A PHYSIOLOGICALLY-BASED QUANTITATIVE SYSTEMS PHARMACOLOGY MODEL OF THE INCRETIN HORMONES GLP-1 AND GIP

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Introduction

The incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are crucial for the regulation of postprandial glucose levels. Their therapeutic effects are mainly achieved by potentiation of insulin secretion (GLP-1 and GIP) and by slowing down the gastric emptying rate (GLP-1) [1].

The reported concentration data on the incretins are highly variable and often not comparable between sources due to high heterogeneity and poor specificity of commercially available assays [2]. Most of the data do not distinguish between the intact forms of the peptides and their primary metabolites and only report "total" concentrations. In addition, some data indicate that our understanding of GLP-1 and GIP metabolism is incomplete.

Objectives

1. Develop a physiology-based (PB) Quantitative Systems Pharmacology (QSP) model of GLP-1 and GIP metabolism to understand and predict the processes involved.
2. Incorporate the meal-induced endogenous secretion of the hormones.

Methods

The PB models for GLP-1 and GIP pharmacokinetics (PK) were developed with PK-Sim® and MoBi® as part of the Open Systems Pharmacology Suite (OSPS), version 7.2 [3]. An extensive literature research was performed to identify the processes involved in the metabolism of GLP-1 and GIP [excerpt: 1,4]. Mean model parameters were estimated by fitting the model to concentration-time profiles of intact GLP-1 and GIP, their primary metabolites, and/or "total peptide".

Data from 20 experiments of intravenous infusions of GLP-1 and/or GIP were used to identify the structure of the model and characterize the observed clearance rate variability. Parameters governing the secretion of the hormones were estimated by fitting the model to data from intraduodenal infusions of glucose [5,6].

Results

The structure of the developed PB model is presented in Figure 1. The model consists of five coupled protein PB sub-models.

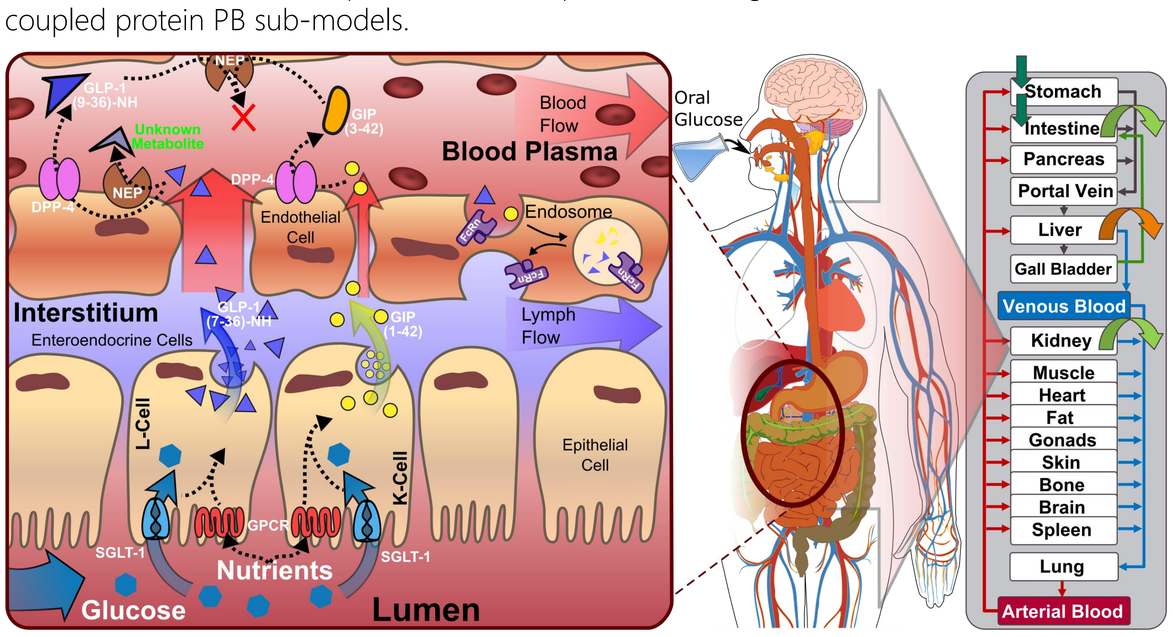

Figure 1: PB models of GLP-1 and GIP with the implemented metabolism: GLP-1 is secreted from the L-Cells located in the intestine. The active form, GLP-1(7-36) amide, is degraded by dipeptidyl-peptidase 4 (DPP-4) to GLP-1(9-36) amide and to an unknown metabolite by the neutral endopeptidase (NEP). The unknown yet measured metabolite is excreted via kidneys, while GLP-1(9-36) amide is degraded by NEP to an unmeasured entity.
GIP is secreted from the K-Cells in the intestine. The active form GIP(1-42) is degraded to GIP(3-42) by DPP-4, and the metabolite is further degraded by NEP.

GLP-1(7-36) amide is secreted from the L-Cells in the intestine and released into the blood. The secreted hormone is rapidly degraded to the inactive form GLP-1(9-36) amide by the enzyme dipeptidyl-peptidase 4 (DPP-4), primarily located in the vascular endothelial cells. GLP-1(9-36) amide is degraded by the enzyme neutral endopeptidase (NEP) to an unmeasured metabolite. A second, not yet specified metabolite of GLP-1(7-36) amide is produced by NEP. This unknown NEP metabolite is eliminated by renal tubular secretion and is probably detected by the assays directed against the "total" GLP-1.

The active form of GIP(1-42) is secreted from the K-Cells located in small intestine and metabolized to GIP(3-42) by DPP-4. GIP(3-42) is degraded by NEP. All modeled compounds are subjects to glomerular filtration.

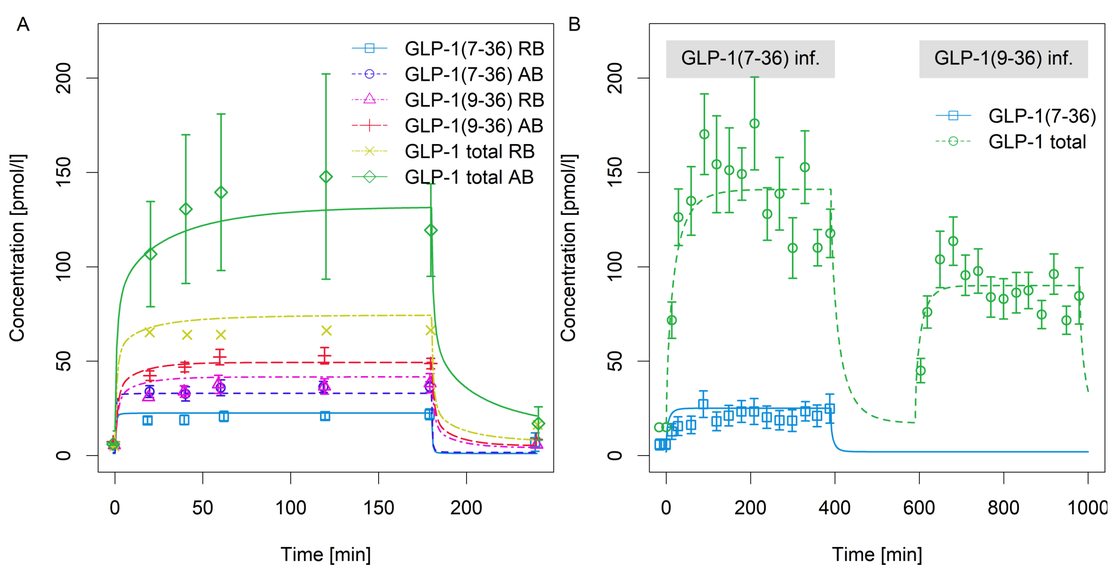

Figure 2: Simulations of intravenous GLP-1 infusions: Panel A: GLP-1(7-36) amide was infused with the rate 1.5 pmol/kg/min from minute 0 to 180. The concentrations of active GLP-1(7-36) amide, the DPP-4 metabolite GLP-1(9-36) amide, and the "total" GLP-1 were measured in arterial and renal venous blood. The total measured concentrations are higher then the sum of GLP-1(7-36) amide and GLP-1(9-36) amide. Data from [7,9]. **Panel B:** GLP-1(7-36) amide was infused with the rate 1.2 pmol/kg/min from minute 0 over 390 minutes. In the second experiment (simulated from minute 600), GLP-1(9-36) amide was infused with the same rate. Concentrations of active and "total" GLP-1 were measured. Data from [8]. AB, arterial blood; RB, renal venous blood

Figure 2 presents exemplary comparisons of simulation results with observed data. The overall performance of the combined GLP-1 and GIP PB models is assessed with a simulated-versus-observed plot in Figure 3, Panel A. The majority of the 483 compared points are within the two-fold deviation range, whereby the deviations in the lower concentration range are to be expected due to low precision of the assays.

To capture the extremely high variability of reported concentrations during intravenous infusion experiments, variation of the relative expression of DPP-4 and NEP in vascular endothelium was necessary. Figure 3, Panel B shows the identified values of the relative expression for each simulated dataset. No correlation between the estimated values and other covariates, such as sex, age, BMI, or healthy or diabetic state, could be observed.

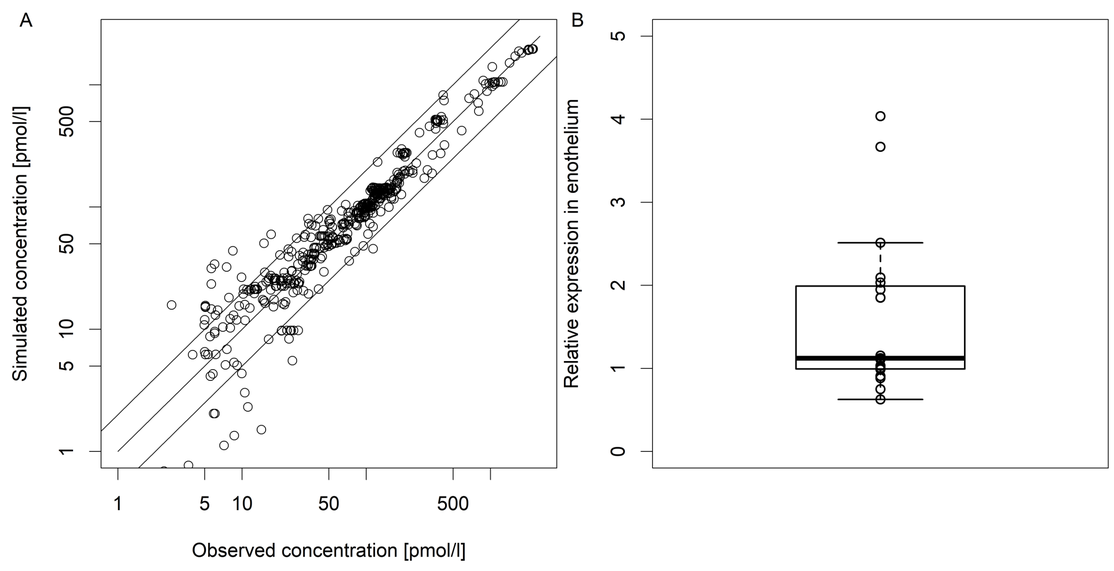

Figure 3: Performance of the combined GLP-1 and GIP models: Panel A:. Comparison of simulated (y-axis) and observed (x-axis) concentrations of GLP-1 and GIP gathered in infusion experiments. Measurements include concentrations of GLP-1(7-36) amide, GLP-1(9-36) amide, "total" GLP-1, GIP(1-42), and "total" GIP. A total of 483 points are compared. **Panel B:** Estimated relative expression values of DPP-4 and NEP located in vascular endothelium.

Secretion processes of GLP-1 and GIP are modeled as constant basal components and glucose-dependent components. Secretion of GLP-1 is potentiated by the presence of glucose in the duodenum, while a certain concentration threshold is necessary to invoke the potentiation. Secretion of GIP depends on the rate of glucose absorption mediated by the sodium-glucose co-transporter 1 (SGLT1) located in the direct proximity of the secreting K-Cells. Figure 5 compares simulated with observed concentrations of the incretins during intraduodenal infusions of glucose at the rates 1.1 kcal/min or 2.2 kcal/min[6].

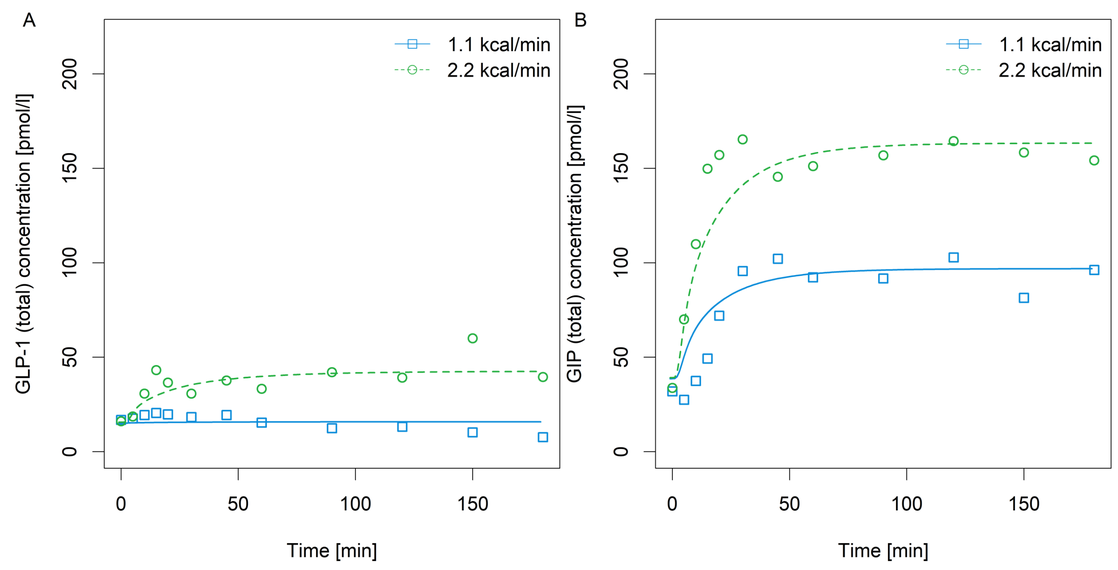

Figure 5: Secretion of GLP-1 (Panel A) and GIP (Panel B) during intraduodenal glucose perfusion. Glucose was infused intraduodenally at rates of 1.1 kcal/min or 2.2 kcal/min and the responses of GLP-1 and GIP were measured [6]. Simulated results (lines) are compared with observed data (symbols). GLP-1 data were normalized to a basal value of 14 pmol/l due to exceptionally low repored values and the unnkown assay used.

Conclusions

The here presented PB QSP model gives new insights into the metabolism of GLP-1 and predicts the existence of a metabolite that is not yet characterized but measured by the assays targeting the "total" GLP-1 concentrations. The model could be used to estimate the concentrations of intact peptides from "total" concentration data, and better understand the observed effects of DPP-4 inhibitors. In a next step, the model will be integrated into a PB QSP Diabetes Platform [10,11] to couple the PK to the pharmacodynamics on gastric emptying, glucose metabolism, and insulin and glucagon secretion.

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