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Extended summary

Mathematical model of standard oral glucose tolerance test for characterization of insulin potentiation in health

Curriculum: Electromagnetics and Bioengineering

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Abstract. Two new formulations, respectively denominated INT_M1 and INT_M2, of an integrated mathematical model to describe the glycemic and insulinemic responses to a 75 g oral glucose tolerance test (OGTT) are proposed and compared. The INT_M1 assumes a single compartment for the intestine, and the derivative of a power exponential function for a monophasic representation of the gastric emptying rate profile. In the INT_M2, a nonlinear three-compartment system model is adopted to produce a more realistic, multiphase gastric emptying rate. Both models were implemented in a Matlab-based, two-step procedure for estimation of seven adjustable coefficients characterizing the gastric emptying rate and the incretin, insulin and glucose kinetics. Model behaviour was tested vs. data of mean plasma glucagon-like peptide 1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), glucose and insulin concentrations provided by two different laboratories, where glycemic profiles observed during a 75 g OGTT were matched in healthy subjects (HC1- and HC2-group) by means of an isoglycemic intravenous glucose (I-IVG) infusion. Under the hypothesis of an additive effect of GLP-1 and GIP on insulin potentiation, our results demonstrated a substantial equivalence of the two models in matching the data. Model parameter estimates showed to be suitable markers of differences observed in the OGTT and matched I-IVG responses from the HC1-group compared to the HC2-group. Model implementation in our two-step parameter estimation procedure enhances the possibility of a prospective application for individualization of the incretin effect in a single subject, when his/her data are plugged in.

Keywords. Gastric emptying, glucose-insulin system, incretin effect, model parameter estimation, oral glucose absorption.

1 Problem statement and objectives

To improve knowledge of diabetes pathophysiology and assess the efficacy of hypoglycemic agents in clinical drug development, increasing relevance is being assumed by integrated simulation models of the glucose-insulin control system during an oral glucose tolerance test (OGTT). After ingestion, glucose is absorbed in the upper gastrointestinal tract, transported to the splanchnic bed and, finally, reaches the peripheral circulation. An augmented glucose-dependent insulin secretion (insulin potentiation [1]), observed after an OGTT, compared to a matched isoglycemic intravenous glucose (I-IVG) infusion, is attributed to the influence of the so called *"incretin effect"* [1,2], mostly due to the gut-derived incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) [3] released in response to nutrient ingestion.

A simulation model of the OGTT, primarily intended to illustrate the importance of incretin within the normal ranges observed clinically in humans, has recently been proposed by Brubaker et al. [4]. Unfortunately, an empiric description of the rate of gastric emptying of ingested glucose constrains this model to the reproduction of glycemia and insulinemia responses to 50 g and 100 g oral glucose loads, and limits the possibility of testing this model vs. data from a standard 75 g dose. In its original formulation [4] the model was characterized by fifteen parameters, ten of which were given numerical values known *a priori* from previously reported measurements, thus leaving five *"adjustable"* parameters. In the absence of a validation against standard OGTT data, the values assigned to these *"adjustable"* parameters appear not fully justified and the predictive capabilities of the model are weak. On this basis, the aim of the present research activity was to set-up an improved model of oral glucose tolerance test that could be tested against data from a standard 75 g glucose dose and could enhance the possibility of a prospective application for individualization of the incretin effect in a single subject, when his/her data are plugged in.

2 Research planning and activities

2.1 Research steps

To set-up a model that could be tested against standard clinical data, three points were considered essential:

- a better mathematical description of oral glucose absorption had to be incorporated to accomplish a more reliable representation of the incretin-induced insulin potentiation [1];
- the improved integrated model had to be implemented in an automatic procedure that allowed estimation of *"adjustable"* parameters by fitting to data;
- reliability of model parameter estimates and the predictive capability of the model, with special emphasis on incretin-induced insulin potentiation, had to be tested against plasma concentrations of GLP-1, GIP, glucose and insulin data from healthy subjects where glycemic profiles observed during a 75 g OGTT were matched, in a subsequent protocol, by means of an I-IVG infusion. From these protocols, the β-cell secretory response evoked by factors other than glucose itself (incretin-induced insulin potentiation, IP) can be quantified as the percentage of the OGTT response by the Equation (1):

$$IP\% = \frac{AUCI_{OGTT} - AUCI_{I-IVG}}{AUCI_{OGTT}} \cdot 100 \quad (1)$$

where $AUCI_{OGTT}$ and $AUCI_{I\text{-}IVG}$ represent the area under the curve of incremental insulin concentration over the OGTT and the matched I-IVG duration, respectively, according to the trapezoidal rule [1].

2.2 Model formulation

Two alternative descriptions of oral glucose absorption reported in the literature were picked up and incorporated in the Brubaker's model [4]. One of these, denoted as M1, assumes a single compartment for the intestine and the derivative of a power exponential function for a monophasic representation of the gastric emptying rate profile [5]. The other, denoted as M2, assumes a nonlinear three-compartment system model to produce a more realistic, multiphase gastric emptying rate [6]. The two versions of our integrated model were denoted as INT_M1 when incorporating the M1, and INT_M2 when incorporating the M2, respectively. INT_M1 consists of sixteen independent parameters, two of which pertaining to the description of glucose absorption, namely ke and β. Nine of these sixteen parameters were given numerical values known *a priori* from reported observations [4,5], while k_e, β, k_5, k_7, k_8, M and γ parameters were assumed as *"adjustable"*. INT_M2 is characterized by eighteen independent parameters, four of which describing glucose absorption, namely c, b, k_{min} and k_{max}. Eleven of these eighteen parameters were fixed on the basis of reported [4,6] observation while k_{min}, k_{max}, k_5, k_7, k_8, M and γ parameters were assumed as *"adjustable"*.

Among the adjustable parameters, k_5, k_7, k_8, M and γ are common to the two models. In particular, k_5 is a marker of the amplitude of the incretin response to oral glucose administration, k_8 is a marker of the insulin response to the incretin while k_7 is a marker of the insulin response irrespective of incretin response; M and γ are coefficients accounting for glucose dynamics.

2.3 Clinical data and model parameter estimation procedure

Model outputs were tested against mean plasma glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), glucose and insulin concentration data from two groups of metabolically healthy subjects submitted to an OGTT and, subsequently, to a matched I-IVG infusion, as reported by Muscelli et al. [7] and Nauck et al. [8]. Profiles of mean GIP and GLP-1 concentrations reported in [7,8] as $pmol \cdot L^{-1}$ were converted into $ng \cdot L^{-1}$ and, then, an incretin, *INC(t)*, signal was determined as the sum of GIP and GLP-1.

Optimal values of adjustable parameters were estimated by setting up a novel two-step weighed least square (WLS) fitting procedure implemented in *Matlab*. First, k_7 was estimated by simulating an I-IVG protocol and fitting the model predicted I(t) to measured insulin data. To this aim the measured isoglycemic *G(t)* profile was used as input. Under these conditions, glucose absorption is not involved, so that k_7 is the only free parameter to be estimated. The subsequent step was to estimate the other six free parameters by simultaneous fit of model outputs to incretin, glucose and insulin data from the OGTT protocol. Measurement errors in *INC*, *G* and *I* data were assumed to be normally distributed random variables with zero mean and a constant percent coefficient of variation (*CV%*) equal to 5.5%, 1.5% and 4%, respectively. The *CV%* of the i-th parameter, p_i, was expressed as

$CV(p_i)\%=SDp_i/p_i \cdot 100$, where SDp_i is the standard deviation computed as the square root of diagonal terms of the inverse of the Fisher information matrix.

3 Analysis and discussion of main results

Granted the suitability of the fixed independent parameters, a novel aspect of the present study was our set-up of a two-step procedure that allows estimation of the seven free parameters of each model from fitting to incretin, glycemia and insulinemia signals.

Due to their capability to approximate both the OGTT and the matched I-IVG insulin responses (Fig. 1), our two models yielded values for *IP%*, which are consistent with the values of *IP%* computed from measured data (Table 1). The implementation of both models in our parameter estimation procedure allowed assessment of k_5, k_7 and k_8 parameters, which appear as suitable markers of the differences in the incretin, glucose and insulin responses between the two groups. A higher k_8 value estimated by both models in the HC1-group, compared to the HC2, indicates the presence, in the former group of an increase of insulin response to incretin, which compensates for a lower incretin response to oral glucose load (lower k_5 in the HC1). In the presence of this compensation, the enhanced insulin potentiation (Table 1) in the HC2-group, compared to the HC1-group, is mainly explained by the observed reduction of suprabasal insulin response to the OGTT-matched profile of glucose infused intravenously, as marked by a lower k_7 in the HC2-group.

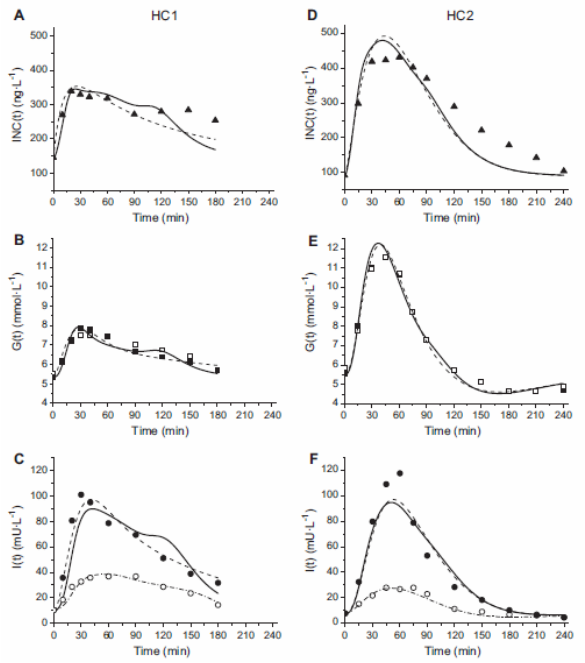

Figure 1. Mean data of plasma incretin (closed triangles in panel A and D), glucose (closed squares in panel B and E) and insulin (closed circles in panel C and F) concentrations in response to 75 g oral glucose challenge are matched by the *INC(t)*, *G(t)* and *I(t)* profiles produced by our models (dashed lines for INT_M1 and solid lines for INT_M2) after optimization of adjustable parameters. Open circles in panel C and F are mean plasma insulin concentration data measured after an intravenous glucose infusion with a temporal profile (open squares in panel B and E) matched to that observed after glucose ingestion (OGTT-matched isoglycemic intravenous glucose, I-IVG infusion). The dash-dot line in panel C and F describes the best fitting I-IVG insulin output.

Table 1. Insulin potentiation (*IP%*).

	IP%		
	INT_M1	INT_M2	EXPERIMENTAL
HC1 group	63.4	62.9	63.0
HC2 group	81.0	81.1	78.1

4 Conclusions

Our results yield the conclusion that INT_M1 and INT_M2 are suitable tools for the reproduction of incretin-induced insulin potentiation observed by comparing standard OGTT and related I-IVG data. Due to the substantial equivalence in the INT_M1 and INT_M2 behavior, the former model constitutes the best compromise between simplicity and predictive capability. Differences in the model parameter estimates in the HC1 compared to HC2-group showed to be suitable markers of differences observed in the OGTT and matched I-IVG responses from the same groups. Model implementation in a two-step parameter estimation procedure enhances the possibility of a prospective application for individualization of the incretin effect in a single subject, when his/her data are plugged in.

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