Model of the Glucose-Insulin-Glucagon Dynamics after Subcutaneous Administration of a Glucagon Rescue Bolus in Healthy Humans

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Model of the Glucose-Insulin-Glucagon Dynamics after Subcutaneous Administration of a Glucagon Rescuer Bolus in Healthy Humans

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In healthy individuals, insulin and glucagon work in a complex fashion to maintain blood glucose levels within a narrow range. This regulation is disturbed in patients with diabetes. The hepatic glucagon response to an oral glucose load depends on the current insulin concentration and thus endogenous glucose production (EGP) cannot be modelled without knowledge of the insulin concentrations of both hormones in plasma. In this manuscript, a new model of the glucagon-glucose-glucaagon dynamics in men including secretion of EGP.

Ten healthy subjects received a 4 mg subcutaneous (SC) glucagon bolus (Glucagen®). Plasma glucose samples were collected until 300 minutes post dose and analyzed for glucagon, insulin, and glucose concentrations. All observations were used to fit a physiological model of the glucagon-glucose-glucaagon dynamics using the non-linear mixed-effects methodology with an improved PK/PD model fit of glucose (in silico simulation of dual hormone artificial pancreas algorithm).

There is currently no consensus on a model describing the endogenous glucose production (EGP) as a function of glucagon. Recent studies argue in favor of a multiplicative effect of insulin and of glucagon on EGP. The model parameter simultaneously describes the glucagon dynamics in healthy humans at both low and high glucagon concentrations (0-300 mIU/L) and physiologically realistic concentrations

Table 1. Average PK and PD parameter estimates and % confidence intervals. *Fixed parameter.

References


Figure 1: 3D PK/PD model fit of glucose (red), interpolated endogenous insulin (blue), and PD model fit of glucagon with 95% confidence interval (teal) for each of the ten subjects.

Figure 2: PK model fit of glucagon (red), interpolated endogenous insulin (blue), and PK model fit of glucose with 95% confidence interval (red) for each of the ten subjects.

4 Results

There is currently no consensus on a model describing the endogenous glucose production (EGP) as a function of glucagon. Recent studies argue in favor of a multiplicative effect of insulin and of glucagon on EGP. The model parameter simultaneously describes the glucagon dynamics in healthy humans at both low and high glucagon concentrations (0-300 mIU/L) and physiologically realistic concentrations.