



Using allometric scaling on an integrated glucose insulin model for humans to investigate anti-diabetics drug effects in rats.

Oskar Alskär, Mats O Karlsson, Maria Kjellsson

Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Background

Proceeding from animal experiments into humans is a major problem in drug development. It would therefore be of importance to be able make good predictions of clinical response based on results from animal studies.

Objective

The aim of this project was to allometrically down-scale an integrated glucose insulin (IGI) model, developed on clinical data [1], to characterize the relationship between glucose and insulin in male Han Wistar rats after an intravenous glucose tolerance test (IVGTT) with and without administration of incretin mimetic Exendin-4 (EX-4).

Methods

Data of blood glucose and plasma insulin from an IVGTT was used in this population analysis. The previously published study [2] was conducted in 28 conscious, healthy male Han Wistar rats, of which 7 were injected with EX-4. Three different glucose doses (0.2, 0.5, 1.0 g glucose/kg LBM) and two different doses of EX-4 (2.4, 3.2 µg/kg LBM) were investigated.

Initially, the glucose/insulin-system was described by modeling the data from the 21 placebo rats. The disposition parameters and feed-back rate constants in the IGI model were allometrically scaled from healthy humans, using an exponent of 1 for volume, 0.75 for clearance and -0.25 for rate constants, estimating only the control mechanisms between glucose and insulin.

In the second step the drug effect of EX-4 was characterized by modeling the data from the 7 drug treated rats. The control mechanisms were fixed to the values obtained in the first step. As no concentration data of EX-4 was available, PK was predicted using a previously published target mediated pharmacokinetic model [3] of EX-4 in rats.

Model development was guided by goodness of fit, objective function value and predictive performance, assessed using VPCs. All modeling was performed using NONMEM 7.2.

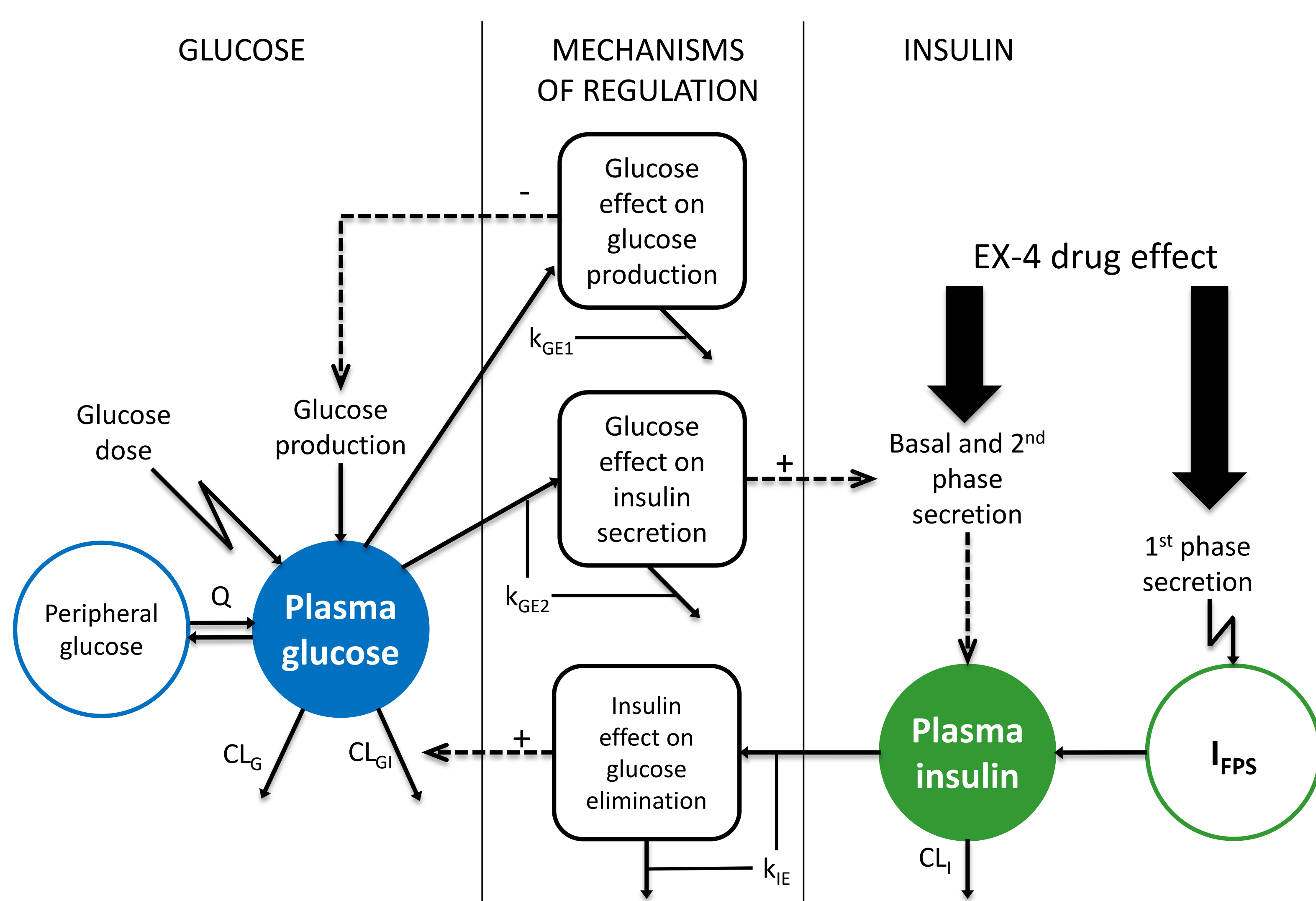


Figure 1. Schematic representation of the IGI model

Results

Using allometric scaling of the system parameters and only estimating the control mechanisms described the placebo data well. The model was able to identify the most plausible effect location of EX-4, on both phases of insulin secretion. A linear model for the EX-4 effect gave the best fit of the investigated concentration-effect relationships. The extremely high insulin concentrations that were observed in the drug treated rats caused glucose to be too rapidly eliminated in the model, therefore a nonlinear insulin-dependent glucose elimination was added to the model and estimated (GELI).

Table 1. Comparison of parameter estimates between different models

Parameter	Placebo model 1 Emax on IFST	Placebo model 2 Emax on IFST and GPRG=0	Human (for comparison)
OFV	-709.376	-673.751	-
IFST (mU)	15.4	14.8	704
IPRG	1.69	1.65	1.42
RESG	0.0752	0.0929	0.0436
RESI	0.312	0.306	0.252
RESE	0.687	0.68	3.31
GPRG	-3.78	0 FIX	-2.79
GSS (mg/dl)	116	119	-
ISS (mU/L)	25.9	27.7	-
IFSTG50 (mg)	36.2	37.7	-
BSV GSS	13.1 %	13.4 %	-
BSV ISS	48.2 %	48.5 %	-

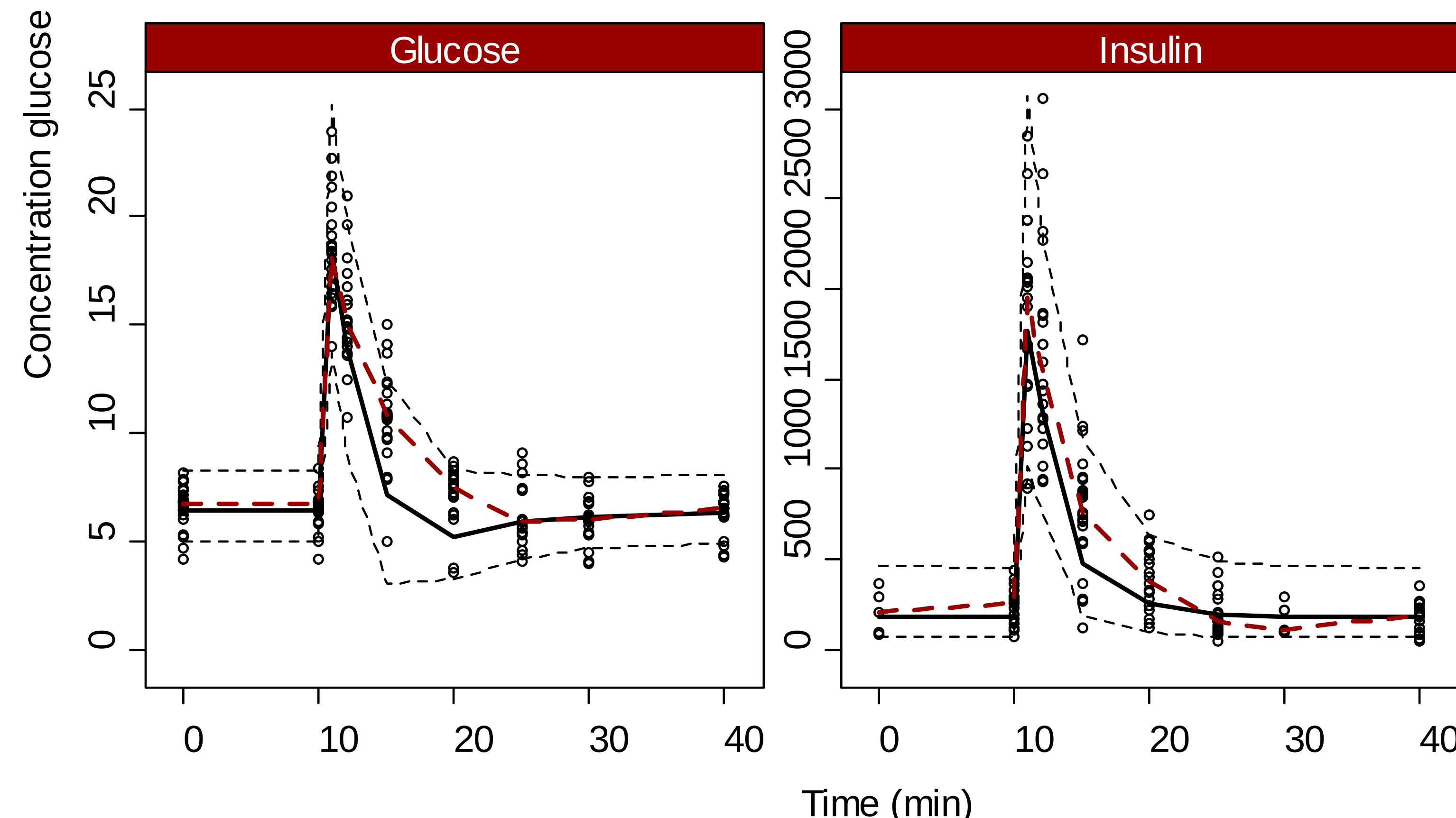


Figure 2. VPC of the allometrically scaled IGI model on placebo data. Red dashed line - median of the observations, black lines - 5th, 50th and 95th percentile of the predictions.

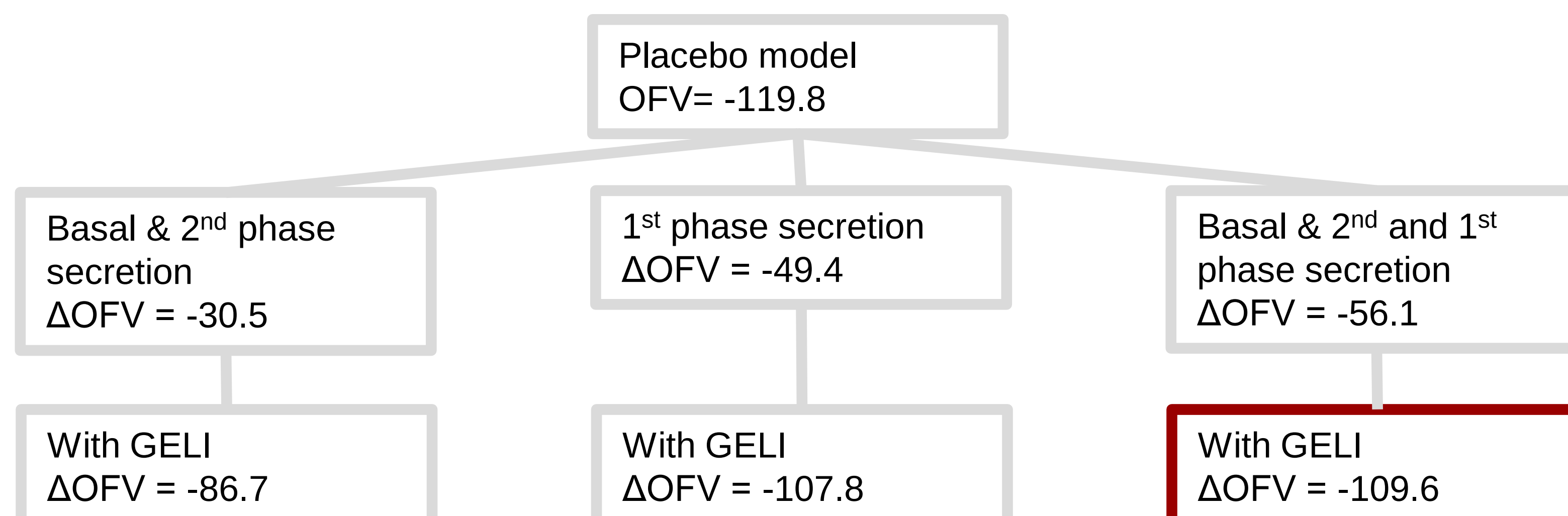


Figure 3. Schematic representation of the model development for drug effect. ΔOFV is compared to placebo model 1 presented in table 1.

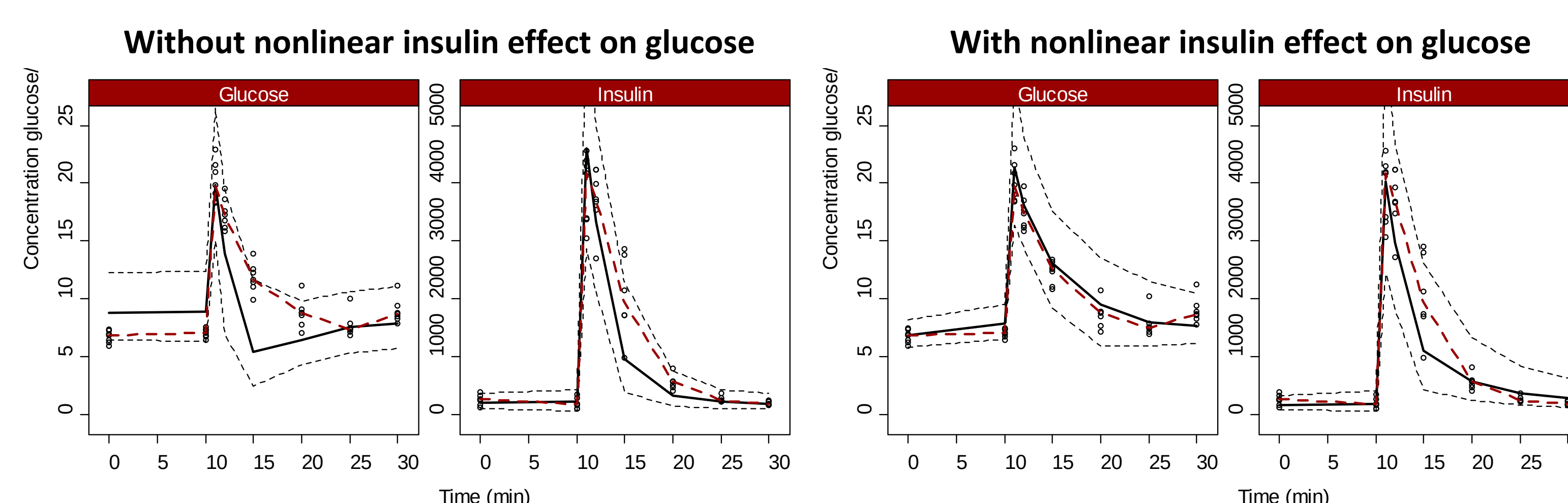


Figure 4. VPC of the drug effect on both the basal & 2nd phase and 1st phase insulin secretion without and with nonlinearity on the glucose elimination.

Conclusions

- It was possible to allometrically down-scale the IGI-model developed for humans to characterize glucose/insulin time course in male Han Wistar rats
- The model could identify the correct mechanism of action and quantify the effect of EX-4

References

- Silber HE, Jauslin PM, Frey N, et al. An integrated model for glucose and insulin regulation in healthy volunteers and type 2 diabetic patients following intravenous glucose provocation. *J Clin Pharmacol*, 2007; 47: 1159-1171.
- Frangioudakis G, Gyte AC, Loxham SJG, Poucher SM. The intravenous glucose tolerance test in cannulated Wistar rats: A robust method for the in vivo assessment of glucose-stimulated insulin secretion. *J Pharmacol Toxicol Met*, 2008; 57: 106-113.
- Gao W, Jusko WJ. Target-mediated pharmacokinetic and pharmacodynamics model of exendin-4 in rats, monkeys and man. *Drug Metab Dispos*, 2012; e-pub.