

# RECEPTOR-BASED MODELS OF INSULIN SATURATION DYNAMICS

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## ABSTRACT

Normalisation of blood glucose by intensive insulin therapy has beneficial effects on the mortality and morbidity of intensive care patients, but also increases the risk of life threatening hypoglycaemia. Attempts to improve the control of blood glucose with model based systems have shown promising results, but require that the saturation of the effect of insulin on glucose balance at high plasma insulin concentrations is modeled appropriately. This saturation is often ignored in commonly used models of glucose metabolism, such as the minimal model, but may be important in patients with reduced insulin sensitivity.

In this paper three simple models of insulin saturation are explored, all of them ascribing saturation to properties of the binding between insulin and its receptor. The models can be fitted to data from patients with normal or near normal insulin sensitivity, and they all predict that the plasma concentration at which half-insulin effect is reached is about 50 mU/l, also in patients with reduced insulin sensitivity. This prediction can be tested against clinical data, and if true will lead to advice on insulin therapy that avoids infusions that exceed 8 U/hour, in order to avoid saturation and the associated risk of hypoglycaemia.

## KEY WORDS

Medical decision support, modelling, intensive insulin therapy, insulin pharmacodynamics

## 1. Introduction

Insulin regulates blood glucose by modifying the uptake of glucose by tissues such as muscle and fat and the uptake or release of glucose by the liver. This net rate of transport of glucose is usually referred to as the endogenous glucose balance, and it does not include glucose absorbed from the intestines. At high concentrations of insulin in the plasma, the effect of insulin on the endogenous balance saturates [1, 2, 3]. Fig. 1 gives an example of such data from Insulin Dependent

Diabetes Mellitus (IDDM) patients showing the saturation at high concentrations of plasma insulin.

In IDDM patients the saturation only plays a modest role. A typical daily dose of insulin is 40 U, corresponding to an average infusion rate of about 0.4 mU/kg/min for a 70 kg patient. In Fig. 1 half insulin effect is reached at an infusion rate of 0.4 mU/kg/min. It can thus be seen that insulin concentrations in IDDM patients tend to fall in a range below that where saturation become prominent and commonly used models of insulin dynamics, such as the minimal model ignore the saturation [4].

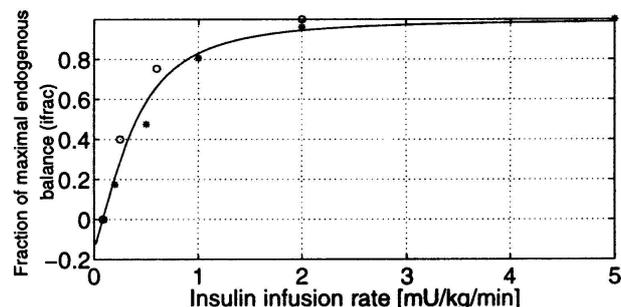


Fig. 1. The fraction of endogenous balance (ifrac) vs. insulin infusion rate. Data marked by \* from [5], data marked by o from [6]. Figure adapted from [7].

Clinically saturation becomes important when treating patients with stress-induced hyperglycaemia with insulin in order to bring their blood glucose down. Protocols that provide intensive insulin therapy to patients in the intensive care unit with stress-induced hyperglycaemia can provide substantial benefits in terms of reductions in morbidity and mortality, but also suffer from the problem that the incidence of life threatening episodes of hypoglycaemia increases. [8, 9, 10]. An insulin infusion rate of 2 mU/kg/min corresponds to an insulin infusion rate of 8.4 U/h for a 70 kg patient, and most protocols allow insulin infusion rates in excess of this. According to Fig. 1 this is clearly in the region where insulin action is almost completely saturated, and this means that insulin is no longer an effective way of modifying the endogenous balance. Even worse, in case of hypoglycaemia, it will take a long time before the extracellular insulin concentration can be reduced, since this largely depends

on a relatively slow diffusion of insulin across the vascular bed, from the extracellular space to the blood stream. Potentially, this can aggravate and prolong episodes of hypoglycaemia. The clinical need to reduce blood glucose in patients with stress-induced hyperglycaemia, while keeping the risk of hypoglycaemia low, has lead to the development of computer-based models and algorithms (11, 12). That in turn leads to a need to develop a model of saturation of insulin effects. The purpose of this paper is to generate models of the saturation of the effects of insulin on the endogenous glucose balance. The models should be able to reproduce data from patients with normal insulin sensitivity, and they should be able to provide a prediction of the behaviour of insulin saturation in patients, a prediction that can be tested against clinical data.

## 2. Three models of insulin dynamics

In the following, three simple models of insulin dynamics will be explored and results compared to the saturation dynamics as given in Fig. 1.

The saturation may be a property of the binding of the insulin to the insulin receptor, which is bound to the cellular membrane, or it may be a property of the intracellular signalling, that translates the binding of insulin to its receptor to a modulation of the endogenous balance. If the mechanism responsible for saturation is part of the intracellular signalling pathway, then a modification of the concentration at which half effect is reached is likely, while that concentration should stay constant, if the effect is due to the properties of the binding between insulin and its receptor. An experimental determination of the threshold of saturation during stress-induced hyperglycaemia has to our knowledge not been performed. However, it is quite clear that saturation does occur, as evidenced by the fact that insulin alone, even in high doses, is not sufficient to normalise blood glucose in patients with severe stress-induced hyperglycaemia [13].

### 2.1 Insulin binding to insulin receptor (IIR)

In this simple model the binding of insulin to the insulin receptor (equation 1) will be assumed to follow a normal mass action relationship (equations 3 and 4).



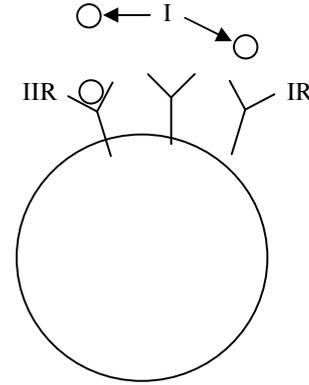
where I represents the interstitial insulin concentration, IR the amount of membrane bound insulin receptors and IIR the amount of insulin-insulin receptor complexes (Fig. 2).

$$R1 = I * IR * k_1 \quad (\text{eq. 2})$$

$$R2 = IIR * k_2 \quad (\text{eq. 3})$$

where R1 is the rate of formation of the insulin-insulin receptor complexes and R1 is the rate of insulin-insulin

receptor complexes unbinding into insulin and the insulin receptor.



**Fig. 2. Model of insulin (I) binding and unbinding to the membrane bound insulin receptor (IR) to form the insulin-insulin receptor complex (IIR).**

In this model it is assumed that the number of insulin receptors remains constant, whether bound or unbound to insulin, i.e. that:

$$IR + IIR = k_3 \quad (\text{eq. 4})$$

It is also assumed that the effect of insulin, EI, is proportional to the number of insulin receptors bound to insulin:

$$IE_{IIR} = IIR * k_4 \quad (\text{eq. 5})$$

If we assume that steady state has been achieved in the reaction given by equation 1, then the two rates, R1 and R2, of equations 3 and 4 are equal:

$$I * IR * k_1 = IIR * k_2 \quad (\text{eq. 6})$$

Insertion of eq. 4 gives:

$$I * (k_3 - IIR) * k_1 = IIR * k_2 \Leftrightarrow$$

$$I * k_3 * k_1 / k_2 = I * IIR * k_1 / k_2 + IIR$$

$$IIR = I * k_3 / (k_2 / k_1 + I) \quad (\text{eq. 7})$$

which together with eq. 5 gives:

$$IE_{IIR} = k_3 * k_4 * I / (k_2 / k_1 + I) \quad (\text{eq. 8})$$

If we let  $V_1 = k_3 * k_4$  and  $Q_1 = k_2 / k_1$ , then we can recognize equation 8 as having the Michaelis-Menten form, with  $Q_1$  as the Michaelis-Menten constant and  $V_1$  as the maximal rate:

$$IE_{IIR} = V_1 * I / (Q_1 + I) \quad (\text{eq. 9})$$

## 2.2 Insulin binding to insulin receptor followed by phosphorylation (IIRP)

This model is similar to model 1, with the addition of kinetics for the endocytosis and phosphorylation of the insulin/insulin receptor complex and for the subsequent recycling of the receptor back to the cell membrane. An intracellular reservoir of phosphorylated insulin receptors has thus been added to the model. Assuming that steady state is achieved and that the insulin effect is proportional to the rate of phosphorylation, then the solution of these equations also leads to Michaelis-Menten kinetics:

$$IE_{IIRP} = V_2 * I / (Q_2 + I) \quad (\text{eq. 10})$$

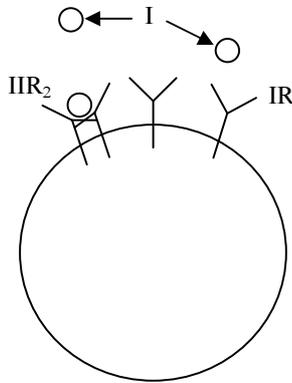
Since this is algebraically equivalent to the solution for the IIR-model, the solution will not be derived here in the interest of brevity.

## 2.3 Insulin binding to an insulin receptor dimer (IIR<sub>2</sub>)

In this model the kinetics of the binding of insulin to its receptor has been modified to reflect that insulin actually binds to a dimer of the insulin receptor. Let us postulate the reaction:



where I represents the interstitial insulin concentration, IR the amount of membrane bound insulin receptors and IIR<sub>2</sub> the amount of insulin-insulin receptor dimer complexes (Fig. 3).



**Fig. 3. Model of insulin (I) binding with the insulin receptor (IR) to form the insulin-insulin receptor dimer (IIR<sub>2</sub>).**

The associated mass action equations will then be:

$$R_3 = I * IR^2 * k_5 \quad (\text{eq. 12})$$

$$R_4 = IIR * k_6 \quad (\text{eq. 13})$$

where R<sub>1</sub> is the rate of formation of the insulin-insulin receptor dimer complexes and R<sub>2</sub> is the rate of insulin-insulin receptor dimer complexes unbinding into insulin and the insulin receptor.

In this model it is assumed that the number of insulin receptors remains constant, whether bound or unbound to insulin, i.e. that:

$$IR + 2 * IIR_2 = k_7 \quad (\text{eq. 14})$$

It is also assumed that the effect of insulin, EI<sub>3</sub>, is proportional to the number of insulin receptors bound to insulin:

$$IE_{IIR2} = IIR * k_8 \quad (\text{eq. 15})$$

If we assume that steady state has been achieved in the reaction given by equation 11, then the two rates, R<sub>3</sub> and R<sub>4</sub>, of equations 12 and 13 are equal:

$$I * IR^2 * k_5 = IIR * k_6 \quad (\text{eq. 16})$$

Insertion of eq. 14 gives:

$$I * (k_7 - 2 * IIR)^2 * k_1 = IIR * k_6 \Leftrightarrow \\ I * k_3 * k_1 / k_2 = I * IIR * k_1 / k_2 + IIR$$

Rearrangement gives:

$$IIR^2 - (k_7 + k_6 / (4 * k_5 * I)) * IIR + k_7^2 / 4 = 0 \quad (\text{eq. 17})$$

Insertion of eq. 15 gives:

$$IE_{IIR2}^2 - (k_7 / k_8 + k_6 / (4 * k_5 * k_8 * I)) * IE_{IIR2} + (k_7 / k_8)^2 / 4 = 0 \quad (\text{eq. 18})$$

Renaming  $\alpha = k_6 / (8 * k_5 * k_8)$  and  $\beta = k_7 / k_8$  gives:

$$IE_{IIR2}^2 - (\beta + 2 * \alpha / I) * IE_{IIR2} + \beta^2 / 4 = 0 \quad (\text{eq. 19})$$

The solutions to this second order equation are:

$$IE_{IIR2} = [(\beta + 2 * \alpha / I) \pm \sqrt{((\beta + 2 * \alpha / I)^2 - \beta^2)}] / 2 \\ = \beta / 2 + \alpha / I \pm \sqrt{((\alpha / I)^2 + \beta * \alpha / I)} \\ = \beta / 2 + \alpha / I * (1 \pm \sqrt{1 + \beta * I / \alpha}) \quad (\text{eq. 20})$$

We want  $IE_{IIR2} \rightarrow 0$  for  $I \rightarrow 0$ , and that eliminates the solution with plus before the square root. We thus have:

$$IE_{IIR2} = \beta / 2 + \alpha / I * (1 - \sqrt{1 + \beta * I / \alpha}) \quad (\text{eq. 21})$$

## 2.4 Comparison to the insulin saturation dynamics in normal subjects

The experimentally determined data points in Fig. 1 were fitted by a function of the form:

$$EI_{exp} = (INF - INF_0) / ((INF - INF_0)^d - k^d)^{1/d} \quad (\text{eq. 22})$$

A least squares fit yielded the parameter values  $INF_0 = 0.083$  mU/kg/min;  $k = 0.539$  mU/kg/min; and  $d = 1.77$  [7]. This is the curve plotted in Fig. 1 and the curve labeled d-power in Fig. 4.

It was also found from experiments performed by different groups (see [7] for references) that for IDDM patients, the average plasma insulin concentration (I) in response to the insulin infusion rate (INFR) could be calculated as:

$$I = \text{INF} * C \quad (\text{eq. 23})$$

where  $C = 98.1 \text{ kg min / l}$ . This conversion factor was inserted into the equations for insulin effects,  $E_{\text{IIR}}$  (eq. 9),  $E_{\text{IIRP}}$  (eq. 10),  $E_{\text{IIR}_2}$  (eq. 22) and the least squares method was used to fit the parameters of the equations to the data points.

Due to the mathematically identical expressions for the insulin effect for the IIR and the IIRP models these gave identical fits, with the Michaelis-Menten constants  $Q_1 = Q_2 = 0.28 \text{ mU/kg/min}$ . All three models gave an intercept with the insulin effect axis at a larger negative value than the d-power fit. The intercept estimates the hepatic glucose production in the absence of insulin.

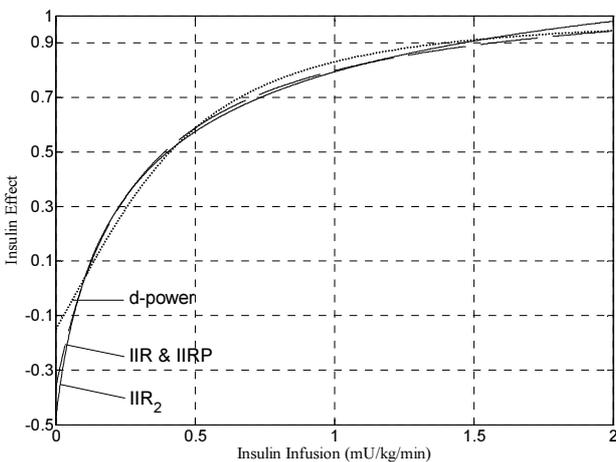


Fig. 4. Insulin effect curves for the three models fitted to experimental data and for the d-power fit from Fig. 1.

It can be seen from Fig. 2, that for low insulin infusion rates, the insulin effect curve for all three models is steeper than the d-power fit to the experimental data. All three models have half-effect at about  $0.3 \text{ mU/kg/min}$ , while the d-power fit has half-effect at  $0.4 \text{ mU/kg/min}$ .

### 3. Conclusion

Three simple models of insulin dynamics have been presented. Two of those, the IIR and the IIRP models, gave identical shapes of the insulin effect curves, corresponding to Michaelis-Menten dynamics (eq.s 9 and 10). The third model,  $\text{IIR}_2$ , gave a shape that corresponded more closely to the curve fitted to the experimental data. Given the noise in the data, it can not be stated that one curve fits the data significantly better than the other. The most important observation is however, that if the saturation is ascribed to the dynamics

of the binding between insulin and its receptor, then all three models give approximately the same value for the plasma insulin concentration at which half-effect is reached, about  $0.3\text{-}0.4 \text{ mU/kg/min}$ , or, using the conversion factor  $C$ , at a plasma concentration of about  $50 \text{ mU/l}$ . This also agrees with the half-effect concentration of about  $30 \text{ mU/l}$  given by Burén [14] for adipose tissue *in vitro*, given that the extracellular insulin concentration seen by the tissues is about 60% of the plasma concentrations [15].

This result can be incorporated in models of the endogenous glucose balance and can be verified against experimental data. If the result provided by these models prove correct, then it has clear implications for computer models that advise on intensive insulin therapy for patients with reduced insulin sensitivity, either due to NIDDM or due to stress-induced hyperglycaemia. In that case, models of the minimal model type [4] can not be used, due to their lack of saturation effects. It is also clear that large insulin infusion rates should be avoided, since saturating insulin doses remove insulin as a factor that can be used to regulate blood glucose and places the patient at risk of hypoglycaemia, if the patients' insulin sensitivity for what ever reason begins to normalize.

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