Glucose Homeostasis Modeling: Improvement of the Insulin Kinetics Component

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Drug Disease Model Resources

Introduction

Models of glucose homeostasis are important for the development of anti-diabetic drugs. Several models have been developed (e.g. [1]); however, the complexity of the processes and the necessity of rich data sets has limited the possibility to account for all mechanisms relevant for glucose homeostasis. One neglected aspect is insulin kinetics, which has typically been assumed to be linear, in contrast to physiological evidence [2].

Objectives

Aim of this work is to develop a model of insulin kinetics on data with a wide insulin span following stimulation of exogenous insulin secretion and endogenous insulin infusion.

Materials & Methods

- **Data** were obtained from:

  A) a frequently-sampled multiple-step hyperglycemic glucose clamp followed by arginine injection and exogenous insulin infusion in 6 healthy subjects [3];

  B) a euglycemic glucose clamp with one or two-insulin levels in 355 non-diabetic subjects with sampling at steady state [4].

- Plasma **insulin kinetics** was described with a circulatory model [5] including heart and lungs, gut, liver, and extra-hepatic organs lumped together (**FIG. 1**).

  • Extra-hepatic insulin clearance was assumed constant [2].

  • Saturation in the liver was described using a Michaelis-Menten-like function with 3 parameters (derived from the equation for f(G) in [6]).

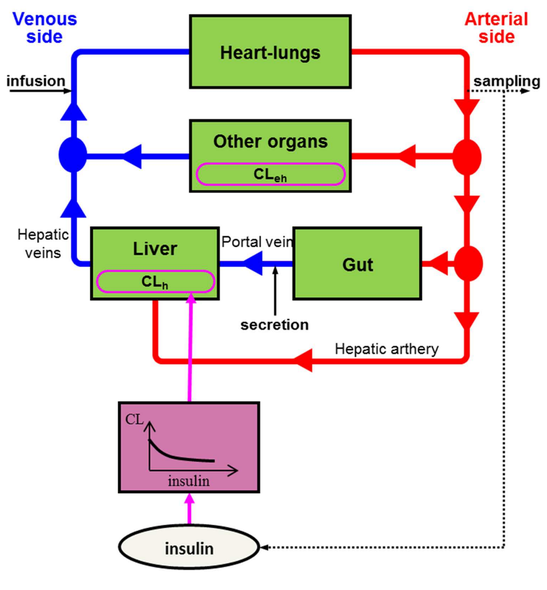

FIGURE 1 Insulin kinetics: a circulatory model of insulin kinetics (green) linked to a model of insulin clearance (pink)

- **Insulin secretion rate** (ISR):

  A) in Study A, it was separately computed by deconvolution of plasma C-peptide;

  B) in Study B, it was considered constant and estimated by simultaneously fitting basal plasma C-peptide concentrations, using Van Cauter's model of C-peptide clearance [7]: ISR = $CL_{c\text{-}pep}$ x $conc_{c\text{-}pep}$.

- Variables used in the Results section:

  • extraction ratio ER = CL / plasma_flow;

  • utilization = CL x conc.

- Parameters were estimated by mixed-effect modeling using Monolix 4.3.2.

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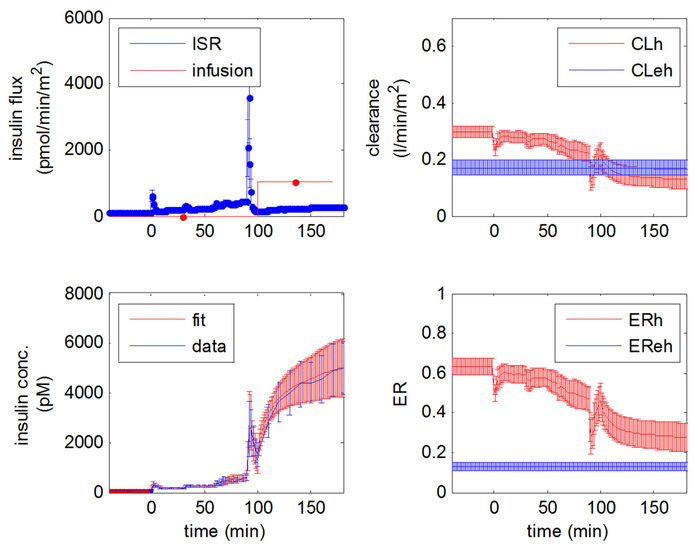
Results

- The model predicted insulin concentration adequately in both studies (**FIG. 2 & 3**).
- The median hepatic extraction ratio was 0.60 in basal conditions (ISR = ~100 pmol/min/m^2) , 0.16 under stimulated insulin secretion (ISR = ~500 pmol/min/m^2) and 0.09 under exogenous insulin infusion (960 pmol/min/m^2).
- Hepatic, extra-hepatic, endogenous and peripheral insulin clearance and their dependence from insulin levels were consistent with literature data [2, 8, 9] (**FIG. 4**).
- **Due to hepatic saturation, doubling basal insulin secretion resulted in a 2.6-fold increase in arterial insulin concentration (from 82 pM to 216 pM), a remarkable effect.**

A) HYPERGLYCEMIC CLAMP



B) EUGLYCEMIC CLAMP

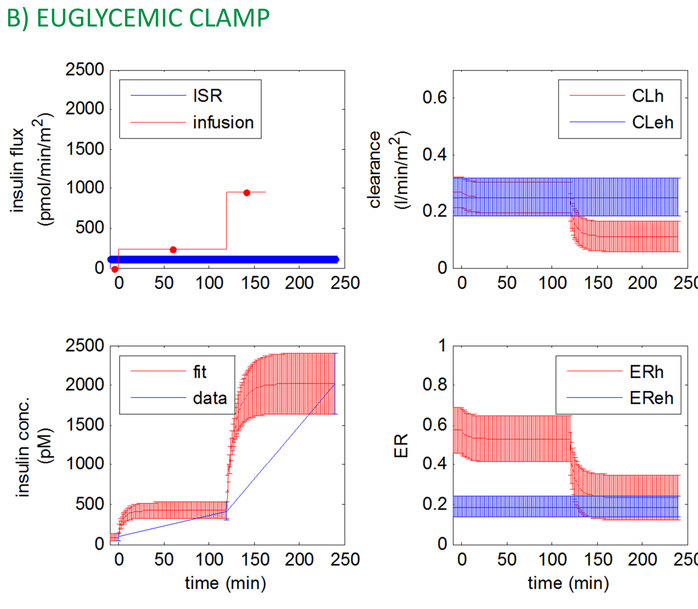
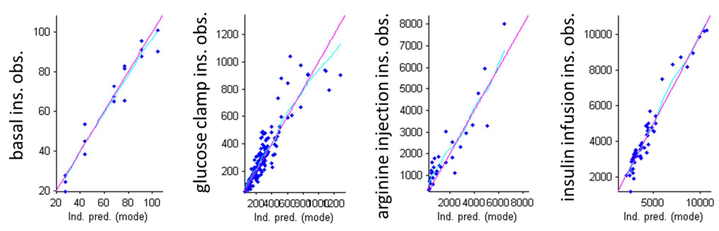


FIGURE 2 Computed or estimated insulin secretion rate (ISR); exogenous insulin infusion; fit of plasma insulin concentration; estimated hepatic (h) and extra-hepatic (eh) insulin clearance (CL) and extraction ratio (ER). Data are shown as mean ± s.e. (in Study A), mean ± s.d. (in Study B)

A) HYPERGLYCEMIC CLAMP



B) EUGLYCEMIC CLAMP

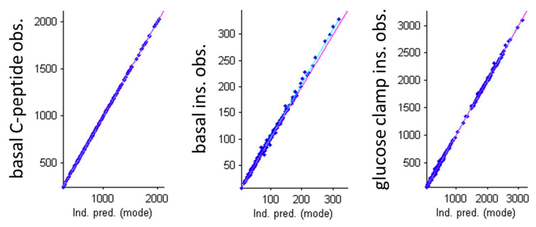
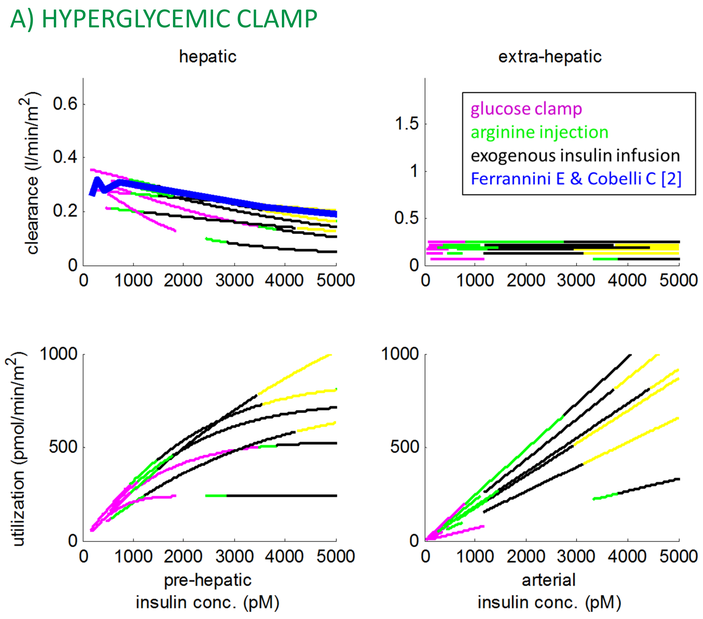
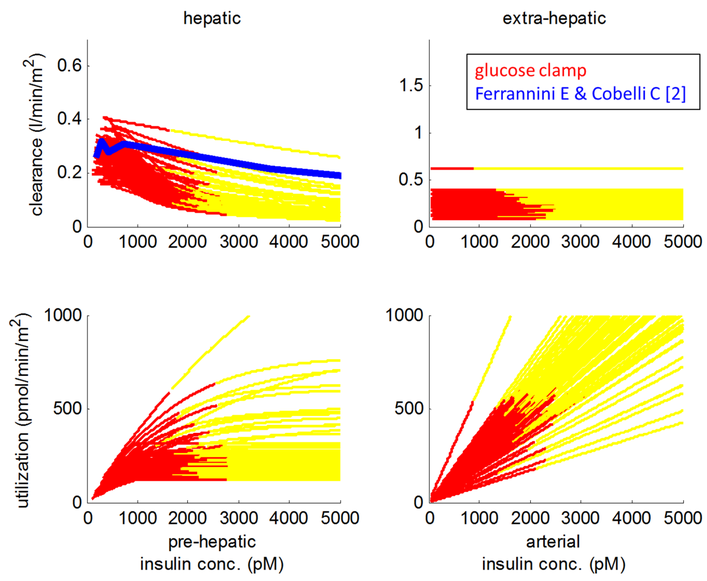


FIGURE 3 Individual predictions vs. observations, with identity line and spline

A) HYPERGLYCEMIC CLAMP



B) EUGLYCEMIC CLAMP



A&B) HYPERGLYCEMIC & EUGLYCEMIC CLAMP TOGETHER

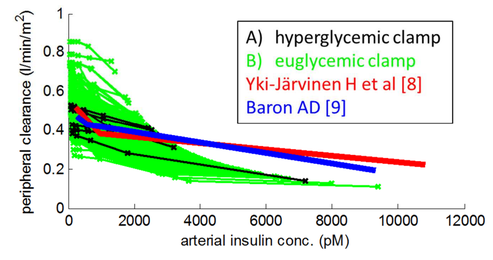


FIGURE 4 Dependence on plasma insulin concentration levels of hepatic and extra-hepatic clearance and utilization, and peripheral clearance. Thin curves are derived from estimated individual parameters for all the subjects in Studies A and B; intervals of concentration values explored in the different parts of the tests are depicted with different colours. Thick lines represent findings from the literature [2, 8, 9]

Conclusions

- A new mechanistic model describing insulin kinetics in non-diabetic subjects under both basal and stimulated physiological conditions and exogenous insulin infusion has been developed.
- Saturation of insulin utilization in the liver significantly modifies insulin kinetics with respect to linear utilization.
- Prediction of the effects of drugs enhancing insulin secretion or of subcutaneous insulin infusion may benefit from the use of this new model in the glucose homeostasis representation.

References

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