Use of labeled oral minimal model to measure hepatic insulin sensitivity

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1Department of Information Engineering, University of Padova, Padua, Italy; and 2Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Department of Internal Medicine, Mayo Clinic and Foundation, Rochester, Minnesota

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Dalla Man C, Toffolo G, Basu R, Rizza RA, Cobelli C. Use of labeled oral minimal model to measure hepatic insulin sensitivity. Am J Physiol Endocrinol Metab 295: E1152–E1159, 2008. First published September 2, 2008; doi:10.1152/ajpendo.00486.2007.—The ability to accurately quantify indexes of the individual role of glucose (GE\textsuperscript{L}) and insulin (SI\textsuperscript{L}) in the suppression of endogenous glucose production (EGP) would improve the understanding of liver metabolism. Measuring these indexes during an ivgltt by minimal modeling of tracer labeled and unlabeled glucose data is often unreliable, possibly due to an inadequate description of EGP included in the Minimal Model. Moreover, a validation of the assumptions of the Minimal Model on EGP data has never been done. Recently, Krudy et al. (Krudys KM, Dodds MG, Nissen SM, Vicini P. Am J Physiol Endocrinol Metab 288: E1038–E1046, 2005) have proposed a PK/PD (pharmacokinetic/pharmacodynamic) model of the EGP profile that occurs during an intravenous glucose tolerance test (IVGTT); however, this model has also not been validated. The aim of this study was thus to test the Minimal Model, the PK/PD model, and six alternative models to accurately describe the known EGP profile and thereby enable simultaneous assessment of SI\textsuperscript{L} and GE\textsuperscript{L}. model-independent estimate of EGP was obtained by a triple-tracer meal protocol (3) to test the ability of the PK/PD Model, of the original Minimal Model, and of some new models to accurately describe the known EGP profile and thereby enable simultaneous assessment of SI\textsuperscript{L} and GE\textsuperscript{L}. MATERIALS AND METHODS

Protocol and Subjects

Twenty normal subjects (age 32 ± 4 yr; BMI 25 ± 1) had a meal (1 g/kg glucose, 10 kcal/kg, 45% carbohydrate, 15% protein, 40% fat) labeled with [1-\textsuperscript{13}C]glucose, to segregate the exogenous, i.e., coming from the meal, and the endogenous glucose (data already reported in Ref. 4). Two additional tracers ([6, 6-\textsuperscript{2}H\textsubscript{2}]glucose and [6-\textsuperscript{3}H]glucose), were infused intravenously with the tracer-to-trace clamp technique (3), i.e., at variable rate mimicking EGP and [1-\textsuperscript{13}C]glucose rate of appearance in plasma (Ra), respectively. Plasma samples were collected at times −120, −30, −20, −10, 0, 5, 10, 15, 20, 30, 40, 50, 60, 75, 90, 120, 150, 180, 210, 240, 260, 280, 300, 360, and 420 min. For details on protocol and measurements we refer to Refs. 3 and 4. After approval from the Mayo Institutional Review Board, all participants gave informed written consent to participate in the study.

EGP Estimates

Virtually model-independent estimates of EGP were obtained by applying the two-compartment model (17) to the clamped tracer-to-trace ratio [6,6-\textsuperscript{2}H\textsubscript{2}]glucose/endogenous glucose (TTR) (3) using the equation

\[
\text{EGP} = \frac{\text{INF}}{\text{TTR}} \cdot V_1 \cdot G_{\text{rad}} \frac{d(TTR)}{dt} + k_1 \left( \frac{q_{2}}{TTR} - Q_2 \right)
\]

where \(G_{\text{rad}}\) is the plasma concentration of endogenous glucose, \(V_1\) is the volume of distribution of the accessible pool and \(k_1\) is the rate constant between the peripheral and the accessible compartment, fixed to 130 ml/kg and 0.07 min\textsuperscript{−1} respectively, according to previous studies.

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studies in normal subjects (17); q2 and Q2 are the amounts of [6,6-2H2]glucose and endogenous glucose in the peripheral compartment, to be evaluated by integrating model equations. As evident from Eq. 1, the estimate of EGP generally depends on the chosen model (e.g. here a two-compartment model) and parameter values. However, the extent of this dependence is minimized in the present study since the intravenous tracer is infused trying to mimic the expected pattern of EGP and thus to minimize TTR time variations (TTR clamp). When this condition is reached, at least approximately (see RESULTS), dTTR/dt is close to zero, and a uniform TTR is maintained throughout the system, i.e., q2/TTR Q2, so that EGP, close to the ratio between the rate of infusion and the TTR, is minimally influenced by the choice of the model.

EGP Models

Eight models were tested. The first is the recently proposed PK/PD Model by Krudys et al. (15), the second is EGP description incorporated in the traditional Minimal Model (5), and the others are six new models derived from it.

PK/PD model. This model is based on the indirect response paradigm, usually adopted in situations when the pharmacodynamic response to a drug is delayed with respect to the time course of its concentration in plasma. It assumes that EGP depends on the amount of releasable glucose in the liver, Gs, and an inhibitory function, H2, reflecting the ability of remote insulin to inhibit glucose production (15):

\[ EGP(t) = k_{out} \cdot [1 - H_2(t)] \cdot G_s(t) \]  

(2)

where \( k_{out} \) is the first-order rate constant describing the loss of hepatic glucose into the systemic circulation. Gs results from the balance between EGP and hepatic glucose formation, related to plasma glucose concentration, G, through the function \( H_1 \):

\[ G_s(t) = -k_{out} \cdot [1 - H_2(t)] \cdot G_s(t) + k_{in} \cdot [1 - H_1(t)] \]  

(3)

\[ G_s(0) = \frac{k_{in}}{2k_{out}} \]

with \( k_{in} \) the apparent zero-order rate constant of hepatic glucose formation. The two indirect response functions \( H_1 \) and \( H_2 \) are given by

\[ H_1(t) = \frac{G(t)}{G_b + G(t)} \]  

\[ H_2(t) = \frac{x(t)}{IC_{50} + x(t)} \]  

(4)

\[ \dot{x}(t) = -p_2 \cdot [x - s_2 \cdot (I(t) - I_b)] \]  

\[ x(0) = 0 \]  

(5)

where \( G_b \) is basal glucose concentration, \( IC_{50} \) the insulin action producing 50% of maximum inhibition of glucose production and \( x(t) \) is insulin action (deviation from basal) on the liver: with \( p_2 \) rate constant describing the dynamics of insulin action on glucose production and \( s_2 \) insulin sensitivity, a parameter governing the magnitude of insulin action.

Minimal model. The Minimal Model (5) assumes the following description of EGP in terms of glucose concentration and insulin action (10):

\[ EGP(t) = EGP_b - GE^{iL} \cdot [G(t) - G_b] - \dot{X}^L \cdot G(t) \]  

(6)

\[ EGP(0) = EGP_b \]

where \( EGP_b \) is the basal EGP, \( GE^{iL} \) liver glucose effectiveness, \( G \) glucose concentration, \( G_b \) its basal value, \( \dot{X}^L \) liver insulin action (deviation from basal), which follows the dynamic equation:

\[ \dot{X}^L = -k_2 \cdot [X^L - k_2 \cdot (I(t) - I_b)] \]  

\[ \dot{X}^L(0) = 0 \]  

(7)

where \( k_1 \) is a rate constant describing the dynamics of insulin action on glucose production and \( k_2 \) is insulin sensitivity, a parameter governing the magnitude of insulin action.

Model 1. Since the Minimal Model description of EGP was unable to fit the data well and to provide reliable and precise indexes (see RESULTS), other models were tested. The first model only considers a direct effect of plasma glucose and insulin concentration on EGP. Model equations are:

\[ EGP(t) = EGP_b - GE^{iL} \cdot [G(t) - G_b] - k \cdot [I(t) - I_b] \]  

\[ EGP(0) = EGP_b \]  

(8)

Model 2. Model 1 failed to fit data (see RESULTS), in particular the late EGP suppression 7 h after meal ingestion (Fig. 1, bottom), since plasma glucose and insulin concentrations have already come back to basal (see Fig. 4, top). A delayed insulin action can account for this fact. From the physiological point of view, one can interpret the delayed insulin action as a signal surrogating the suppression of FFA level; in fact, insulin lowers FFA concentration, and this makes the liver suppress EGP. Thus, in Model 2, insulin action on EGP is delayed with respect to plasma insulin concentration, as in the Minimal Model (Eq. 7) but, at variance with the Minimal Model, is not multiplied by glucose concentration:

\[ EGP(t) = EGP_b - GE^{iL} \cdot [G(t) - G_b] - X^L(t) \]  

\[ EGP(0) = EGP_b \]  

\[ X^L(t) = -k_1 \cdot [X^L(t) - k_2 \cdot (I(t) - I_b)] \]  

\[ X^L(0) = 0 \]  

(9)

Model 3. Although Model 2 showed an improvement on the PK/PD Model, the Minimal Model, and Model 1 in fitting the data (see RESULTS), parameter estimates were often imprecise and assumes unreliable values. This could be due to the inability of the model to distinguish between the contributions of plasma glucose and delayed insulin action in suppressing glucose production. Therefore Model 3 introduced an additional delay in the insulin action model:

\[ \dot{X}^L = -k_1 \cdot [X^L(t) - k_2 \cdot (I(t) - I_b)] \]  

\[ X^L(0) = 0 \]  

(10)

Model 4. This model incorporates the notion (9) that a portal insulin signal controls the rapid suppression of EGP in addition to plasma
glucose concentration and delayed insulin. Portal insulin signal is approximated by insulin secretion rate [derived by deconvolution from C-peptide data (18)]:

\[
E_{GP}(t) = E_{GP} - GE_l \cdot [G(t) - G_b] - X^l(t) - X^{sec}(t)
\]

\[
E_{GP}(0) = E_{GP}
\]

with

\[
X^{sec}(t) = \begin{cases} k_1 \cdot [SR(t) - SR] & \text{if } [SR(t) - SR_b] \geq 0 \\ 0 & \text{if } [SR(t) - SR_b] < 0 \end{cases}
\]

where SR is insulin secretion rate, SR_b is its basal value, and k_1 is a parameter governing the magnitude of glucose derivative control.

Model 5. Model 4 did not provide good results in terms of reliability of estimated parameters (see RESULTS). A possible explanation is that the model is not able to distinguish between the plasma glucose and insulin secretion control, which, apart from the first minutes, show similar pattern (see Fig. 3, top and middle). We thus tested a model that assumes the control of EGP suppression by portal insulin (i.e., insulin secretion) and delayed insulin, but not by glucose concentration:

\[
E_{GP}(t) = E_{GP} - X^l(t) - X^{sec}(t)
\]

\[
E_{GP}(0) = E_{GP}
\]

with \(X^l\) and \(X^{sec}\) defined as in Eqs. 10 and 12, respectively.

Model 6. Model 5 provided good data fit and parameter estimates (see RESULTS). However, glucose control on EGP is not explicitly, but only implicitly, included in the portal insulin signal. This renders difficult the definition of hepatic glucose effectiveness. To avoid this inconvenience, we exploit the notion that the above insulin secretion during a meal can be modeled as a sum of two components, proportional to the glucose rate of change (through a parameter \(k_{can}\)) and to above-basal glucose concentration (through a parameter \(k_c\)), respectively (6). It is of note that in Ref. 6 the latter component is proportional to delayed (~10 min) glucose concentration; conversely, here, since such delay was not identifiable, we used the glucose concentration.

Model equations are

\[
E_{GP}(t) = E_{GP} - k_{can} \cdot [G(t) - G_b] - X^l(t) - X^{sec}(t)
\]

\[
E_{GP}(0) = E_{GP}
\]

with \(X^l\) defined as in Eqs. 10 and 15, where \(k_{can}\) is a parameter governing the magnitude of glucose derivative control.

\[
X^{sec}(t) = \begin{cases} k_c \cdot \frac{dG(t)}{dt} & \text{if } \frac{dG(t)}{dt} \geq 0 \\ 0 & \text{if } \frac{dG(t)}{dt} < 0 \end{cases}
\]

Liver Indexes

Model 6 was selected as the best model to describe EGP data (see RESULTS). Indexes of hepatic glucose effectiveness (GE_l) and insulin sensitivity (S_l) can be derived from model parameters as follows:

\[
GE_l = \frac{\partial E_{GP}}{\partial G} \bigg|_{ss} = k_G
\]

\[
S_l = \frac{\partial E_{GP}}{\partial I} \bigg|_{ss} = \frac{1}{G_b} \frac{\partial X^l}{\partial I} \bigg|_{ss} = \frac{1}{G_b} \frac{\partial X^{sec}}{\partial I} \bigg|_{ss} = \frac{k_2}{G_b}
\]

Disposal Indexes

To assess the relative role of production vs. disposal in glucose tolerance, the disposal glucose effectiveness and insulin sensitivity were estimated as follows. First, virtually model-independent estimates of the R_e in plasma of ingested glucose were obtained, with an equation similar to Eq. 1, by substituting EGP with R_e, TTR with the ratio [6-\(^3\)H]glucose/endogenous glucose, G_b with exogenous glucose, and Q_1 and Q_2 with the amounts of [6-\(^3\)H]glucose and exogenous glucose in the peripheral compartment.

Disposal indexes GE_D and S_D were then estimated by identifying the labeled Minimal Model (10) on tracer glucose data using R_e as known input (for details we refer to Ref. 12). This allowed us to express GE_l and S_l as a percentage of the total glucose effectiveness and insulin sensitivity, calculated as the sum of their liver and disposal components, i.e., GE_T = GE_D + GE_l and S_T = S_D + S_l.

Parameter Estimation

All models were numerically identified by nonlinear least squares (7, 11), as implemented in SAAM II [Simulation Analysis and Modeling software (2)]. Error of GE_l estimates was assumed to be independent, Gaussian, with zero mean and unknown constant standard deviation. Glucose and insulin concentrations and, for Models 4 and 5 insulin secretion rate, are the model forcing functions assumed to be known without error. For the labeled-meal Minimal Model measurement error on tracer glucose data was assumed to be independent, Gaussian, with zero mean and known standard deviation (12).

Statistical Analysis

Model performances were compared on the basis of several criteria (see Ref. 11 for details): precision of parameter estimates [expressed as coefficient of variation (CV)], parameter physiological plausibility, ability to describe the data [weighted residual square sum (WRSS)], model parsimony [Akaike information criterion (AIC)], and residual independence (Anderson run test).

RESULTS

TTR and EGP

The clamped [6,6-\(^2\)H]glucose/endogenous glucose TTR is shown in Fig. 1, top, and estimated EGP in Fig. 1, bottom. TTR is not perfectly constant, but it varies, as expected, in a limited range, thus confirming that the EGP estimate is virtually model independent.

Model Comparison

Weighted residuals of the eight tested models are shown in Fig. 2. As summarized in Table 1, all the eight models provided similar WRSS. The PK/PD model and Models 4 and 6 had slightly lower WRSS, essentially due to the higher number of parameters, and their AIC was only modestly higher. The run test supported randomness of residuals only for the PK/PD Model and Models 4, 5, and 6, whereas the Minimal Model and Models 1, 2, and 3 did not provide a good fit of the data. However, the PK/PD Model, like the Minimal Model and Model 1, provided imprecise parameter estimates (CV >100%). Precision with Model 4 was somewhat better, but parameter values were not plausible for all subjects, since either negative or unrealistically high values were observed for some of them. On the other hand, Models 5 and 6 provided precise (CV ~20%) and reliable estimates of the parameters, with no negative values. In summary, the Minimal Model and Models 1, 2, and 3 were excluded due to the non-whiteness of their residuals; the PK/PD Model was excluded due to poor precision (high CV) and Model 4 due to unreliability of parameter estimates. Of the remaining models, Models 5 and 6,
Model 5 is physiologically appealing, since the inclusion of insulin secretion allows one to describe portal insulin action; however, glucose control in the liver cannot be estimated independently of portal insulin action (Fig. 3, middle, where $X^{sec}$ incorporates both glucose and portal insulin). Model 6 overcomes this issue by describing insulin secretion as a sum of two components proportional to glucose rate of change and glucose above basal, respectively. Therefore, we selected Model 6 as the best able to reliably predict the postprandial EGP pattern.

**Liver vs. Disposal Indexes and Insulin Action Profile**

Figure 3, top, shows plasma glucose and insulin concentration superimposed on the same graph to facilitate the comparison with model-predicted control signals, shown in Fig. 3,

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### Table 1. Comparison of EGP models

<table>
<thead>
<tr>
<th>Run Test</th>
<th>Precision (average CV, %)</th>
<th>Plausibility of Parameter Values</th>
<th>WRSS (mean ± SD)</th>
<th>AIC (mean ± SD)</th>
<th>No. of Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK/PD Model</td>
<td>Yes</td>
<td>&gt;500</td>
<td>No</td>
<td>17.95±0.22</td>
<td>71.53±0.28</td>
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<tr>
<td>Minimal Model</td>
<td>No</td>
<td>290</td>
<td>No</td>
<td>18.95±0.22</td>
<td>70.72±0.27</td>
</tr>
<tr>
<td>Model 1</td>
<td>No</td>
<td>422</td>
<td>No</td>
<td>19.95±0.22</td>
<td>72.03±0.25</td>
</tr>
<tr>
<td>Model 2</td>
<td>No</td>
<td>49</td>
<td>No</td>
<td>18.77±0.64</td>
<td>70.50±0.79</td>
</tr>
<tr>
<td>Model 3</td>
<td>No</td>
<td>20</td>
<td>Yes</td>
<td>18.90±0.31</td>
<td>70.66±0.37</td>
</tr>
<tr>
<td>Model 4</td>
<td>Yes</td>
<td>42</td>
<td>No</td>
<td>18.10±0.31</td>
<td>71.71±0.37</td>
</tr>
<tr>
<td>Model 5</td>
<td>Yes</td>
<td>24</td>
<td>Yes/No</td>
<td>19.00±0.20</td>
<td>70.78±0.17</td>
</tr>
<tr>
<td>Model 6</td>
<td>Yes</td>
<td>26</td>
<td>Yes</td>
<td>18.11±0.31</td>
<td>71.42±0.50</td>
</tr>
</tbody>
</table>

EGP, endogenous glucose production; PK/PD, xxxx xxxx/xxx xxxx; WRSS, weighted residual square sum; AIC, Akaike information criterion.
the sum of XDer and GEL effectiveness, GEL, and insulin sensitivity, SIL (in Fig. 4, indicating that SIL and SID account for, respectively, 34 and 66% of postprandial insulin action, whereas GE^L and GE^D account for 42 and 58%, respectively, of postprandial glucose effectiveness.

**DISCUSSION**

The efficiency of glucose and insulin control on glucose production plays an important role in glucose homeostasis. It is therefore of interest to quantify the ability of glucose and insulin to suppress glucose production when the system is perturbed by a physiological stimulation such as meal ingestion. The available method to estimate both liver glucose effectiveness and insulin sensitivity consists of using the unlabeled and labeled models to measure, respectively, total (i.e., periphery + liver) and peripheral indexes. Hepatic indexes are then calculated as the difference between the two. Previous studies indicate that indexes derived during an IVGTT using the traditional Minimal Model are unreliable (8, 10, 20). Caumo et al. (8) suggested that the above inconsistencies are symptoms of model error, related, e.g., to the single-compartment description of glucose kinetics (that they investigated) or to the description of glucose and insulin effect on EGP. In fact, the Minimal Model assumes that insulin action on the liver has the same time course (i.e., the same delay with respect to plasma insulin concentration) of insulin action on glucose disposal. Moreover, EGP suppression includes a term linearly dependent on glucose and a term equal to the product of glucose concentration and insulin action, which means that the effect of insulin on the liver is glucose mediated. Recently, a PK/PD Model of EGP during IVGTT has been also proposed (15). However, all of these modeling strategies have not been assessed during an oral perturbation, i.e., a meal or an OGTT.

The objective of the present study was to compare the ability of a series of models to predict EGP during a meal: the PK/PD Model (15), the traditional Minimal Model (5), and six evolutions of it. These models were identified on the available model-independent EGP profiles during a meal. Testing the models on these EGP gold standard data instead of plasma glucose concentration data avoids the need to describe glucose disposal and the control of insulin on it and, thus, possible compensation between errors affecting production and disposal. Classical criteria typically used in model selection were adopted: the model’s ability to describe the data, the precision of parameter estimates, the physiological plausibility of the parameter values, and model parsimony. Our analysis shows that neither the traditional Minimal nor the PK/PD Model is a reliable description of EGP: the Minimal Model is unable to fit the data, and both the Minimal and PK/PD Models provided imprecise and unreliable parameter estimates. This is not surprising, since both models were originally proposed to describe the rapid changes in glucose and tracer glucose concentrations that occur after intravenous injection of glucose rather than model-independent EGP data, as in the present study. In addition to the PK/PD and the Minimal Models, six new models have been tested. Model 1 assumes a direct control of EGP suppression by plasma glucose and insulin concentrations; with Model 2, EGP suppression linearly depends on plasma glucose and a delayed insulin signal; Model 3 is similar to Model 2 but with a more pronounced delay in insulin signal;
Model 4, in addition to plasma glucose and delayed insulin controls, incorporates the notion that portal insulin also contributes to inhibit EGP; Model 5 simplifies Model 4 by removing plasma glucose control; and finally, Model 6 assumes that EGP suppression is linearly dependent on plasma glucose concentration, delayed insulin action, and glucose derivative.

The comparison among the eight models is reported in Table 1 and can be summarized as follows.

The Minimal Model and Models 1, 2, and 3 were excluded due to the non-whiteness of their residuals; the PK/PD Model was excluded due to poor precision (high CV) and Model 4 due to unreliability of parameter estimates. Models 5 and 6 showed similar performances in terms of model ability to fit the data and precision of parameter estimates. However, with Model 5 glucose control on the liver cannot be estimated independently from portal insulin action. Not including glucose control on EGP suppression is a questionable assumption and prevents the definition of glucose effectiveness. In fact, in Ref. 19 it is shown that glucose concentration per se has an effect on glucose production. There, 28 subjects participated in either a euglycemia, a sustained-hyperglycemia, or a glucose profile study, with endogenous secretion suppressed by somatostatin and insulin and glucagon concentrations maintained at the same level by exogenous infusion. EGP patterns, calculated with a multiple-tracer technique, were different on the three occasions. Moreover, Model 5 also requires measurement of C-peptide concentration to reconstruct insulin secretion by deconvolution, while Model 6 does not. Nonetheless, a possible explanation of the good performance obtained with Model 5 is that glucose controls EGP in part indirectly by stimulating insulin secretion. Thus, it is likely that neither Model 5 (which assumes no direct effect of glucose on EGP), nor Model 6 (which assumes only a direct effect of glucose on EGP) completely fits the physiology. A model that takes into account both effects (as Model 4) would be the most appropriate. However, the present data do not allow one to distinguish these two components of glucose effectiveness on the liver (see RESULTS). This problem can be overcome if one interprets parameter GE as an overall measure of the ability of glucose

![Table 2. Liver and disposal glucose effectiveness and insulin sensitivity estimated from Model 6 (left) and hot meal Minimal Model (right), respectively.](attachment:image.png)

Nos. in parentheses indicate coefficients of variation (CV%).

![Fig. 4. Relative roles of liver and disposal glucose effectiveness (top) and insulin sensitivity (bottom).](attachment:image.png)
to inhibit glucose production both directly and indirectly (i.e., by stimulating insulin secretion). Therefore, we propose using Model 6, keeping in mind the above-cited interpretation of this parameter.

The rationale behind this model is that the above-basal insulin secretion can be described with two components: one proportional to the glucose rate of change and the other one proportional to above-basal glucose concentration (6). Thus, Model 6 provides an estimate of parameter $k_G$, which accounts for both the control of plasma glucose and portal insulin on EGP suppression; parameter $k_{GR}$, which account for glucose derivative control on the fast suppression of EGP; parameters $k_1$, which quantifies the delay between plasma insulin and delayed insulin action, and $k_2$, which determines its amplitude. The inclusion of this derivative control significantly improves the ability of the model to fit EGP data in the first 30 min and makes Model 6 superior than other models. However, a comment on available sampling schedule is in order. Our data are frequently sampled in the first 30 min (1 sample each 5 min), and this allowed us to detect the rapid suppression of EGP due to the portal insulin signal; it is likely that a simpler model, such as Model 3, can perform sufficiently well when data are less frequently sampled.

Model 6 differentiates from the traditional Minimal Model in the description of the delayed insulin action. First, it is not multiplied by glucose concentration, which means that glucose and insulin act independently on the liver; then, insulin action on glucose production follows a different time course from the effects of insulin on glucose disposal (Fig. 3, bottom); finally, the delayed insulin action is described with a two-compartment chain. The superiority of this description compared with the single-compartment delay was evident in all models employing it, including Model 6. In particular, the latter always provided a good fit of the data and a reliable and precise parameter estimates (average CV 26%), whereas a model assuming a single delay for insulin action gave imprecise and inaccurate parameter estimates (not shown).

Model 6 also provides indexes of both liver glucose effectiveness, $GE^L$, and insulin sensitivity, $SI^L$, estimated with precision. Their definition follows the traditional formulation of the Minimal Model: i.e., $GE^L$ is the ability of glucose to promote EGP suppression, and $SI^L$ is the ability of insulin to increment EGP suppression. To understand the relative role of the liver vs. periphery in maintaining glucose homeostasis, indexes of glucose and insulin control on glucose disposal ($GE^D$ and $SI^D$) have been estimated from the hot Minimal Model, identified on tracer glucose data using the Ra profile estimated with the TTR clamp technique as known inputs. This permits calculation of $GE^D$ and $SI^D$ and, thus, of total indexes $GE^{TOT} = GE^D + GE^L$ and $SI^{TOT} = SI^D + SI^L$. Hence, the relative role of the liver vs. periphery can be determined. Model 6 indicates that during a meal $GE^L$ and $SI^L$ represent 42 and 34% of total glucose effectiveness and insulin action, respectively (Fig. 4).

Many surrogate indexes of whole body, peripheral, and hepatic insulin resistance have been proposed. For instance, Matsuda and DeFronzo (16) defined hepatic insulin resistance index as the product between basal EGP (measured with a 3-[3H]glucose infusion) and fasting plasma insulin concentration (FPI); on the other hand, Abdul-Ghani et al. (1) proposed a new surrogate index of liver insulin resistance derived from area under glucose and insulin concentrations measured in the first 30 min of an OGTT. They reported that this index significantly correlates with the Matsuda-DeFronzo index ($r = 0.64, P < 0.0001$). $SI^L$ modestly correlates with the inverse of these two surrogate indexes [$r = 0.44$ and $r = 0.46$, with $1/(FPI \times EGP)$ and $1/(AUC_G \times AUC_I)$, respectively]. However, the Matsuda-DeFronzo is a basal index of hepatic insulin resistance, since it ignores the change in EGP that occurs as insulin and glucose concentrations change over time. Thus, subjects who have similar “basal” insulin action but a difference in the ability of glucose and/or insulin to suppress glucose production cannot be distinguished. On the other hand, the Abdul-Ghani et al. index assumes that glucose utilization is minimally increased during the initial 30 min after food ingestion and that glucose $R_0$ in the first 30 min is zero. These assumptions are rather critical, since results obtained using a triple-tracer approach in 204 subjects showed that glucose $R_0$ almost doubles with respect to its basal value in the first 30 min after glucose intake, whereas meal glucose $R_0$ peaks right around 30 min after a meal (4).

In conclusion, the present study indicates that the traditional Minimal Model (5) does not accurately predict the pattern of change that occurs after a meal ingestion. In addition, the PK/PD Model (15) is also inadequate to fit EGP data, at least during a meal. Of the six new models proposed, Model 6 best describes EGP data and provides reliable indexes of glucose and insulin control on the liver. Although Model 6 will require further validation, especially in impaired-glucose-tolerant and impaired-fasting-glucose subjects, the present study suggests that it will likely provide an accurate assessment of the pattern of change of endogenous glucose production that occurs after food ingestion and will enable simultaneous assessment of hepatic insulin action and glucose effectiveness.

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