Interaction Between Glucose Metabolism and Endogenous Insulin Release in Hypertension

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The minimal model approach was applied to examine the dynamic interaction between glucose metabolism and endogenous insulin release during an intravenous glucose tolerance test (IVGTT) in a group of hypertensive patients (H group) compared with a group of normotensive subjects (N group). A modified version of the classical minimal model of C-peptide kinetics and secretion was used to evaluate the total amount of insulin secretion per unit of distribution volume (TIS) together with 3 indexes of β-cell function (the basal, ϕ_b, first, ϕ_1, and second phase, ϕ_2, β-cell sensitivity to glucose). These indexes were associated with estimates of glucose effectiveness (S_G) and insulin sensitivity (S_I) provided by the classical minimal model of glucose kinetics. No significant differences were found in ϕ_b, ϕ_1, and ϕ_2 estimates between the H group and the N group. In the H group, the average TIS was 54% higher ($P < .05$) than in the N group, while S_G and S_I estimates showed a 44% decrease ($P < .05$) and a 51% decrease ($P < .05$), respectively. These results suggest that hyperglycemia observed in our H group during IVGTT is a compensatory response to insulin resistance (low S_I) and to the reduced ability of glucose to promote its own metabolism (low S_G). This hyperglycemic state causes a larger than normal stimulation of β cell, which explains insulin hypersecretion (higher TIS) even in the presence of normal β-cell sensitivity values of ϕ_b, ϕ_1, and ϕ_2.

HYPERINSULINEMIA AND GLUCOSE intolerance are metabolic diseases commonly observed in patients with essential hypertension.[1-4] The understanding of the etiology of these metabolic aberrations requires a quantitative evaluation of the major determinants of glucose disposal in the normal and hypertensive state. To this aim, a fair amount of studies, including our own,[3,5-12] have been performed to estimate indexes that quantify the ability of insulin to promote glucose disposal (insulin sensitivity [S_I]) and the ability of glucose to promote its own metabolism (glucose effectiveness [S_G]). To complement the quantitative picture provided by the indexes of S_I and S_G, it is important to estimate indexes that characterize the β-cell function by aid of an appropriate model.

Time course of prehepatic insulin secretion rate and indexes of glucose control on insulin secretion can be derived, in clinical studies, from the C-peptide minimal model technique applied to plasma C-peptide levels measured during an intravenous glucose tolerance test (IVGTT).[13-15] Kautzky-Willer et al[8] reported an application of this method to hypertensive patients and concluded that an elevated insulin secretion is a specific characteristic of hypertension. This conclusion, however, was inferred from the use of the classical minimal model of C-peptide kinetics and secretion,[13] the reliability of which was recently questioned by Toffolo et al.[14] Their test of the classical C-peptide minimal model in a group of normal subjects showed that the kinetic parameter estimates were consistently biased versus the true individual values, determined from a separate experiment. Moreover systematic errors were present in the prediction of C-peptide data when kinetic parameters were fixed to the true individual values. In contrast to the classical minimal model of C-peptide kinetics and secretion, a new 2-compartment minimal model of C-peptide kinetics and secretion was shown to be more reliable. Based on these previous reports, the aim of the present study was (1) to apply this new 2-compartment minimal model to estimate indexes of β-cell function in a group of hypertensive patients (H group) versus a group of normal subjects (N group), (2) to apply, to the same subjects, a minimal model of glucose kinetics,[16] which allows estimation of S_I and S_G, and, eventually, (3) to associate the indexes provided by these 2 different models to characterize the dynamic interaction between endogenous insulin release and glucose metabolism in hypertension.

MATERIALS AND METHODS

Subjects

Six normotensive subjects (N group) and 7 hypertensive patients (H group) were studied. All of them were volunteers and gave informed consent to the procedures, which were approved by the Ethics Committee of the Istituto Nazionale Riposo e Cura Anziani (INRCA), Ancona, Italy. Normotensive subjects had a seated diastolic blood pressure (DBP) of $\leq$ 85 mm Hg and a seated systolic blood pressure (SBP) of $\leq$ 130 mm Hg. On average ($\pm$ SE), SBP was 117 $\pm$ 4 mm Hg and DBP was 75.8 $\pm$ 2.7 mm Hg. The hypertensive patients were recruited among the outpatients of the Metabolic Disease and Diabetes Unit of INRCA, who were under antihypertensive drug therapy with calcium channel blockers or angiotensin-converting enzyme (ACE) inhibitors for more than 2 years. Before antihypertensive drug therapy, SBP and DBP were, on average, 152 $\pm$ 3 and 97.8 $\pm$ 3.2 mm Hg, respectively. In accordance with previous reports,[8,9,17,18] the antihypertensive drug therapy is not supposed to affect the metabolic syndromes of insulin resistance.

These populations were screened before participation with a history and physical examination, a complete blood count, fasting serum glucose, and routine chemistries. Subjects were excluded from participation if they had a past history of diabetes mellitus, had a fasting serum glucose greater than 120 mg $\cdot$ dL^{-1} and/or had evidence from the screening tests of underlying illness or significant laboratory abnormalities.

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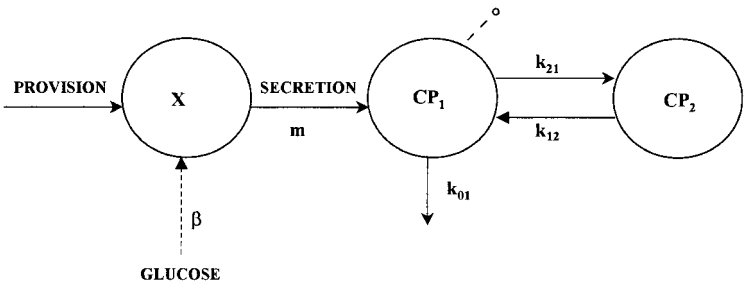

Fig 1. Minimal model of C-peptide kinetics and production proposed by Toffolo et al.[14] CP_1 and CP_2 are the C-peptide concentrations in the accessible and peripheral compartments, respectively; X, is the C-peptide level in the β cell; k_{01}, k_{21}, and k_{12} are kinetic parameters; m and β are the secretory parameters.

All the subjects were European. On average (± SE) the N group (3 women and 3 men) and the H group (1 woman and 6 men) were, respectively, 42 ± 7 and 61 ± 2 years old. Clinical data of interest for the characterization of the metabolic picture in the 2 groups are presented in Table 1.

IVGTT

In both the N group and H group, a standard IVGTT was performed at the Metabolic Disease and Diabetes Unit of the INRCA Institute of Ancona. Starting time was 8:30 AM after an 8-hour overnight fast. A needle was inserted into an antecubital vein of the patient. The patency of the needle was maintained with a controlled saline infusion throughout the study. At time 0, glucose (300 mg · kg^{-1}) was injected over 1 minute into a contralateral antecubital vein. Three basal blood samples (2 mL) were obtained at -15 and -5 minutes and immediately before the injection. Twenty-four additional blood samples were collected at 2, 3, 4, 5, 6, 8, 10, 12, 15, 20, 25, 30, 35, 40, 60, 80, 100, 120, 140, 160, 180, 210, 240, and 300 minutes. Blood was promptly centrifuged and glucose immediately measured by the glucose oxidase method with an automated glucose analyzer. The remaining plasma was stored at -20°C for later insulin and C-peptide determination. Insulin was measured by commercially available radioimmunoassays (Biodata S.p.A, Guidonia Montecelio, Rome, Italy). The sensitivity and intra- and interassay precision of the insulin were 1 μU · mL^{-1}, (5.4% ± 1.0%) and (5.5% ± 1.2%), respectively. The cross reactivity for human proinsulin was 14%. C-peptide was measured by commercially available radioimmunoassays (Biochem Iimmunosystems Italia S.p.A, Milano, Italy). The sensitivity and intra- and interassay precision of the C-peptide were 0.025 pmol · mL^{-1}, (5.8% ± 2.4%) and (5.7% ± 0.8%), respectively.

Data Analysis

Data of plasma glucose and C-peptide concentrations from the IVGTT were used to estimate the parameters of a modified version of the classical minimal model of C-peptide kinetics and secretion recently proposed by Toffolo et al.[14] Its schematic representation is shown in Fig 1. Together with the time course of insulin secretion per unit of distribution volume (SR), this model provides 3 characteristic indexes of β-cell function: the basal (ϕ_b), first (ϕ_1), and second phase sensitivity to glucose (ϕ_2). The index of basal sensitivity to glucose quantifies the ability of the β cell to secrete insulin during the steady state condition. The indexes of first and second phase sensitivity to glucose quantify the ability of the β cell to secrete insulin during the first and the second dynamic phases observed after a glucose load. These indexes are presented in detail in Appendix 1 together with the equations of the model and the concepts incorporated in the scheme of Fig 1.

The temporal dynamics of plasma glucose and insulin concentrations observed during the IVGTT were submitted to the classical minimal model of glucose kinetics,[16] displayed in Fig 2 to estimate characteristic indexes of glucose metabolism: the S_G index and the S_I index. The S_G quantifies the ability of glucose per se to enhance its own disappearance and to inhibit hepatic glucose production independent of any dynamic change on insulin. The S_I index measures the ability of insulin to enhance plasma glucose disappearance and to inhibit hepatic glucose production. These indexes are presented in detail in Appendix 2 together with the equations of the model and the concepts incorporated in the scheme of Fig 2.

Parameter Estimation Procedures

The numerical identification of the C-peptide minimal model of Fig 1 requires knowledge of C-peptide kinetic parameters k_{21}, k_{12}, k_{01} for each subject. However, Toffolo et al[14] demonstrated that there is no loss of accuracy in the estimated secretion parameters when standard values of C-peptide kinetic parameters are used instead of individual values. In accordance with this finding, the kinetics parameters, k_{21}, k_{12}, k_0, were fixed to standard values computed following the method of Van Cauter et al.[15] The unknown secretory parameters, m, α, β, h, and the initial condition, X_0, were estimated using a weighted nonlinear least-squares estimation technique implemented by the SAAM II software (SAAM Institute, University of Washington, Seattle, WA[19]). Weights were optimally chosen, ie, equal to the inverse of the variance of the glucose measurement errors.[20] The errors associated with total C-peptide measurement were assumed to be normally distributed random variables with 0 mean and a constant percent coefficient of variation equal to 6%. When the decay of the second phase insulin secretion rate is very fast ($1/\alpha$ very small), parameter α is usually estimated with poor precision. In the circumstances where $1/\alpha$ was negligible, a simplified version of the C-peptide model described was adopted (see Appendix 2).

The parameters of the classical minimal model of glucose kinetics

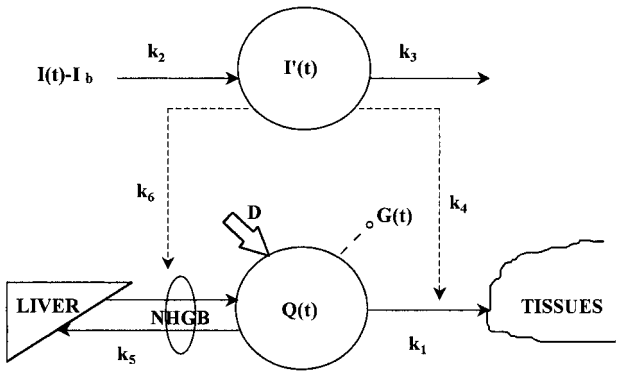

Fig 2. The minimal model of glucose kinetics.[16] NHGB is the net hepatic glucose balance; D, represents the glucose dose (300 mg/kg); k_i, i=1,. . .,6 are rate constants characterizing material fluxes (solid lines) or control actions (dashed lines). G(t) and I(t) are glucose and plasma insulin concentrations at time t. I'(t) is insulin concentration at time t in a compartment remote from plasma.

were estimated, together with a measure of their precision, using the same estimation technique described above for the identification of the C-peptide minimal model. The errors associated with total glucose measurement were assumed to be normally distributed random variables with 0 mean and a constant percent coefficient of variation equal to 1.5%. Glucose samples between 2 and 5 minutes were not considered to improve the approximation of glucose kinetics by single-compartment description.

Goodness of Data Fit

The goodness of data fit resulting from the parameter estimation process was evaluated by examining the weighted residuals, which are the differences between the data and the model-predicted values, divided by the SD of the data. Because the data are small in number, empirical visual methods were adopted, for instance, the weighted residuals were plotted against time to detect possible inconsistencies between experimental data and predicted model response.[20]

Statistical Analysis

Statistical comparison of hypertensive patients and normotensive control subjects was tested for significance by 2-tailed nonpaired Student's t test. Not significant (NS) means a value of $P \geq .05$. All data and results are given as mean ± SE.

RESULTS

Clinical data of interest for the characterization of the metabolic picture in the 2 groups are presented in Table 1. No significant differences between the 2 groups were observed in body mass index (BMI) and fasting plasma cholesterol, triglycerides, insulin, and glucose concentrations. The H group showed a 65% increase in average fasting plasma C-peptide that was statistically significant ($P < .05$). Throughout the entire IVGTT, we observed higher average glucose, insulin, and C-peptide levels in the H group compared with the N group (Fig 3).

Estimates of S_G, S_I, and β-cell sensitivity to glucose of basal (ϕ_b), first (ϕ_1), and second phase (ϕ_2) are reported, together with their precision, in Table 2 for the N group and in Table 3 for the H group. On average, the H group featured significantly ($P < .05$) reduced S_G and S_I estimates compared with the N group, whereas no significant differences were found in ϕ_1, ϕ_2, and ϕ_b estimates between the 2 groups.

In each subject, the total amounts of insulin secreted by the β cell per unit of distribution volume (TIS) was computed as the integral from 0 to 300 minutes of the time course of prehepatic insulin secretion, SR, provided by the C-peptide minimal model (Fig 4, equation 5). Average (± SE) TIS was 15.5 ± 2.9 pmol · L^{-1} in 300 minutes in the N group and 23.8 ± 2.4 pmol · L^{-1} in 300 minutes in the H group, $P < .05$. The time courses of SR averaged over the N group and over the H group are displayed in Fig 4.

To assess the goodness of glucose data fit, we analyzed weighted residuals. Figure 5 shows that the average weighted residuals have a satisfactory behavior consistent with the hypothesis that the measurement error was a random variable normally distributed, around 0.

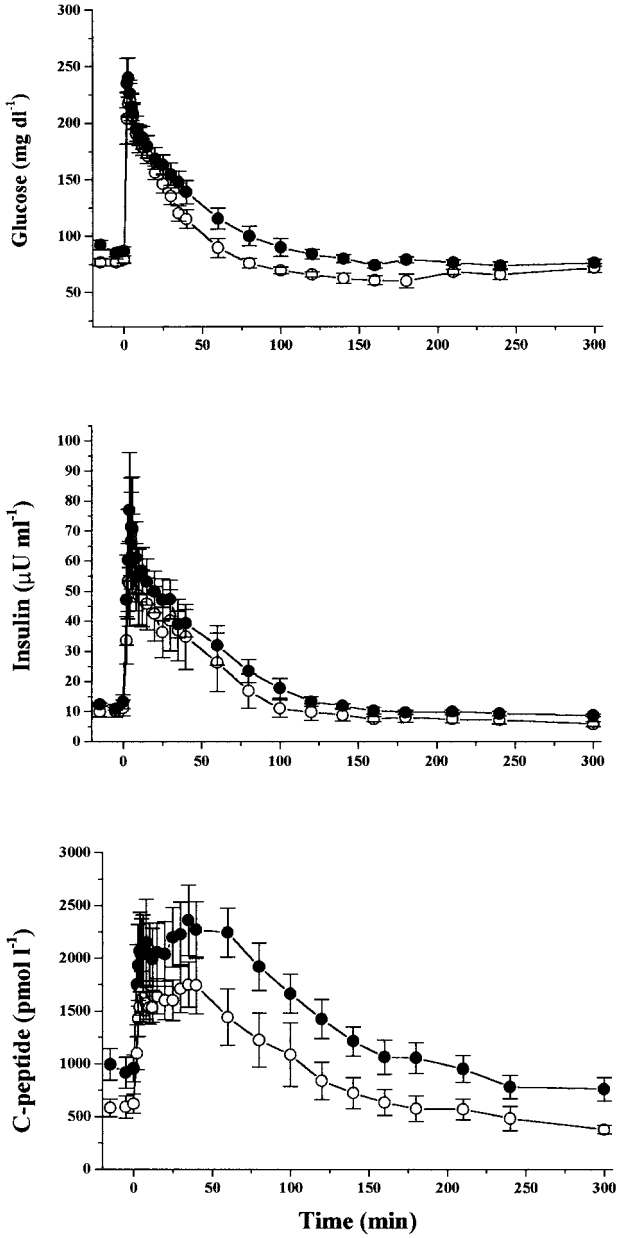

Fig 3. Plasma glucose (A), insulin (B), and C-peptide (C) concentrations during IVGTT in the H group (●) and the N group (○). Values are expressed as means ± SE.

Table 1. Metabolic Picture of the Hypertensive Patients and Normotensive Control Subjects

Variable	H Group (n = 7)	N Group (n = 6)	P
BMI (kg/m^2)	27.0 ± 2.2	26.2 ± 0.8	NS
Triglycerides (mg/dL)	124 ± 22	138 ± 53	NS
Cholesterol (mg/dL)	183 ± 10	189 ± 24	NS
Glucose (mg/dL)	88.4 ± 3.8	79.2 ± 3.2	NS
Insulin (μU/mL)	12.0 ± 0.9	11.5 ± 2.5	NS
C-peptide (pmol/L)	1,022 ± 138	619 ± 90	$P < .05$

NOTE. Values are mean ± SE over n cases. BMI defined as the ratio between body weight and the square of height. NS, not significantly different ($P > .05$).

Table 2. Estimates of Glucose Metabolism Indexes and β-Cell Sensitivity Indexes From Normotensive Control Subjects

Subject no.	S_G (10^2 min^{-1})	S_I (10^4 $min^{-1}/[\mu U\ mL]$)	ϕ_1 (10^9)	ϕ_2 (10^9 min^{-1})	ϕ_b (10^9 min^{-1})
1	2.55 (14)	8.34 (17)	136 (6)	20.1 (4)	5.46 (8)
2	1.32 (26)	3.88 (11)	314 (20)	18.1 (14)	7.16 (8)
3	2.60 (10)	2.95 (11)	174 (17)	22.9 (5)	7.08 (8)
4	1.55 (13)	4.68 (5)	262 (5)	14.7 (6)	4.34 (8)
5	1.42 (5)	4.03 (9)	82.7 (10)	25.9 (5)	17.4 (8)
6	2.85 (7)	2.42 (7)	298 (6)	11.2 (8)	5.19 (8)
Mean ± SE	2.05 ± 0.28	4.38 ± 0.85	211 ± 38	18.8 ± 2.2	7.8 ± 1.9

NOTE. The percent coefficient of variation, in parentheses, gives a measure of the precision of the parameter estimate. The parameters S_G, S_I, ϕ_1, ϕ_2, and ϕ_b are defined in text.

Table 3. Estimates of Glucose Metabolism Indexes and β-Cell Sensitivity Indexes From Hypertensive Subjects

Subject no.	S_G (10^2 min^{-1})	S_I (10^4 $min^{-1}/[\mu U\ mL]$)	ϕ_1 (10^9)	ϕ_2 (10^9 min^{-1})	ϕ_b (10^9 min^{-1})
1	1.07 (7)	2.00 (9)	316 (45)	11.3 (13)	12.7 (8)
2	1.08 (61)	1.77 (53)	177 (16)	24.2 (6)	8.56 (8)
3	1.38 (27)	3.51 (4)	385 (17)	26.3 (11)	11.9 (8)
4	1.20 (11)	1.00 (16)	74.5 (9)	19.1 (4)	7.95 (8)
5	0.50 (32)	2.90 (5)	268 (6)	38.7 (5)	20.7 (8)
6	0.78 (32)	1.24 (13)	266 (7)	30.4 (5)	13.2 (8)
7	1.97 (14)	2.35 (6)	350 (8)	23.7 (5)	5.19 (8)
Mean ± SE	1.14 ± 0.17	2.11 ± 0.34	262 ± 40	24.8 ± 3.2	11.4 ± 1.9

NOTE. The percent coefficient of variation, in parentheses, gives a measure of the precision of the parameter estimate. The parameters S_G, S_I, ϕ_1, ϕ_2, and ϕ_b are defined in text.

DISCUSSION

Hyperinsulinemia as a primary cause for or compensatory response to insulin resistance has been suggested to elevate blood pressure through several actions, including activation of the sympathetic nervous system[21] and a direct effect on the kidney, causing sodium retention.[22] Thus, a further insight into insulin metabolism in hypertension is of great interest. Various approaches are available to measure the time course of insulin secretion. However, only the minimal model method provides functional indexes of glucose control on insulin secretion, namely, indexes of basal, ϕ_b, first, ϕ_1, and second phase, ϕ_2, β-cell sensitivity to glucose.[23] Association of these indexes with those characterizing glucose disposal (eg, S_I and S_G) is important to clarify the etiology of glucose intolerance in hypertension. The reliability of the minimal model method, however, depends on the accuracy of the insulin secretion description built into the minimal model. A reliable description of insulin secretion in normal humans has been recently accomplished by Toffolo et al[14] making use of a modified version of the classical C-peptide minimal model. The application of this new model for quantitative evaluation of β-cell function in essential hypertension is the novelty of the present study.

Observation of no significant differences in ϕ_b, ϕ_1, and ϕ_2 indexes between the H group and the N group suggests that high blood pressure does not affect the β-cell sensitivity to glucose during both the steady state and dynamic conditions. According to the TIS index, however, the total amount of insulin, per unit of volume, secreted during the IVGTT in the H group was 54% higher ($P < .05$) than the corresponding amount secreted in the N group. Explanation of this metabolic abnormality requires the analysis of simultaneous estimates of S_I and S_G indexes. In our H group, the estimates of S_I and S_G were 51% lower ($P < .05$) and 44% lower ($P < .05$), respectively, when compared with the corresponding estimates from the N group. Lower S_I and S_G values indicate, respectively, the presence of an overt insulin resistance and a reduced ability of glucose to promote its own metabolism in the H group that caused a postload hyperglycemia (Fig 3A). These abnormalities are commonly observed in essential hypertension.[1-11]

Some discrepancy in age and gender distribution between

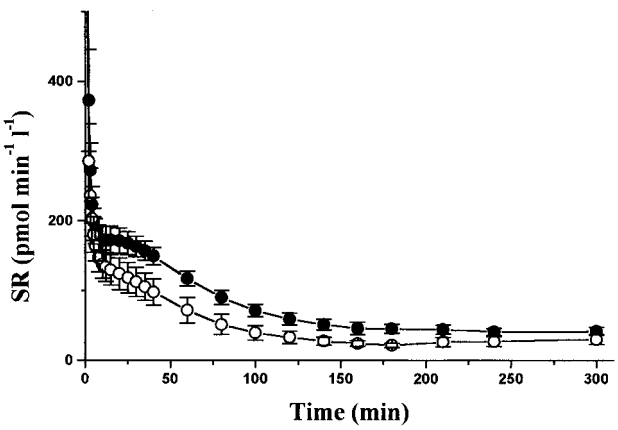

Fig 4. Average (± SE) time courses of β-cell insulin release per unit of distribution volume (SR) as predicted by the minimal model of C-peptide kinetics for the N group (○) and the H group (●).

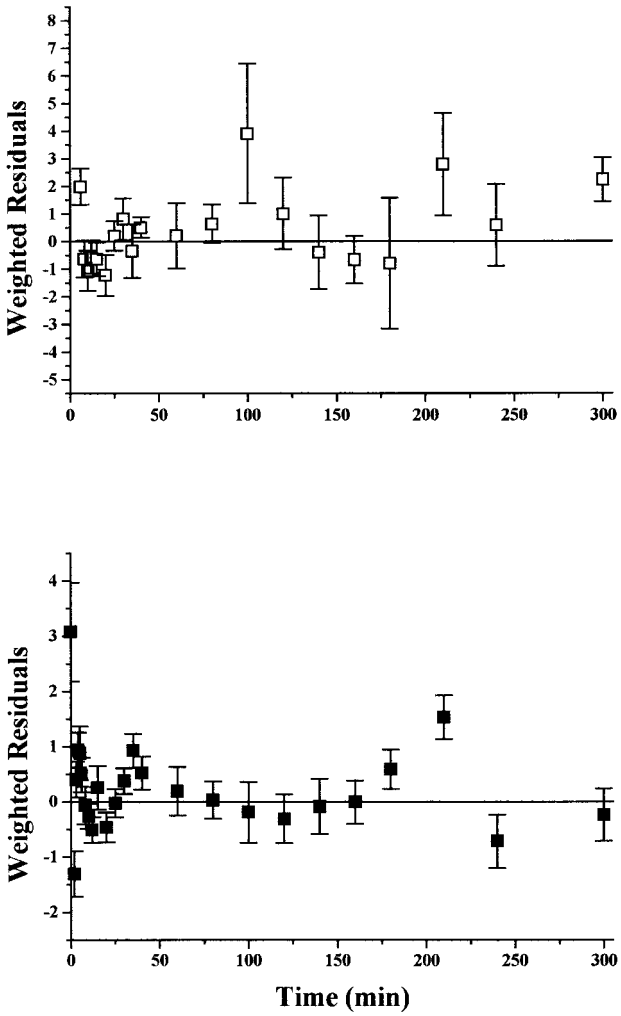

Fig 5. (A) Mean weighted residuals for the classical minimal model of glucose kinetics (means ± SE). Data between 0 and 5 minutes were excluded in model identification to mitigate the approximation of the single-compartment description of glucose kinetics. (B) Mean weighted residuals for the minimal model of C-peptide kinetics (means ± SE).

our N and H groups (see Materials and Methods) is not supposed to have a significant impact on S_I, because it has been reported by Chen et al[24] that the clustering features of insulin resistance are independent of age and sex in both black and white populations. Moreover, the estimates of S_G and S_I in our N group are similar to those reported by Cobelli et al[25] for normal humans, even though the age in our N group (42 ±7 years) was higher than that of Cobelli's group (28 ± 1 year).

Our results are in agreement with previous reports[5,6,8] in suggesting that insulin hypersecretion (inferred from 54% higher TIS level) in the H group cannot be considered consistently associated with impaired β-cell sensitivity to glucose. More likely, insulin hypersecretion is to be ascribed to hyperglycemia following reduced S_I and S_G. These alterations in glucose metabolism may explain the finding by Gress et al[26] that the risk of non–insulin-dependent diabetes mellitus (NIDDM) in hypertensives is about twice that in the normotensive population.

Higher plasma insulin and C-peptide levels observed throughout the entire IVGTT suggest impaired insulin metabolism in our H group, and are thus in agreement with the finding by Swislocki[27] of an impaired insulin clearance in essential hypertension. A contradiction to this conclusion may be found in that, under basal conditions, insulin plasma concentrations in our N and H groups were not significantly different, whereas C-peptide plasma concentration was significantly higher in the H group. This fact brings the focus on the role the liver plays in modulating insulin appearance in the periphery. In accordance with Kautzky-Willer et al,[8] higher hepatic insulin extraction in essential hypertension may act as a compensating mechanism to avoid peripheral hyperinsulinemia following β-cell insulin hypersecretion documented by a higher level of the TIS. Compared with insulinemia, the basal level of C-peptide plasma concentration, which is a marker of β-cell insulin secretion, remains high, because this hormone is not affected by hepatic extraction.

APPENDIX 1

The Modified Minimal Model of C-Peptide Kinetics and Secretion

The model is shown in Fig 1 and is described by the following equations:

$$\dot{C}P_1(t) = -[k_{01} + k_{21}]CP_1(t) + k_{12}CP_2(t) + mX(t) \qquad CP_1(0) = 0 \tag{1}$$

$$\dot{C}P_2(t) = k_{21}CP_1(t) - k_{12}CP_2(t) \quad CP_2(0) = 0 \tag{2}$$

$$\dot{X}(t) = -mX(t) + Y(t) \quad X(0) = X_0 \tag{3}$$

$$\dot{Y}(t) = -\alpha\{Y(t) - \beta[G(t) - h]\} \quad Y(0) = 0 \tag{4}$$

CP_1 and CP_2 (pmol · L^{-1}) are C-peptide concentration above basal in the compartment 1 (accessible compartment) and 2 (peripheral compartment), respectively; X(pmol · L^{-1}) and Y(pmol · L^{-1} · min^{-1}) are, respectively, the C-peptide amount and provision in the β cell, both normalized to the distribution volume of compartment 1; k_{ij} (min^{-1}) values are C-peptide kinetic parameters; m (min^{-1}), α (min^{-1}), β (min^{-1}), and h (mg dL^{-1}) are secretory parameters. The secretion rate (above basal) is mX and enters compartment 1. The initial condition X_0 (pmol · L^{-1}) represents the stored amount of C-peptide, and it is responsible for first phase secretion, while second phase secretion derives from provision Y, which is controlled by the glucose concentration, G (mmol L^{-1}) through parameters β and h. By adding to mX the basal secretion rate given by $k_{01}CP_{1b}$ (suffix b denotes the end test basal value), one obtains the β-cell secretion, SR (pmol · L^{-1} min^{-1}):

$$SR(t) = k_{01}CP_{1b} + mX(t) \tag{5}$$

In addition to SR in each subject, the model also allows the estimation of 3 indexes of β-cell function. The first phase sensitivity to glucose, ϕ_1 (dimensionless), is given by the ratio between the incremental amount of C-peptide secreted during

first phase and the maximum increment of the plasma glucose concentration, ΔG (mmol L^{-1}):

$$\phi_1 = \frac{X_0}{\Delta G} \tag{6}$$

the second phase sensitivity to glucose, ϕ_2 (min^{-1}), is given by the parameter describing the stimulatory effect of the glucose concentration on provision:

$$\phi_2 = \beta \tag{7}$$

Finally, the basal sensitivity to glucose, ϕ_b (min^{-1}), is given by:

$$\phi_b = \frac{k_{01}CP_{1b}}{G_b} \tag{8}$$

where G_b is the end-test glucose concentration.

The Simplified Version of C-Peptide Minimal Model

If the kinetics of the system are fast ($1/\alpha$ is very small), the provision Y becomes:

$$Y(t) = \beta[G(t) - h] \tag{9}$$

Insulin secretion is:

$$SR(t) = mX(t) \tag{10}$$

where X(t) is now the solution of a first-order process:

$$\dot{X}(t) = -mX(t) + \beta[G(t) - h] \quad X(0) = X_0 \tag{11}$$

Model parameters are X_0, m, b, h.

APPENDIX 2

The Classical Minimal Model of Glucose Kinetics

The minimal model of glucose disappearance (Fig 2) assumes a monocompartmental description of glucose kinetics during an IVGTT.[16] Insulin exerts its action from an insulin compartment remote from plasma. The equations of the model are as follows:

$$\dot{Q}(t) = -[p_1 + X(t)] \cdot Q(t) + p_1 \cdot Q_b \quad Q(0) = Q_b + D \tag{12}$$

$$\dot{X}(t) = -p_2 \cdot X(t) + p_3 \cdot [I(t) - I_b] \quad X(0) = 0 \tag{13}$$

$$G(t) = Q(t)/V \tag{14}$$

where:

$$X(t) = (k_4 + k_6) \cdot I'(t) \tag{15}$$

$$p_1 = k_1 + k_5 \tag{16}$$

$$p_2 = k_3 \tag{17}$$

$$p_3 = k_2 \cdot (k_4 + k_6) \tag{18}$$

D ($mg \cdot kg^{-1}$) is the glucose dose; k_i coefficients ($i = 1,\ldots,6$) are rate constants characterizing either material fluxes (solid lines in Fig 1) or control actions (dashed lines in Fig 1); Q(t) is glucose mass ($mg \cdot kg^{-1}$) and Q_b is its basal (end-test) steady-state value; G(t) and I(t) are plasma glucose ($mg \cdot dL^{-1}$) and insulin ($\mu U \cdot mL^{-1}$) concentrations at time t; I'(t) is insulin concentration, at time t, in a compartment remote from plasma; G_b and I_b are baseline (end-test) glucose and insulin concentrations, respectively, computed as the average of the last 2-3 points; V ($dL \cdot kg^{-1}$) is the distribution volume. From equation 14 results Q_b $G_b \cdot V$.

The minimal model provides indices of S_G and S_I, which are defined as follows:

$$S_G = -\left.\frac{\partial \dot{G}(t)}{\partial G(t)}\right|_{ss} = p_1 \quad (min^{-1}) \tag{19}$$

$$S_I = -\left.\frac{\partial^2 \dot{G}(t)}{\partial I \partial G(t)}\right|_{ss} = \frac{p_3}{p_2} \quad (min^{-1}/\mu U\ mL^{-1}) \tag{20}$$

The suffix ss, in equations 19 and 20, denotes steady state.

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