Validation of a Complex Glucose Metabolism Model

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Introduction

The mathematical description of the processes that regulate the production and uptake of glucose increase our understanding of the complex balance between metabolites and hormones. Such a description can ultimately aid in the development of tools to manage glycemia in diabetes and stress-induced hyperglycemia.

Methods

The ability of a glucose metabolism model [1] to simulate the published experimental data was assessed. Data published by Sacca et al. [2] consisted of pancreatic clamp experiments where glucose was infused for 90 minutes at a rate of 6.5 mg/kg min⁻¹ into a peripheral vein of five male non-diabetic subjects. The rates of hepatic glucose output, splanchnic glucose uptake, and peripheral (all non-splanchnic) uptake were measured every 15 minutes using a labeled glucose technique. We compared the experimental data to model estimates of these rates. Then, using data published by DeFronzo et al. [3] and Basu et al. [4], we refined specific model parameter values and reran the simulations.

Results

Using the original model parameter values published by Sorensen in his 1985 doctoral thesis, the model accurately estimated the time course of hepatic glucose output and peripheral glucose uptake. However, there was considerable difference in the model’s estimation of splanchnic (hepatic and gut) glucose uptake; the estimated steady-state values were twofold greater than experimental values. Once we modified the parameters governing the rate hepatic glucose uptake, the model accurately simulated the experimental data.

Conclusions

The original relationship between glucose and its uptake by the liver as developed by Sorensen used data from both clamp studies and oral glucose tolerance tests. Hepatic glucose uptake estimates from oral glucose tolerance tests were distinctly larger than estimates derived from experiments using intravenous glucose. The magnitude of this difference supports the need to model the glucose absorption from the gut differently than intravenous infusion of glucose.

Splanchnic Glucose Uptake

Splanchnic glucose uptake \( (r_{SGU}) \) is the sum of hepatic \( (r_{HGU}) \) and gut \( (r_{GGU}) \) glucose uptake. Since the model assumes a constant rate of gut glucose uptake \( (r_{GGU}) \), a direct comparison between reported measures and model estimates of \( r_{GGU} \) are possible under steady-state plasma insulin concentrations.

\[
\begin{align*}
    r_{SGU} &= r_{HGU} + r_{GGU} \\
    r_{HGU} &= r_{L} M_{HGU}^{GM} M_{HGU}^{LM} \\
    M_{HGU}^{GM} &= A(1 + \tanh[B(G_{L}^{H} - C)]
\end{align*}
\]

Glucose-mediated Hepatic Glucose Uptake

Review of the simulation of the validation dataset using the original model parameters shows an overestimation of splanchnic glucose uptake. The problem appears to be the relationship between glucose and its effect on the uptake of glucose by the liver. A separate training dataset is used to adjust the parameters of the glucose-mediated hepatic glucose uptake expression. The original and updated parameters of this expression are given in the table below.

There is insufficient data to derive all parameters of

\[
M_{HGU}^{GM} = A(1 + \tanh[B(G_{L}^{H} - C)]
\]

Therefore, A was adjusted to fit the experimental data. Then, C was adjusted so

\[
M_{HGU}^{GM} \big|_{C=1} = 1
\]

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<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
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References