Insulin Signalling & Glucose Homeostasis

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1 The Whole-Body Level

The whole-body level is adopted from Dalla Man et al. [1]. The module for insulin-responding glucose uptake is subdivided proportionally (20/80) into muscle and adipose tissue parts. The parameters are all the same and a schematic overview of the whole-body level is given by Figure 1.

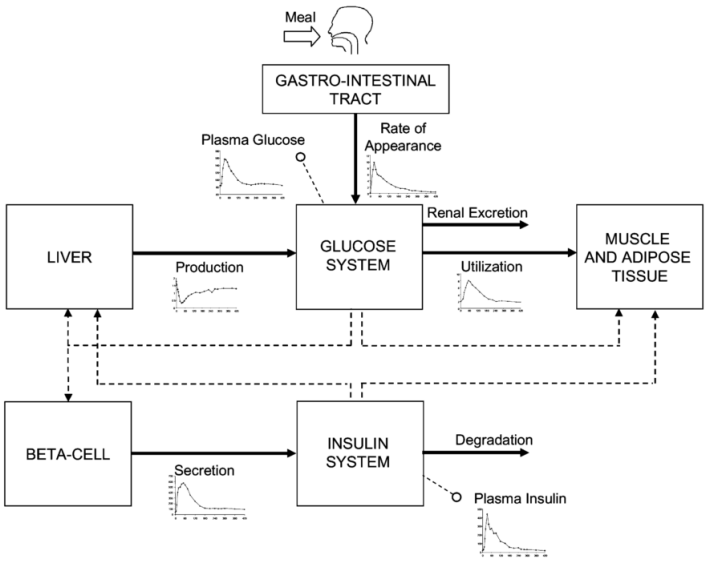

Figure 1: The whole-body level

1.1 Glucose kinetics

The glucose kinetics module describes the dynamic change in glucose concentration in the two compartments plasma and tissues and is shown in Figure 2.

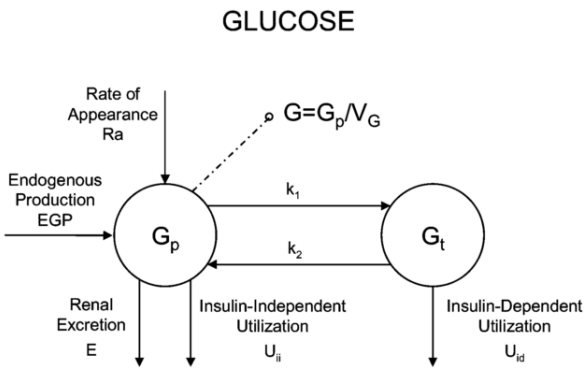

Figure 2: Glucose kinetics

1.2 Insulin kinetics

The insulin kinetics module describes the dynamic changes in insulin concentration in the two compartments plasma and liver and is shown in Figure 3.

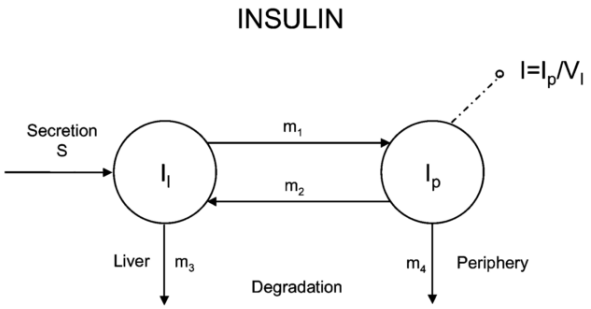

Figure 3: Insulin kinetics

1.3 Glucose rate of appearance (GI)

The GI absorption model is adopted from Dalla Man et al. [2]. In this model, the glucose enter the system and travel through three compartments before it appears in the plasma. The glucose transit through the stomach and intestine by assuming the stomach to be represented by two compartments (one for solid and one for triturated phase), while a single compartment is used to describe the gut. Figure 4 shows a schematic of the model.

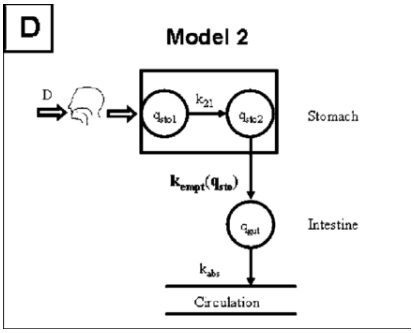

Figure 4: Glucose rate of appearance

1.4 Endogenous glucose production (liver)

The glucose production in the liver is dependent on glucose in the plasma, a delayed insulin signal from the plasma and insulin in the portal vein. The functional description of EGP in terms of glucose and insulin signals is described in Dalla Man et al. [3]. Figure 5 shows a schematic of the model.

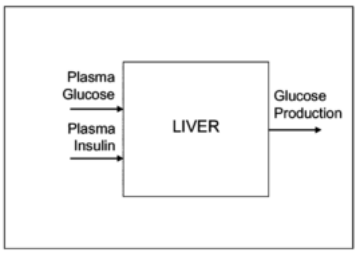

Figure 5: Glucose rate of appearance

1.5 Glucose Uptake

The glucose uptake by the insulin sensitive tissues is a sum of glucose uptake in muscle and adipose tissue. Figure 6 shows a schematic of the model.

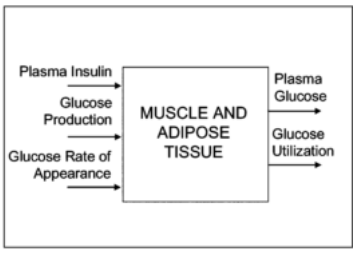

Figure 6: Glucose uptake in muscle and adipose tissue

1.5.1 Muscle tissue

The glucose uptake in the muscle tissue depends on the interstitial insulin and the glucose tissue concentrations.

1.5.2 Adipose tissue

The glucose uptake by the adipose tissue (vglucoseuptake) is described below in the adipose tissue level, in the section Glucose uptake dynamics.

1.6 Insulin Secretion (β cells)

Insulin is produced and secreted from the beta cells in the pancreas. The amount of insulin that is secreted is calculated from the glucose concentration in the plasma

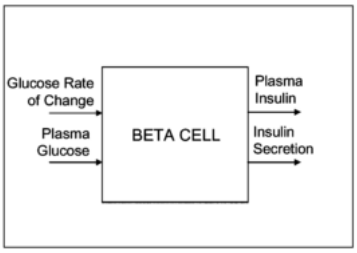

Figure 7: Insulin secretion

1.7 Glucose Renal Excretion

When the concentration of glucose in the blood is high, glucose will be excreted to the kidneys. However, this will not happen for healthy individuals so we set the renal excretion to 0.

2 The Adipose Tissue Level

The adipose tissue level is developed by us in this study. We have tested a number of hypotheses to find a minimal model (Md3), partly based on Brännmark et al. [4], that can explain all our experimental data and fit the module constraints from the whole-body level. This hypothesis we have then expanded to include interesting proteins within the adipocyte. The parameters of this level were optimized to gather all the acceptable parameter sets. A schematic overview of the adipose tissue level is the following figure.

2.1 IRS1 and X dynamics

The insulin receptor substrate is activated by phosphorylation from active insulin receptor states from the insulin binding level described below. Also, positive feedbacks from downstream proteins further activate IRS1. The unknown

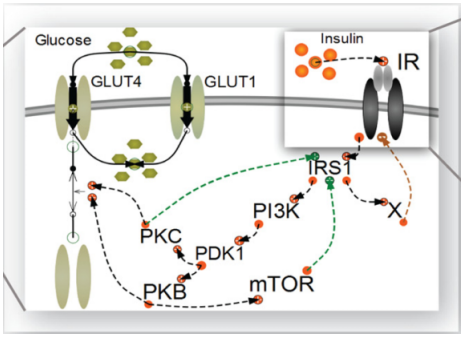

Figure 8: The adipose tissue level

protein X is activated by IRS1iP and act as a negative feedback to the insulin receptor. This part of the adipose tissue level is adopted from and further described in Brännmark et al. [4], with the difference that we have now replaced the insulin receptor states with corresponding ones from the insulin binding level. Recall that we mark connections between the adipose tissue level and the insulin binding level with green.

2.2 PI3K and PDK1 dynamics

PI3K is activated by IRS1 and subsequently PDK1 is activated by PI3K. We assume that the activations follow simple mass-action kinetics.

2.3 PKC and PKB dynamics

Both PKB and PKC are activated by PDK1 in its active form. We assume that the activations follow simple mass-action kinetics.

2.4 mTOR and GLUT4 dynamics

mTOR is activated by PKB in its active form. The glucose transporters (GLUT4) are moving from the cytosol to the plasma membrane both at a basal level and when activated by PKB and PKC. We assume that the activations follow simple mass-action kinetics.

2.5 Glucose uptake dynamics

The glucose uptake in the adipose tissue comes in this model from three terms; glucose transporter 1 (non-insulin dependent), glucose transporter 4 (insulin-dependent through the insulin signaling cascade and thus through GLUT4), and blood flow (directly insulin-dependent). We assume that the glucose uptake also depends on the interstitial glucose concentration (G_t, from the whole-body level) and that the dependency is saturated.

2.6 Parameters

3 The Insulin Binding Level

The insulin binding level is taken from Kiselyov et al. [5]. We took the model structure and merged with our adipose tissue module. The parameters in Kiselyov et al. [5] were fitted to data from other cell types so we used optimization to gather the acceptable parameter sets. A schematic overview of the insulin binding level is found below.

3.1 The inactive receptor states

The following insulin receptor states can bind one or two insulin molecules, or be unbound. The states that bind at least one insulin molecule can be activated.

3.2 The active receptor states

When insulin is bound to the receptor it can be activated and also phosphorylated. The active states activate IRS1 at the adipose tissue level (above).

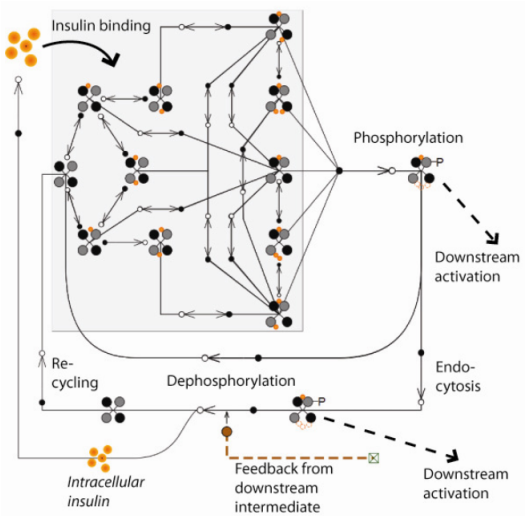

Figure 9: The insulin binding level

3.3 The internalisation process

We included internalization in the insulin binding model to be able to relate the insulin binding level with the adipose tissue level. This part is based the Mifa model in Brännmark et al. [4].

3.4 Reactions

Here all reactions of the insulin binding level are gathered. Most of the reactions follow simple mass action kinetics, but R44 and R45 that belong to our addition of internalization are saturated. These reactions describe the action of a feedback from a downstream signaling intermediate (XP) and these equations are based on Brännmark et al. [4]. All other reactions are from Kiselyov et al. [5].

3.5 Variables

The variables S1 and S2 describe the interstitial concentration of insulin as a monomer (S1) and as a dimer (S2) in molars. The dimer will not form in the low insulin concentrations in the physiological situation.

3.6 Parameters

For two of the parameters, K4 and K8, we used the values from Kiselyov et al. [5], and for the others we used optimization to find the acceptable values.

References

[1] Chiara Dalla Man, Robert A Rizza, and Claudio Cobelli. Meal simulation model of the glucose-insulin system. *IEEE transactions on biomedical engineering*, 54(10):1740–1749, 2007.

[2] Chiara Dalla Man, Michael Camilleri, and Claudio Cobelli. A system model of oral glucose absorption: validation on gold standard data. *IEEE Transactions on Biomedical Engineering*, 53(12):2472–2478, 2006.

[3] Chiara Dalla Man, Gianna Toffolo, Rita Basu, Robert A Rizza, and Claudio Cobelli. A model of glucose production during a meal. In *Engineering in Medicine and Biology Society, 2006. EMBS'06. 28th Annual International Conference of the IEEE*, pages 5647–5650. IEEE, 2006.

[4] Cecilia Brännmark, Robert Palmér, S Torkel Glad, Gunnar Cedersund, and Peter Strålfors. Mass and information feedbacks through receptor endocytosis govern insulin signaling as revealed using a parameter-free modeling framework. *Journal of Biological Chemistry*, 285(26):20171–20179, 2010.

[5] Vladislav V Kiselyov, Soetkin Versteyhe, Lisbeth Gauguin, and Pierre De Meyts. Harmonic oscillator model of the insulin and igf1 receptors' allosteric binding and activation. *Molecular systems biology*, 5(1):243, 2009.