Glucose Homeostasis Modeling: Improvement of the Insulin Action Component

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Introduction

Glucose homeostasis models are important for predicting the effects of antidiabetic drugs. Some relevant models already exist [1]; however, the complexity of the system requires refinements of the model components to achieve better accuracy. In current models, glucose clearance is typically dependent on insulin but not on glucose concentration. This is not correct [2], but a quantitative analysis of the phenomenon is lacking.

Objectives

This study aims at developing a suitable mathematical expression of glucose utilization as a function of glucose concentration and insulin concentration at its site of action, based on in house experimental data.

Materials & Methods

- Data were obtained from a combined hyperglycemic/hyperinsulinemic clamp [3] in 8 healthy subjects, with glucose (5-18 mmol/L) and insulin (20-10000 pmol/L) spanning wide ranges. A glucose tracer was used to calculate glucose clearance.
- A model (A) was developed based on a circulatory model of glucose kinetics [4] and a model for insulin action that includes a simplified description of interstitial diffusion and insulin-controlled glucose transport across the cell membrane (**FIG. 1**). Model parameters were estimated using both Matlab/Simulink (single-subject approach) and NonMEM 7.2 (population approach).
- A prototypal glucose homeostasis model (B) was then set up by adding a β-cell [5], a glucose appearance [6] and a glucose kinetics [7] submodel (**FIG. 5**). Model B was used to simulate an oral glucose tolerance test (OGTT), including or excluding the glucose effect on clearance of model A.

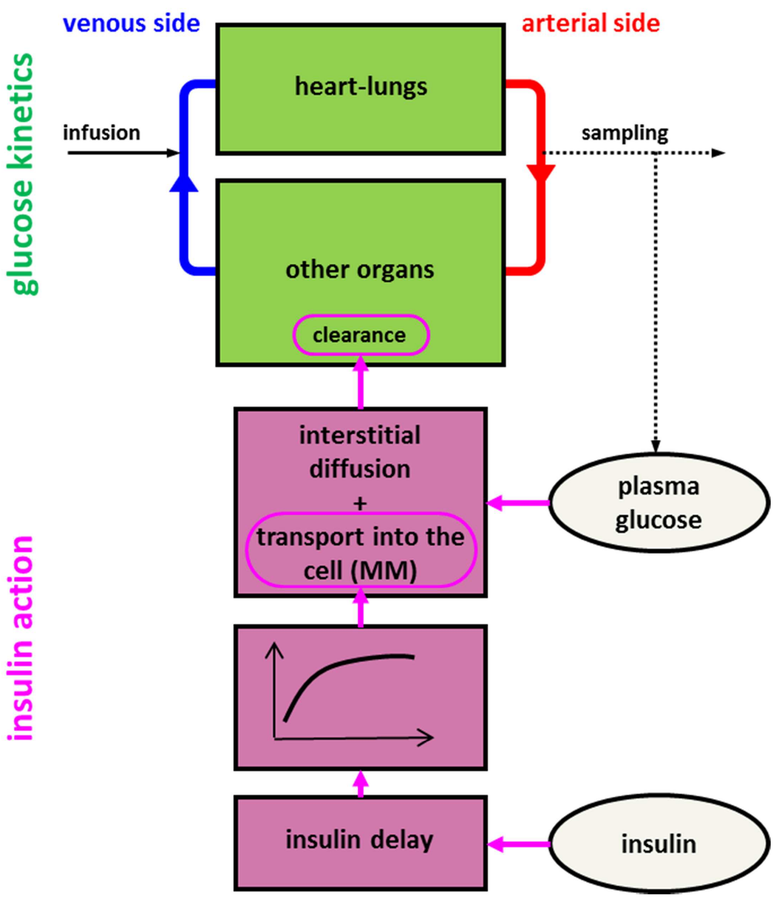

FIGURE 1 Model A: a circulatory model of glucose kinetics (green) linked to a model for insulin action (pink)

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Results

- Parameter estimation from model A provided a good fit of the tracer data (**FIG. 2**). The model was able to reproduce a characteristic feature of these data, i.e., the lack of glucose clearance increase in presence of hyperinsulinemia accompanied by hyperglycemia (**FIG. 3**).
- The prediction of the dependence of glucose clearance on glucose concentration was qualitatively in agreement with what is known from the literature. In a representative subject, glucose clearance at an insulin concentration of 500 pM was reduced from 81 to 42 mL $min^{-1}m^{-2}$ when glucose was raised from 5 to 10 mM (**FIG. 4**).
- The OGTT simulation with model B showed that the impact of the glucose effect on clearance was remarkable: including vs. excluding the effect produced an increase in 2-h glucose post OGTT from 6.7 to 7.6 mM (**FIG. 6**).

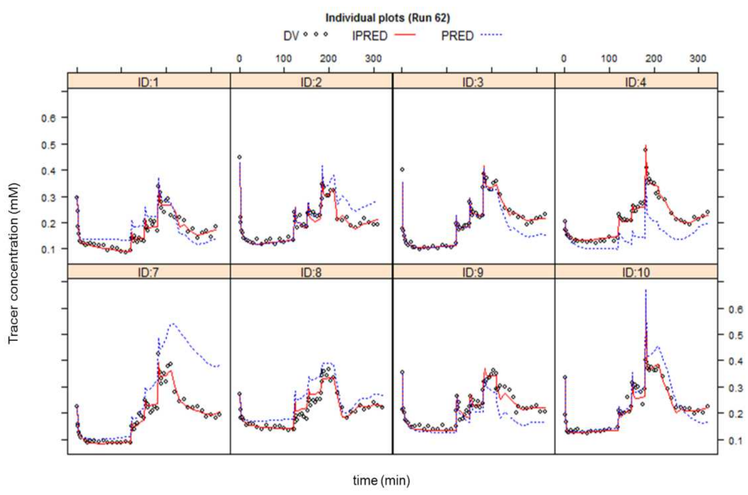

FIGURE 2 Fit of tracer data from NonMEM 7.2 (model A)

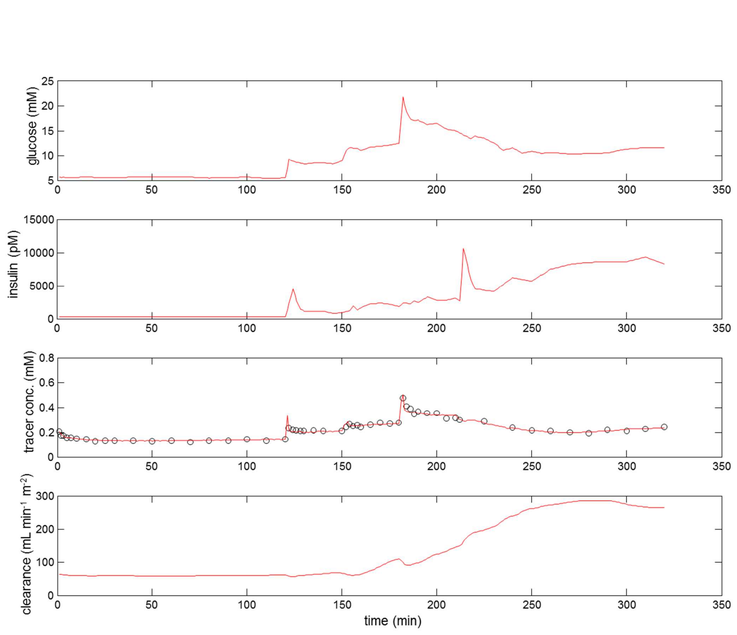

FIGURE 3 Measured insulin, glucose and tracer concentration, fit of tracer data, clearance from the estimated model, in a representative subject (model A)

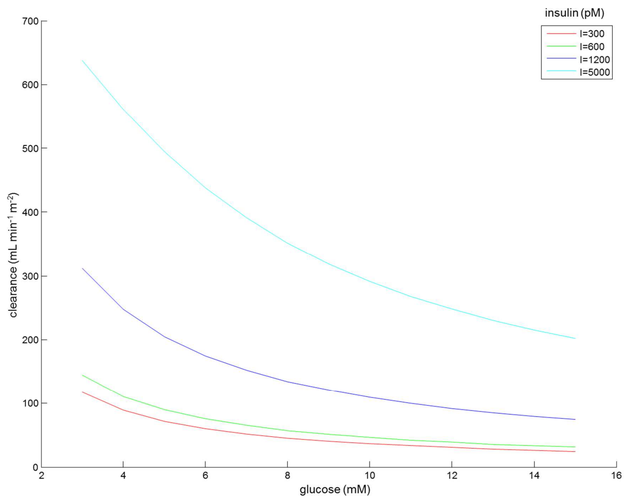

FIGURE 4 Glucose effect on glucose clearance at different insulin levels from model A estimated on a representative subject

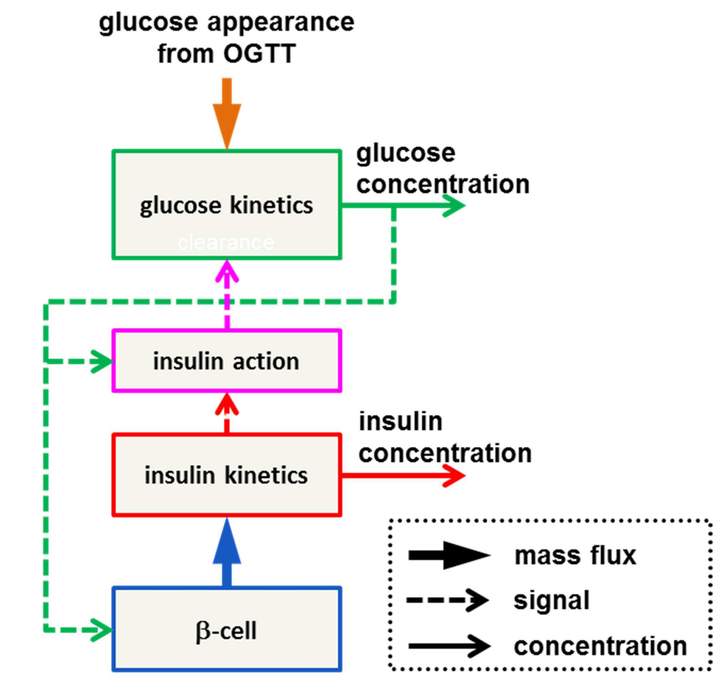

FIGURE 5 Model B: a prototypal glucose homeostasis model used for simulating an OGTT (FIG. 6)

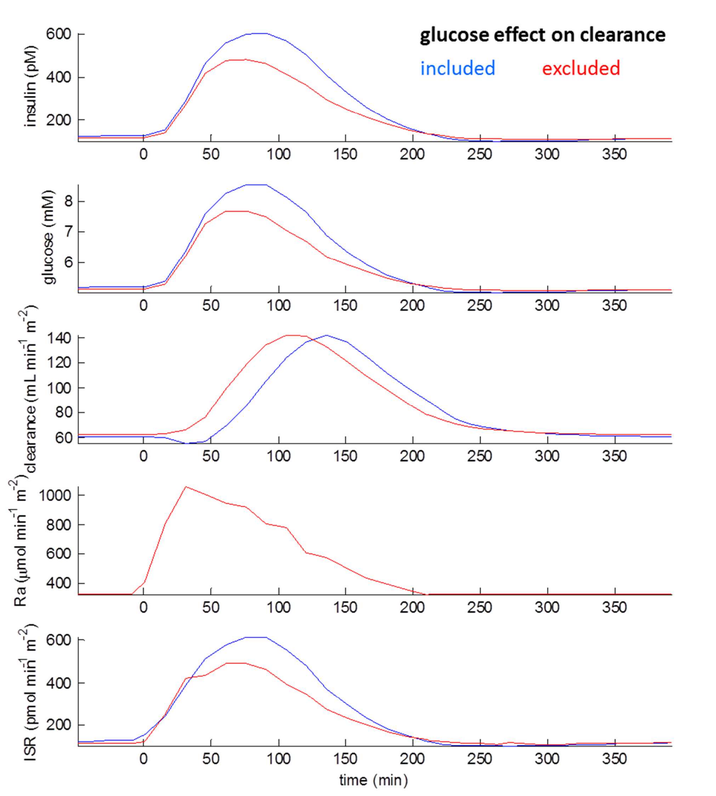

FIGURE 6 The effect of including or excluding glucose effect on glucose clearance on a OGTT experiment (simulation from model B)

Conclusion

- The new glucose clearance model can describe experimental characteristics that cannot be reproduced by more classical models.
- Accounting for the dependence of glucose clearance on glucose concentration has a remarkable impact on glucose homeostasis.
- Thus, this model is expected to improve the representation of glucose homeostasis, with benefit for the prediction of drug effects.

References

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