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A Model of Glucose Production During a Meal

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Abstract— **The efficiency of glucose and insulin control on glucose production (EGP) plays an important role in glucose homeostasis and its derangement in diabetes. Therefore the ability to accurately quantify indices of the individual role of glucose (GE^L) and insulin (S_I^L) in the suppression of EGP would allow to improve the understanding of liver metabolism. Measuring these indices by minimal modelling of tracer labelled and unlabelled glucose data is often unreliable, possibly due to an inadequate description of EGP included in the minimal model (EGP^{MM}). Moreover a validation of EGP^{MM} on EGP data has never been done. Here EGP^{MM} and alternative EGP descriptions were tested on recent model-independent EGP data of 20 subjects obtained with a triple-tracer meal protocol. Model performances were compared in terms of data fit and physiological plausibility. EGP^{MM} was not able to describe EGP data, while one of the new model showed a good fit and provided accurate and precise estimates of hepatic sensitivity indices: GE^L=0.013 ± 0.001 dl/kg/min; S_I^L =5.71 ± 0.48 10^{-4} dl/kg/min per μU/ml (36% and 41%, respectively, of total sensitivity indices GE^{TOT} and S_I^{TOT}). This novel approach will allow to enhance our understanding of the role of the liver in pathophysiological states.**

I. INTRODUCTION

The liver is the primary source of endogenous glucose production (EGP) in the body. When plasma glucose increases, due to an exogenous source, *e.g.* during a meal, insulin secretion is stimulated and EGP is suppressed due to both glucose and insulin signals. In pathological situations, such as diabetes, the control of glucose and insulin on EGP is impaired [1]. Therefore the ability to assess the individual role of glucose (GE^L) and insulin (S_I^L) in the suppression of EGP during a meal would allow to improve the understanding of liver metabolism. The current method used to measure hepatic glucose and insulin sensitivity indices from labelled IVGTT data consists in employing simultaneously unlabelled (cold) and tracer labelled (hot) minimal models [2] [3]. From the cold model total (*i.e.* liver + periphery) indices GE^{TOT} and S_I^{TOT} are estimated, while the hot model provides peripheral indices GE^P and S_I^P; liver indices GE^L and S_I^L are then calculated as difference between total and peripheral ones. However, estimates of GE^L and S_I^L are often unreliable [3], [4], [5]. This rises doubts on the adequacy of EGP description which is implicit in the minimal model (EGP^{MM}).

Here we take advantage of the availability of a very recent, virtually model-independent, estimate of EGP provided by a triple tracer meal protocol [6], we test EGP^{MM} and alternative models directly on EGP data. Testing models on EGP data is important because possible compensations between kinetics and EGP misdescriptions are avoided, thus allowing a better definition of EGP model validity.

II. MATERIALS AND METHODS

A. Data base and protocol: twenty normal subjects (age=32 ± 4; BMI=25 ± 1) had a meal (1 g/kg glucose, 10 kcal/kg, 45% carbohydrate, 15% protein, 40% fat) labeled with [1-^{13}C]-glucose, in order to segregate the exogenous, *i.e.* coming from the meal, glucose from the endogenous one. Two additional tracers ([6,6-$^2H_2$]-glucose and [6-^{3}H]-glucose), were infused intravenously with the tracer-to-tracee clamp technique, *i.e.* at variable rate mimicking EGP and ^{13}C-glucose rate of appearance in plasma (Ra_{meal}), 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, 420.

B. Triple tracer estimation of EGP and Ra_{meal}.: the tracer-to-tracee clamp technique minimizes non-steady state error. Virtually model-independent estimates of EGP and Ra_{meal} were obtained by applying the two compartment model [7] to the clamped tracer-to-tracee ratios [6,6-$^2H_2$]-glucose/endogenous glucose (TTR_{EGP}) and [6-^{3}H]-glucose/exogenous glucose (TTR_{Rameal}) respectively [6] (Figures 1 and 2).

C. Minimal Model description of EGP: the cold minimal model [2] assumes the following description of EGP (EGP^{MM}) in terms of glucose concentration and insulin action [3]:

$$EGP^{MM}(t) = EGP_b - GE^L \cdot (G(t) - G_b) - X^L(t) \cdot G(t) \qquad (1)$$

where EGP_b is the is basal EGP, GE^L liver glucose effectiveness, G glucose concentration, G_b its basal value, X^L liver insulin action which follows the dynamic equation:

$$\dot{X}^L(t) = -p_2 \cdot [X_L - S_I^L \cdot (I - I_b)] \qquad X_L(0) = 0 \qquad (2)$$

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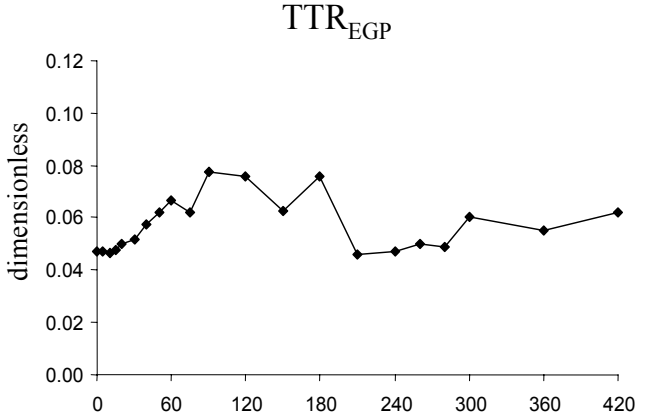


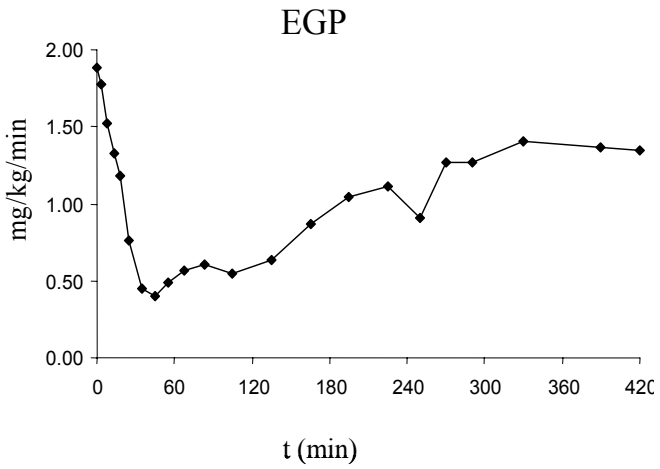
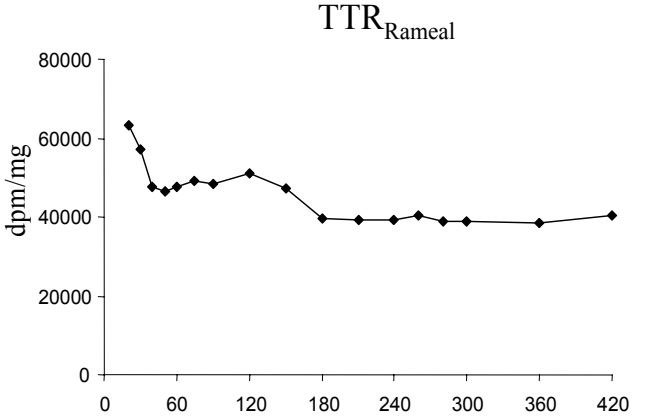


Figure 1: Upper panel: clamped tracer-to-tracee ratio TTR_{EGP}. Lower panel: endogenous glucose production.



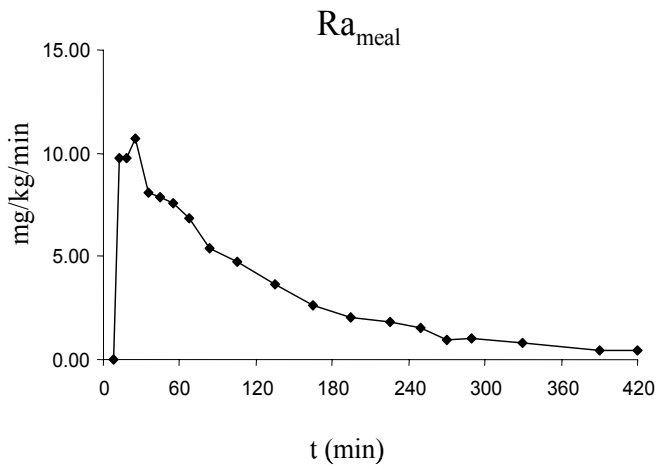


Figure 2: Upper panel: clamped tracer-to-tracee ratio TTR_{Rameal}. Lower panel: meal rate of appearance.

where p_2 is a rate constant describing the dynamics of insulin action on glucose production and utilization and S_I^L is liver insulin sensitivity.

D. New Model 1: since the minimal model description of EGP is unable to fit the data well and to provide reliable and precise sensitivity indices (see Results) other models were tested. Better results in terms of reliability and precision of estimated parameters were obtained by using a new description of EGP (equation 3), where insulin action on glucose production, at variance with EGP^{MM}, is not multiplied by glucose concentration; a different description is assumed for X^L, by introducing a liver specific rate constant k_1:

$$\begin{cases} EGP(t) = EGP_b - GE^L \cdot (G(t) - G_b) - X^L(t) & EGP(0) = EGP_b \\ \dot{X}^L(t) = -k_1 \cdot X^L(t) + k_1 \cdot X_1(t) & X^L(0) = 0 \\ \dot{X}_1(t) = -k_1 \cdot X_1(t) + k_2 \cdot [I(t) - I_b] & X_1(0) = 0 \end{cases} \quad (3)$$

where k_2 is a parameter governing the magnitude of insulin action.

Liver insulin sensitivity index is given by:

$$S_I^L = -\left.\frac{\partial EGP}{\partial I}\right|_{ss} \cdot \frac{1}{G_b} = \frac{k_2}{k_1} \cdot \frac{1}{G_b} \quad (4)$$

E. New Model 2: another model assumes that the fast suppression of EGP is due to a portal insulin signal [8] in addition to plasma glucose concentration and delayed insulin signal (X^L, which follows eq 3). Since the portal insulin signal is an anticipated version of plasma insulin concentration, we approximate it with the derivative of insulin concentration:

$$EGP(t) = \begin{cases} EGP_b - GE^L \cdot (G(t) - G_b) - X^L(t) + k_3 \cdot \dfrac{dI(t)}{dt} & if \ \dfrac{dI(t)}{dt} \geq 0 \\ EGP_b - GE^L \cdot (G(t) - G_b) - X^L(t) & if \ \dfrac{dI(t)}{dt} < 0 \end{cases} \quad (5)$$

$$EGP(0) = EGP_b$$

where k_3 is a parameter governing the magnitude of portal insulin action.

Liver insulin sensitivity index is given by:

$$S_I^L = \frac{k_2}{k_1} \cdot \frac{1}{G_b} + k_3 \cdot \frac{(\mathrm{I}_{max} - I_b)}{AUC(I - I_b) \cdot G_b} \qquad (6)$$

F. Two Compartment Hot Minimal Model: In order to understand the relative role of liver vs periphery in glucose tolerance, peripheral indices GE^P and S_I^P were estimated by identifying the two compartment hot minimal model [9] on tracer glucose data using Ra_{meal} as known input (for details we refer to [9]). This allowed us to calculate the total glucose effectiveness and insulin sensitivity as the sum of their liver and peripheral components, *i.e.* $GE^{TOT}=GE^P+GE^L$ and $S_I^{TOT}= S_I^P+ S_I^L$.

G. Parameter Estimation: All models were numerically identified by nonlinear least squares [10,11], as implemented in SAAM II (Simulation Analysis and Modelling software [12]). Measurement error of EGP data was assumed to be independent, gaussian, with zero mean and unknown constant standard deviation. Glucose and insulin concentrations are the model forcing functions, assumed to be known without error. For the two compartment hot minimal model measurement error on tracer glucose data was assumed to be independent, gaussian, with zero mean and known constant standard deviation.

III. Results

Minimal Model: the model is unable to fit EGP data by showing consistent overestimation. In Figure 3 average weighted residuals are shown. Moreover it does not provide reliable and precise estimate of GE^L and S_I^L: GE^L =0.007 ± 0.002 dl/kg/min (range: -0.007 to 0.024; CV%=64 ± 9); S_I^L=3.22 ± 0.47 10^{-4} (range: -0.12 to 8.05; CV%=124 ± 72);

Model 1: at variance with EGP^{MM}, model 1 provides a quite accurate description of EGP profile, as shown in Figure 4 where average weighted residuals obtained in the 20 subjects are reported.

All parameters of the model were estimated with good precision: GE^L=0.016 ± 0.002 dl/kg/min, CV%=20±7; S_I^L =5.45 ± 0.46 10^{-4} dl/kg/min per μU/ml, CV%=18±3. When compared with the total indices calculated as $GE^{TOT}=GE^P+GE^L$ and $S_I^{TOT}= S_I^P+ S_I^L$, GE^L and S_I^L represent 39% and 40% of the total, respectively.

Model 2: this model, at variance with the previous ones, provides a very accurate description of EGP profile also in the first minutes of the experiment, as shown in Figure 5 where average weighted residuals obtained in the 20 subjects are reported.

All parameters of the model were estimated with good precision: GE^L=0.013 ± 0.001 dl/kg/min, CV%=18±4; S_I^L =5.71 ± 0.48 10^{-4} dl/kg/min per μU/ml, CV%=11±1. When compared with the total indices calculated as $GE^{TOT}=GE^P+GE^L$ and $S_I^{TOT}= S_I^P+ S_I^L$, GE^L and S_I^L represent 36% and 41% of the total, respectively.

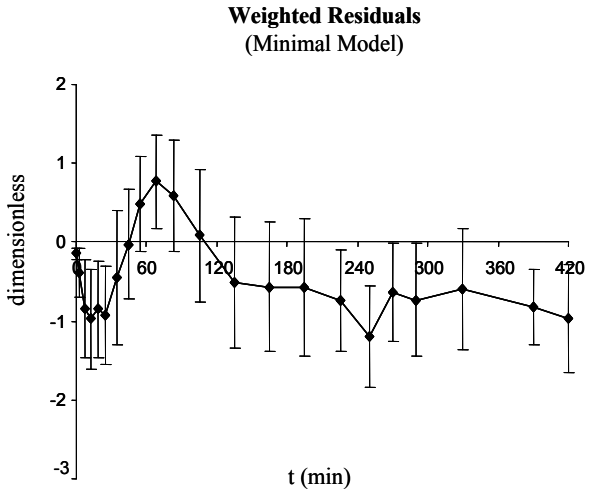


Figure 3: Average weighted residuals of the Minimal Model

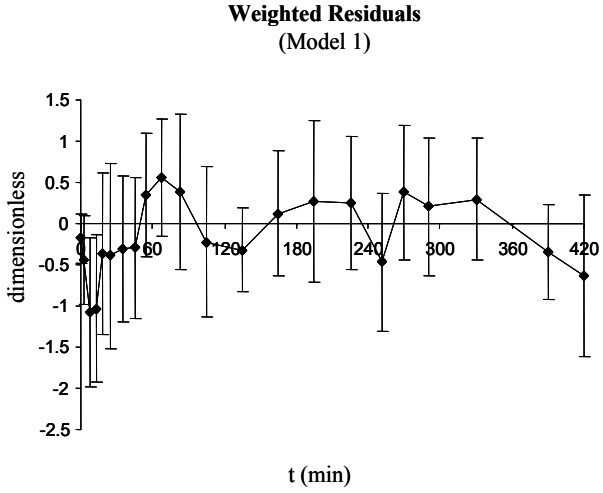


Figure 4: Average weighted residuals of Model 1

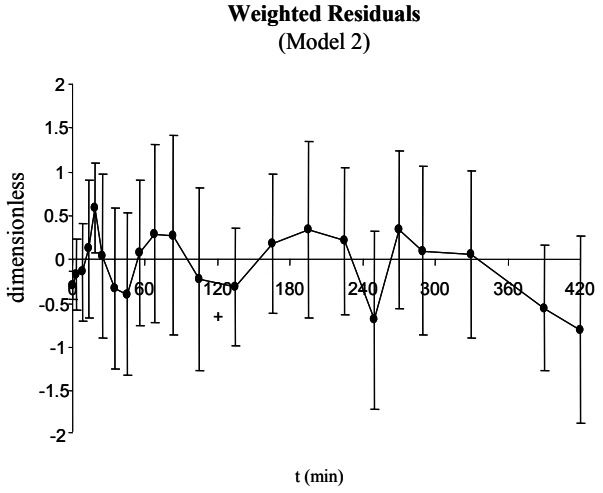


Figure 5: Average weighted residuals of Model 2

Peripheral indices: the hot minimal model fits tracer glucose data well and all parameters were estimated with good precision: GE^P=0.023 ± 0.001 dl/kg/min, S_I^P=10.90 ±2.06 10^{-4} dl/kg/min per μU/ml.

IV. Discussion

The efficiency of glucose and insulin control on glucose production plays an important role in glucose homeostasis and its derangement as in diabetes. It is therefore of great interest to quantify the ability of glucose and insulin to suppress glucose production when the system is perturbed as during a meal.

The current method to estimate both liver glucose effectiveness and insulin sensitivity consists in identifying cold and hot minimal model on, respectively, cold and hot data of a labelled IVGTT to measure, respectively, total (*i.e.* periphery +liver) and peripheral indices. Hepatic indices are then calculated as the difference between the two.

Unfortunately, calculated indices are often unreliable [3], [4], [5], in all likelihood due to an inadequate description of insulin and glucose control on EGP suppression. The minimal model in fact assumes that 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 control of insulin is glucose-mediated.

However the minimal model was never validated on EGP data. Here, we take advantage of the very recent availability of a virtually model-independent estimate of EGP provided by a triple tracer meal protocol [6]: using EGP data, instead of glucose concentration, avoids possible compensations between kinetics and EGP misdescriptions, thus allowing a clear assessment of EGP model validity.

We have tested EGP^{MM} on EGP data and our results show that it is unable to fit experimental data. Conversely, the newly proposed EGP models, and in particular model 2, which also takes into account also the control of a portal insulin signal on EGP suppression [8], fits EGP data well and provides reliable indices of GE^L and S_I^L estimated with good precision (CV<20%).

In order to understand the relative role of the liver *vs.* periphery in maintaining glucose homeostasis, indices of glucose and insulin control on glucose disposal (GE^P and S_I^P) have to be estimated. To this purpose the two compartment hot minimal model was identified on tracer glucose data, using the Ra_{meal} profile estimated with the tracer-to-tracee ratio clamp technique as known input: knowing GE^P, S_I^P, one can then calculated total indices $GE^{TOT}=GE^P+GE^L$ and $S_I^{TOT}= S_I^P+ S_I^L$, thus allowing the relative role of the liver vs periphery to be assessed. With model 2, GE^L and S_I^L represent 36% and 41% of total respectively.

V. Conclusion

With this study we have shown that the description of EGP implicit in the minimal model is in all likelihood inadequate and could be responsible of the unreliable estimates of hepatic glucose effectiveness and insulin sensitivity. Two new models have been proposed; one of these is able to describe EGP data well and provides reliable indices of glucose and insulin control on the liver. This new description of EGP is being incorporated in the glucose kinetics oral minimal model [13] in order to estimate both hepatic and peripheral indices directly from cold and tracer glucose concentration data of a labelled meal.

This novel assessment will allow to enhance the quantitative parametric picture of the control of insulin and glucose on liver metabolism, thus favouring a better understanding of the pathophysiology of diabetes and its therapy.

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