{-1} \cdot m^{-2} \cdot mM^{-1}$)	148 ± 38‡	53 ± 15
Dynamic control (p_d) ($pmol \cdot m^{-2} \cdot mM^{-1}$)	908 ± 276‡	220 ± 67
Glucose at reference secretion§ (mmol/l)	7.2 ± 0.7‡	11.7 ± 1.1
Potentiation factor max/min ratio‖	7.2 ± 1.5¶	2.6 ± 0.5
Potentiation factor mean time# (h)	5.9 ± 0.2**	7.1 ± 0.2

*Parameter at 10 mmol/l glucose. †Not comparable with control subjects because of the different reference glucose level. ‡$P < 0.05$, control vs diabetic subjects. §Glucose concentration at which the dose-response function predicts an insulin secretion of 300 $pmol \cdot min^{-1} \cdot m^{-2}$. ‖Ratio between the maximum and minimum values of the potentiation factor. ¶$P < 0.005$, control vs diabetic subjects. #Mean time for the potentiation factor (see RESEARCH DESIGN AND METHODS). **$P < 0.01$, control vs. diabetic subjects.

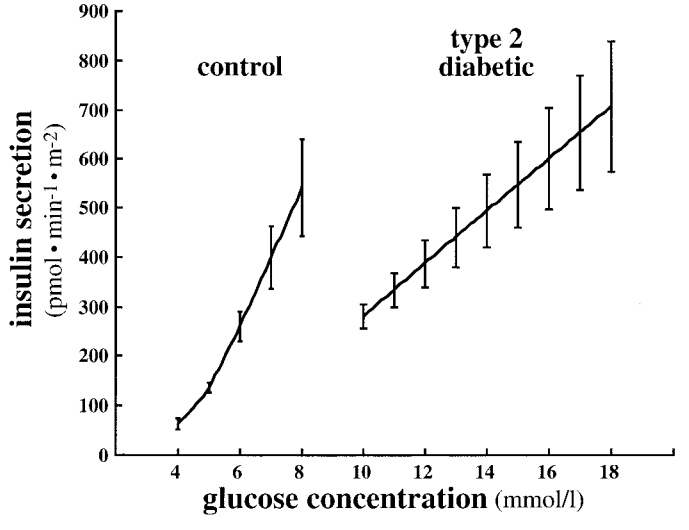

FIG. 4. Dose-response functions in control and type 2 diabetic subjects. Error bars are drawn at 1 mmol/l glucose concentration intervals.

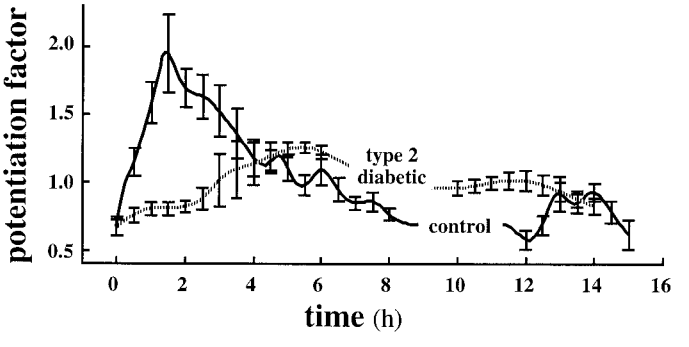

FIG. 5. Potentiation factor in control and type 2 diabetic subjects. Error bars are drawn every 30 min.

when glucose concentration falls compared with the period during which it rises. This phenomenon has also been interpreted as a time delay of insulin secretion with respect to glucose concentration (8,9), following a paradigm proposed by Licko (13). The existence of a delay cannot be excluded. The mathematical representation of the delay used in Breda et al. (8), Toffolo et al. (9), and Licko (13), however, does not appear to be adequate to explain our experimental data, because different delays would be necessary to explain the first and the last insulin secretion peak. Our analysis thus supports the concept that the apparent delay, when observed, is in reality a potentiation phenomenon. This is in accord with classical perfused pancreas experiments [e.g. (1)], which clearly show that during a square-wave glucose stimulation the onset and the offset of insulin secretion (not considering the initial peak) are not symmetrical (as the proposed delay model would predict).

One limitation of our model is that the separation between the contribution of the dose-response function $f(G)$ and the potentiation factor $P(t)$ to total insulin secretion rests on the smoothness constraints imposed on the potentiation factor, because with no constraints on $P(t)$, Eq. 2 has multiple solutions. The logic of this choice is that as much as possible of the insulin secretion changes should be linked with the glucose changes through $f(G)$, leaving it to $P(t)$ to explain the secretion changes that cannot be accounted for by $f(G)$. If the true insulin secretion were a quasi-linear function of glucose concentration like $f(G)$ (i.e., without potentiation), then our approach would yield the correct $f(G)$, and $P(t)$ would equal 1 (because it is for this solution that the regularization terms of Eq. 6 are minimal, i.e., zero). On the other hand, in those cases in which total insulin secretion does not appear to be clearly related to glucose concentration, the estimation of the dose-response function and the potentiation factor are less precise. The present results, however, indicate that both the dose-response function and the potentiation factor are generally well determined. On average, in both subject groups, the quantitatively dominant secretory component is the static component, whereas potentiation accounts for the evident changes in the dose response during the experiment (Fig. 3). The dose-response functions are clearly separated between groups (Fig. 4). In addition, the coefficient of variation of dose response within each group, which includes the variance of the estimation error, is not very different from that calculated in previous studies in which the dose response was directly assessed (14), suggesting that the estimation error has an acceptable variance.

Another limitation of our approach is that the potentiation factor does not include only true potentiation, but also secretory phenomena that may exist but are not explicitly represented in the model, such as circadian rhythms or pulsatility. This makes the physiological interpretation of the potentiation factor more complex.

The obvious advantage of the present analysis for clinical investigation is that it allows calculation of the β-cell dose-response function from a meal test, which is simpler and more physiological than performing complex formats of glucose infusion. Furthermore, it does feature potentiation, which is a well known but not much explored phenomenon.

When the dose-response functions are compared, our analysis confirms that β-cell function is markedly impaired in diabetes. Our results also show, in accord with expectation, that the coefficient of the dynamic insulin secretion component, which is an index of early-phase insulin secretion, is reduced in diabetes.

New findings are those concerning the potentiation factor. We show that potentiation, broadly defined as a change in the relationship between glucose concentration and insulin secretion, plays a differential role in euglycemic and hyperglycemic conditions. In particular, in diabetic subjects, potentiation is markedly blunted, and its onset is much delayed. The sharp potentiation peak observed in control subjects at the first meal is missing in diabetic subjects, and potentiation reaches its maximum only 5–6 h after the first meal. The current data cannot elucidate the mechanisms underlying this difference, as several factors may have affected the β-cell response (e.g., repeated exposure to glucose, entero-insular factors, regulatory hormones, nonglucose secretagogues). Differences in age, physical fitness, BMI, and total caloric intake (but not meal composition, which was the same in the two groups) may also have played some role. However, a blunted and delayed potentiation in type 2 and gestational diabetes has been reported previously (15,16). Our study thus confirms this finding and quantifies it. Furthermore, it shows that this defect is distinct from the other secretory defects, i.e., the rightward shift in the dose-response function and the depressed dynamic component. In patients with diabetes, an impaired first-phase insulin response is reputed to feed forward on the subsequent regulatory response to hyperglycemia. This analysis shows also that the lack of a sufficient potentiation response may contribute substantially to the delayed regulatory response.

In summary, in its current formulation, our model of insulin secretion extracts multiple indexes of β-cell function from a physiological meal test. These indexes are the dose-response function relating insulin secretion to glucose concentration, and a parameter expressing the ability of glucose concentration changes to stimulate insulin secretion. In addition, for multiple meal tests, the model yields the time course of a factor representing potentiation of insulin secretion. Testing the model in normotolerant subjects and diabetic patients appears to retrieve known defects in insulin secretion but also to uncover new facets of β-cell dysfunction.

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APPENDIX A

The dose-response function $f(G)$ is described by the equation

$$f(G) = p_3 G + (p_4 - p_3)\frac{\dfrac{\log(\cosh(p_1(G - p_2))) - \log(\cosh(p_1 p_2))}{p_1} + \tanh(p_1 p_2)G}{1 + \tanh(p_1 p_2)}$$

It can be verified by standard techniques that *1)* $f(0) = 0$ and $f(G) > 0$ for $G > 0$; *2)* p_2 is the glucose level at which the slope of $f(G)$ changes from the initial value p_3 to the final value p_4; *3)* p_1 determines the curvature of the function around the threshold glucose level p_2: if p_1 is high (e.g., 10 for the current glucose levels in mmol/l), the transition from the initial slope p_3 to the final slope p_4 is brisk; if p_1 is low (e.g., 0.1), the transition is gradual. The equation for $f(G)$ is derived assuming that the slope of $f(G)$ is a sigmoid function represented by a hyperbolic tangent, i.e., the slope changes more or less rapidly between near-constant values.

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