A Model for Glucose Control of Insulin Secretion During 24 h of Free Living

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The aim of this work was to develop a mathematical model describing the functional dependence of insulin secretion on plasma glucose concentrations during 24 h of free living. We obtained hourly central venous blood samples from a group of healthy volunteers who spent 24 h in a calorimetric chamber, where they consumed standardized meals. Insulin secretory rates were reconstructed from plasma C-peptide concentrations by deconvolution. The relationship between insulin release and plasma glucose concentrations was modeled as the sum of three components: a static component (describing the dependence on plasma glucose concentration itself, with an embedded circadian oscillation), a dynamic component (modeling the dependence on glucose rate of change), and a residual component (including the fraction of insulin secretion not explained by glucose levels). The model fit of the individual 24-h secretion profiles was satisfactory (within the assigned experimental error of glucose and C-peptide concentrations). The static component yielded a dose-response function in which insulin release increased quasi-linearly (from 40 to 400 pmol/min on average) over the range of 4–9 mmol/l glucose. The dynamic component was significantly different from zero in coincidence with meal-related glucose excursions. The circadian oscillation and the residual component accounted for the day/night difference in the ability of glucose to stimulate insulin release. Over 24 h, total insulin release averaged 257 ± 58 nmol (or 43 ± 10 U). The static and dynamic component together accounted for ~80% of total insulin release. The model proposed here provides a detailed robust description of glucose-related insulin release during free-living conditions. In nondiabetic subjects, non–glucose-dependent insulin release is a small fraction of total insulin secretion. Diabetes 50 (Suppl. 1):S164–S168, 2001

Quantiﬁting insulin secretion is an important step in the study of disordered carbohydrate metabolism. A well-established approach is based on measurement of plasma C-peptide concentrations. C-peptide is secreted in equimolar amounts with insulin; both are transported to the liver, from which insulin is removed to a substantial (~50%) extent, whereas hepatic extraction of C-peptide is negligible. Thus, the systemic (venous) appearance of C-peptide equals insulin secretion. Because C-peptide kinetics are linear, systemic C-peptide appearance can be calculated by deconvolution from the measurement of plasma C-peptide concentrations and from a C-peptide kinetic model (1). The calculated systemic C-peptide appearance equals insulin secretion. Among other applications, this method has been successfully used to evaluate the 24-h profiles of insulin secretion in healthy subjects and obese patients (2).

The β-cell dose-response function, i.e., the relationship between glucose concentration and insulin secretion, has been derived exclusively from experiments using impulsive (3) or graded intravenous glucose infusions (4) over periods of a few hours. Under conditions of free living, the ingestion of mixed meals—with their contents of insulin secretagogues other than glucose (mostly amino acids [5]), the release of gastrointestinal peptides that potentiate glucose-induced insulin release (e.g., gastric inhibitory polypeptide [6]), and the accompanying neural activation (7)—give reason to expect that the β-cell glucose dose-response function should be different from that reconstructed from intravenous glucose administration. This, however, has not been determined. We therefore measured the 24-h profile of insulin secretion and developed a model to relate it to the concomitantly measured glucose concentrations. We report here the results obtained in a group of healthy subjects.

RESEARCH DESIGN AND METHODS

Experimental design. Seven healthy volunteers (four women, three men, age 35 ± 4 years [range 23–56], BMI 26 ± 0.4 kg/m² [25–28]) agreed to spend 24 h in a calorimetric chamber. During this period, four meals were administered for a total caloric intake of 30 kcal/kg of lean body mass (20% breakfast, 40% lunch, 10% afternoon snack, and 30% dinner). Diet composition was 17% protein, 35% fat, and 48% carbohydrate. In the afternoon, a 40-min session of bicycle exercise was performed at 40% of the individual maximal aerobic capacity. Hourly blood samples were drawn from a central venous catheter derived outside the chamber through long plastic tubing for the measurement of glucose, insulin, and C-peptide concentrations. The protocol was reviewed and approved by the Institutional Ethics Committee of the Catholic University of Rome.

Modeling. The model used is schematized in Fig. 1. The model 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 following differential equation:

\[
\frac{dG}{dt} = -kG(t) + R(t)
\]

where \(G(t)\) (expressed in millimoles per liter) is glucose concentration, \(k = 0.012 \text{ min}^{-1}\) is an assigned constant, and \(R(t)\) is a function of time, represented in discrete form as a piece-wise linear function over 20-min intervals. Equation 1 yields a glucose concentration profile continuous in time and its derivative is positive and is zero otherwise:

\[
q(t) = p_2 \sin(t + p_3)
\]

where \(G\) (in millimoles per liter) is the glucose concentration, \(t\) is time (in hours), and \(p_1, p_2, p_3\) are parameters. The term \(q(t)\) represents the circadian modulation. When the modulating term \(q(t)\) is zero, the dose-response function (Eq. 2a) is a curvilinear convex function. The parameter \(p_1\) represents the intercept for \(G = 0\), \(p_2\) is the slope of the curve for high \(G\) values, and \(p_3\) determines the curvature (i.e., for high [with respect to 1] values of \(p_3\), the dose-response function is quasi-linear), whereas for low values of \(p_3\), the dose-response curve exhibits a pronounced convexity. The parameters \(p_1\) and \(p_3\) are the amplitude and phase \(0 \leq p_1 < 2\pi\) of the circadian oscillation, respectively.

The second insulin secretion component \([S(t)]\) expresses a static relationship between insulin secretion and glucose concentrations, i.e., it embodies a \(β\)-cell dose-response function, assumed to be modulated by a circadian rhythm, represented by means of a sinusoidal function with a 24-h period:

\[
S(t) = p_1 \ln(1 + p_2 e^{G(t)}) - \ln(1 + p_2) + p_4 + q(t)
\]

where \(p_1, p_2, p_3, p_4\) are parameters. The term \(q(t)\) is the convolution between the individualized two-exponential function with zero mean. Because \(S(t)\) may take on both positive and negative values, it represents an additive correction term rather than a real secretion component.

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

\[
S(t) = S_1(t) + S_2(t) + S_3(t) = \sum_{i=1}^{3} S_i(t)
\]

The model for \(C\)-peptide kinetics is the two-exponential model proposed by Van Cauter et al. (8), in which model parameters are determined in each individual on the basis of the subject’s sex, weight, height, and age. \(C\)-peptide concentration \([C(t)]\) is the convolution between the individualized two-exponential \(C\)-peptide impulse response \(h(t)\) and \(C\)-peptide secretion given in Eq. 4:

\[
C(t) = h(t) \ast S(t)
\]

where \(\ast\) 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 Eq. 5). The model predicts glucose and \(C\)-peptide concentration once the parameters \(p_1, p_2, p_3, R(t)\), and \(S(t)\) (Eq. 1) and \(S(t)\) (Eq. 4) are known. Conversely, \(p_1, p_2, R(t)\), and \(S(t)\) 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 \(S(t)\), as done in deconvolution schemes. The regularization method used adds penalty terms for \(R(t)\) and \(S(t)\) to the standard sum of squares term, which eliminates the spurious oscillations that \(R(t)\) and \(S(t)\) would otherwise exhibit. The function that the least-squares algorithm actually minimizes is as follows:

\[
\sum w_1[G(t) - \overline{G(t)}]^2 + \sum w_2[C(t) - \overline{C(t)}]^2 + w_3 \sum [R(t)]^2 + w_4 \sum [S(t)]^2
\]

Figure 2 shows the observed daily profile of plasma glucose and \(C\)-peptide concentrations. It can be appreciated that the model fit is satisfactory. The model residuals, i.e., the differences between the measured and the model-predicted glucose and \(C\)-peptide concentrations, were not systematically different from zero at most of the time points. Small deviations...
from zero (0.1 mmol/l) were observed only for the largest glucose concentration swings.

Table 1 reports the parameters characterizing \(S_5\)-cell function in each study subject. The slope of the dose-response function \(S_5\) varied less than threefold and was correlated with the parameter of the derivative component \(p_6\) \((r = 0.86, P < 0.02)\). The amplitude of the circadian component \(p_4\) was correlated with the amplitude of the residual insulin secretion component \(SDr\) \((r = 0.81, P < 0.05)\).

Figure 3 shows the mean values of insulin secretion and its components throughout 24 h. The static component (Eq. 2), which also includes the circadian modulation, is the most important component. In fact, in an integral sense, the absolute value of the difference between total insulin secretion and the static component (the two lines shown in the top panel of Fig. 3) is <30% of total insulin secretion. The dynamic component accounts for ~9% of total insulin secretion. The values of the 24-h integral of total insulin secretion are given in Table 1: the group average was 257 nmol (43 U) with a less than twofold range.

Figure 4 shows the \(\beta\)-cell dose-response function in a typical subject (subject number 3). The dose-response function is plotted for a zero value of the circadian modulation. The circles depict the residual insulin secretion component \(S_r(t)\), which is the vertical distance between the circles and dose-response line. The figure shows that the dose-response function is reasonably well identified despite uncertainty due to the residual insulin secretion component. The mean \(\beta\)-cell dose-response function is shown in Fig. 5.

DISCUSSION

The C-peptide deconvolution method was developed more than a decade ago to measure 24-h profiles of insulin secretion (2). Separate experiments have been necessary to explore the dependence of insulin secretion on plasma glucose concentrations (4). In this article, we have combined the C-peptide deconvolution methodology with a formal description of glucose control of insulin secretion. The obvious advantage of this approach is that the 24-h secretion profile and its functional relation to glucose concentration are determined in the same experiment.

Our model of insulin secretion is based on well-established concepts of \(\beta\)-cell function as well as experimental observations. Because of the complexity of the mechanisms governing \(\beta\)-cell function and the limitations imposed by experimental data, the model contains some simplifications. One assumption is that insulin secretion depends on plasma glucose concentration alone. Insulin secretion is known to respond also to secretagogues other than glucose, such as amino acids and free fatty acids (5). However, in the setting of free-living conditions, these secretagogues are expected to change in quasi-synchrony with the changes in glucose concentration, making differentiation of the effects difficult. Thus, the influence of other substrates is likely to be embed-

![FIG. 2. Mean (± SE) plasma glucose (A) and C-peptide (B) concentrations over 24 h. The symbols represent the data, and the solid line represents the model fit.](image-url)

<table>
<thead>
<tr>
<th>Subject</th>
<th>(S_5) (pmol/min)</th>
<th>(\Delta S_5) (pmol \cdot min(^{-1}).mmol(^{-1}))</th>
<th>(p_2) (pmol/min)</th>
<th>(p_4) (pmol \cdot min(^{-1}).mmol(^{-1}))</th>
<th>(p_6) (pmol \cdot mmol(^{-1}).h)</th>
<th>(SDr) (pmol/min)</th>
<th>TIS [nmol (U)]</th>
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<tr>
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<td>0.072</td>
<td>64</td>
<td>18:32</td>
<td>2,481</td>
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</tr>
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</table>

The SD for \(T_{max}\) is in hours. \(\Delta S_p\), slope of the dose-response function at 5 mmol/l glucose concentration; \(p_2\), parameter quantifying the curvature of the dose-response function (higher curvature = lower \(p_2\) value); \(p_4\), amplitude of the circadian modulation; \(p_6\), parameter of the dynamic component; \(S_5\), insulin secretion at 5 mmol/l glucose concentration; \(SDr\), standard deviation of the residual insulin secretion component; \(T_{max}\), time of the day for maximum amplitude of the circadian modulation; TIS, 24-h integral of total insulin secretion.
ded in the relationship between glucose concentration and insulin secretion, although our results indicate that such influence is probably small (see below).

The static relationship between glucose concentration and insulin secretion we adopted (the dose-response function, Eq. 2a) is a mathematical function that can be linear or curvilinear depending on the parameters. The choice of a linear dose-response function is supported by the studies of Byrne et al. (4) in which graded glucose infusions were used to stimulate insulin secretion. Hovorka et al. (9) used a threshold-linear function in their meal test. In our study, a quasi-linear function was appropriate in most cases (Fig. 5), but in some subjects, a curvilinear function was necessary to fit the dose-response relationship, particularly at low glucose concentrations. The dose-response function obtained in our group of subjects (Fig. 5) was very similar to that obtained by Byrne et al. (4) in overnight fasted subjects receiving graded intravenous glucose infusions. Thus, insulin secretion increased tenfold quasi-linearly between 4 and 9 mmol/l glucose. This finding was somewhat unexpected considering the strong potentiation of insulin release provided by gastrointestinal factors. It is possible that oral glucose-induced enhancement of insulin release 1 manifests itself as a derivative control (i.e., the dynamic component of insulin secretion formalized in our model), 2 is hidden in an apparently circadian modulation, or 3 is a transient phenomenon (more evident on a scale of minutes than hours). Only paired experiments, in which the oral glucose–induced glucose profile is mimicked by precise intravenous glucose infusions, can clarify whether and how gastrointestinal factors alter the glucose-insulin dose-response function over a 24-h period. Nevertheless, the current results do suggest that oral administration of glucose does not result in a major increase in β-cell response to glucose per se in comparison with intravenous glucose.

The dynamic dependence of insulin secretion on the rate of change of glucose concentration has been established in tests in which glucose concentration was abruptly increased (3,10). During an oral glucose or mixed meal test, this secretory component is definitely less evident because the changes in glucose concentration are slower. In the meal test model by Hovorka et al. (9), this component was not featured. Our model includes the dynamic component \( S_d(t) \).

Although its contribution to total insulin secretion is small (Fig. 3), we found that the coefficient expressing the dependence of insulin secretion on the derivative of glucose concentration \( p_6 \) is correlated with the slope of the dose-response function \( S_5 \), suggesting that a dynamic component reflecting the sensitivity of the β-cell to glucose concentration changes is indeed present.

The addition of a circadian modulation of insulin secretion \( q(t), Eq. 2b \) was essential to predict C-peptide concentrations adequately. Without \( q(t) \), insulin secretion would have been significantly overestimated during the night compared with the diurnal period. The modulation was described as a vertical time-dependent shift of the dose-response function during the 24 h, following a sinusoidal pattern. Indeed, this variation is not necessarily a true circadian rhythm but can reflect other phenomena, e.g., daytime potentiation of insulin secretion due to exposure to meal-related hyperglycemia. Such a potentiation is in fact well documented in some experimental conditions (10). Circadian rhythms in insulin secretion have also been reported (11,12), but differences in the experimental protocols make direct comparison with the present findings difficult.

The functional mechanisms of insulin secretion discussed above were still not sufficient to explain the observed variations...
MODELING GLUCOSE CONTROL OF INSULIN SECRETION

FIG. 5. Mean (± SE) β-cell glucose dose-response function of the whole group. Error bars are shown at selected plasma glucose concentrations.

in C-peptide concentration. For this reason, we included a residual secretion component [S_r(t)], with which C-peptide concentration could be predicted within the expected measurement error. S_r(t) was not constrained to a specific functional form but was allowed to take on an arbitrary smooth zero-mean time course. The residual component was quite variable from subject to subject. On average, S_r(t) was most significant between 1400 and 2200, whereas during the remaining period of time, its value was small. The peaks observed at 1530 and 2130, i.e., in concomitance with lunch and dinner, may reflect potentiation of the insulin response by previous exposure to hyperglycemia (10), whereas the negative values between these two peaks might be due to an inhibitory effect of the exercise bout that was performed by all subjects at 1730 (13). The existence of a potentiation phenomenon underlying both these variations in insulin secretion and the 24-h oscillation may explain the observed correlation between the amplitude of the oscillation and the SD of the residual component.

The residual secretion component adds some uncertainty to the determination of the dose-response function and the dynamic secretory component. Figure 4, which represents an average case and where the scatter around the dose-response function is due to the residual component, shows that despite S_r(t), the dose-response function is identified with sufficient accuracy. As for the dynamic secretion component S_d(t), it should be noted that the actual response to glucose concentration changes is different from that predicted by the dynamic component alone because total secretion is the sum of the static component and both S_d(t) and S_r(t). For instance, the peak of the dynamic response predicted at 1700 (Fig. 3) is virtually abolished by the negative peak of S_r(t). However, even when S_d(t) and S_r(t) are considered together, an increase in secretion corresponding to the time periods during which the derivative of glucose concentration is positive is observed (except at 1700). This indicates that the incorporation of a dynamic secretion component in the model is appropriate. Furthermore, the correlation observed between the parameter of the dynamic component (g_p, Eq. 3) and the slope of the dose-response function (∆S_r) suggests that both reflect an aspect of β-cell function. With regard to total insulin secretion, our approach is very similar to that used by Polonsky et al. (2), with the only differences being that our sampling schedule was less frequent and that C-peptide kinetics were not determined from individual bolus injections but from anthropometric data according to a validated approach (8,14). In this respect, our results essentially reproduce the previous findings (2).

In summary, the model for glucose control of insulin secretion we present in this work yields an accurate profile of insulin secretion, the dose-response function for glucose-induced insulin secretion, and additional fine-tuning parameters of β-cell function. Phenomena such as non-glucose-dependent insulin release, potentiation, and memory, which have been predicted on the basis of short-term experiments using intravenous glucose, have proven difficult to model when dealing with 24-h free-living conditions; however, they are likely to be embedded in the features of the model. Whereas the main quantitative results in our healthy volunteers are fully consistent with the available literature, only the application of the model to different pathophysiological conditions can test its ability to provide new insight into the mechanisms of insulin release.

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REFERENCES