

A mechanistic model for the involvement of the neonatal Fc receptor in IgG disposition



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Introduction

A recognised function of the neonatal Fc receptor (FcRn) is to protect IgG from catabolism by endosomal proteases, via FcRn-IgG binding in endosomes. The bound IgG is recycled back into circulation, escaping the catabolism. Successful quantification of this binding/recycling process can inform the understanding of the kinetics and effect level of an endogenous or exogenous IgG.

Objectives

The objective of the work reported here was to build a mathematical model that could be used to describe the circulating level of an endogenous or exogenous IgG under normal physiological conditions and to predict its level change when the system was perturbed by a number of causes such as disease conditions and pharmacological treatments.

Methods

We described the physiological model in Figure 1, where an FcRn antibody deprives IgG binding to the receptor, by the general model in Figure 2, which describes relevant pathways as first-order processes.

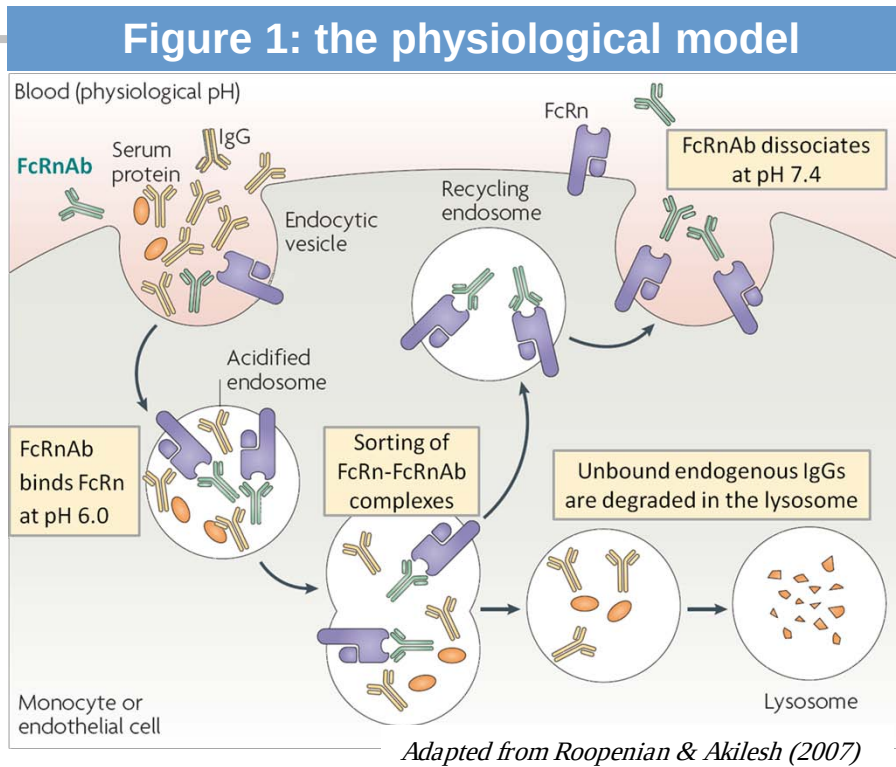
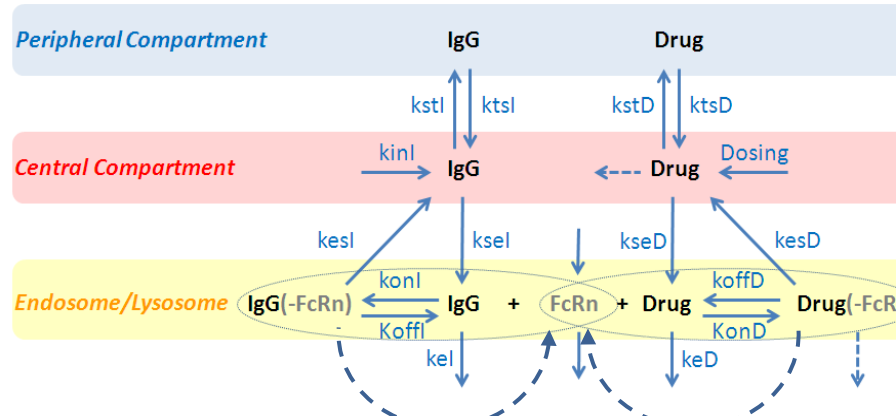


Figure 1: the physiological model



A literature search was conducted to identify models that can serve as building blocks of the one in Figure 2 (Figure 3 and Table 1).

Figure 3: relevant binding models

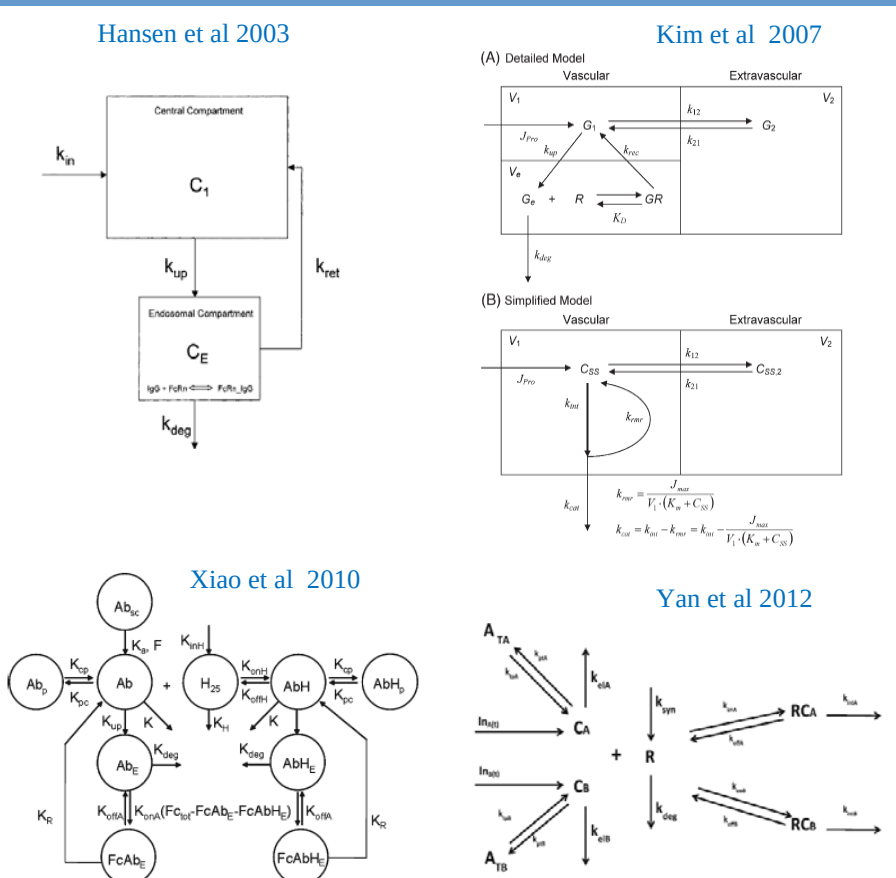


Table 1: summary of available models

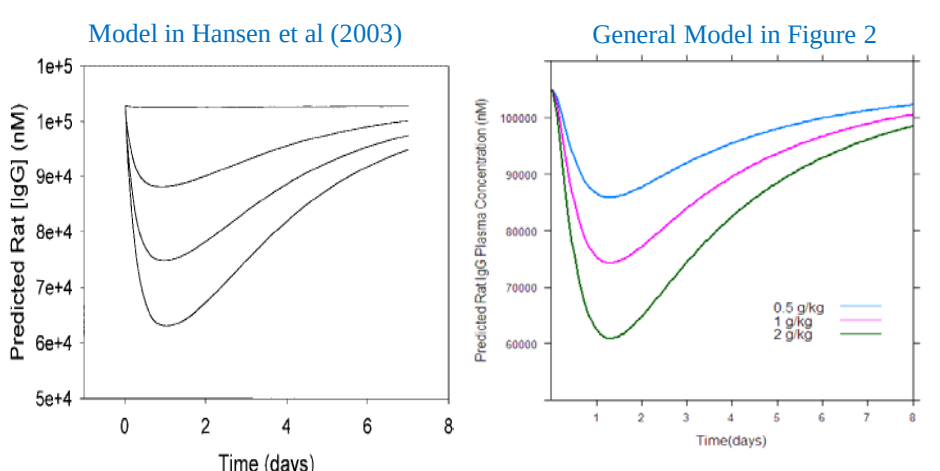
	Same KDs	Rapid binding	Constant total FcRn	kup=kret	Vs=Ve	Species
Hansen et al 2003	Yes	Yes	Yes	Yes	Yes	Rat/Mouse
Kim et al 2007	n.a.	n.a.	n.a.	No	n.a.	Human
Xiao et al 2010	Yes	Yes	Yes	Yes	No	Monkey
Yan et al 2012	No	Yes	No	Yes	Yes	Rat

We initially assumed rapid binding and adopted the “differential method” of solving rapid binding target-mediated drug disposition models in competing conditions proposed by Yan et al (2012). The general model (Figure 2) was used to reproduce the simulations in Hansen et al (2003) using endogenous IgG affinity parameters reported by Datta-Mannan et al (2007) and to reproduce the simulations in Kim et al (2007). Subsequently the model was implemented without the rapid binding assumption and the results were compared to those with the assumption. Finally the mathematical properties of the model were explored.

Results

- The simulations under rapid binding assumption were in good agreement with the profiles predicted by Hansen et al (Figure 3). This was expected because assuming that the molecules have the same KD, the general model virtually collapses to the reduced one in Hansen et al.

Figure 4: simulations with same KD



- The model was parameterized using plasma IgG basal level, volumes of distribution, IgG production rate and IgG uptake rate into the endosome. Basal concentrations of both IgG and FcRn in the endosome and FcRn synthesis rate were derived. In absence of any drug, changing kint and Jpro in the general model from 1/8 to 8 folds produced a pattern of new steady state concentrations that was comparable to Kim et al (2007), although the general model remained to be further evaluated to capture the lower IgG profiles (Figure 5).
- Using the general model, it could be shown that the **minimal achievable ratio of plasma IgG vs its basal level would be: $k_{in}/k_{sel}/IgG(0)/V_s$** . Hence the determinants for the maximal effect of an intervention that aimed to reduce plasma IgG were identified. Figure 6 shows the effects on the speed and extent of IgG reduction by increasing dose (left panel) and KD (right).
- The simulations of the model with and without assuming rapid binding were in good agreement in the parameter range tested.

Figure 5: simulations in absence of drug

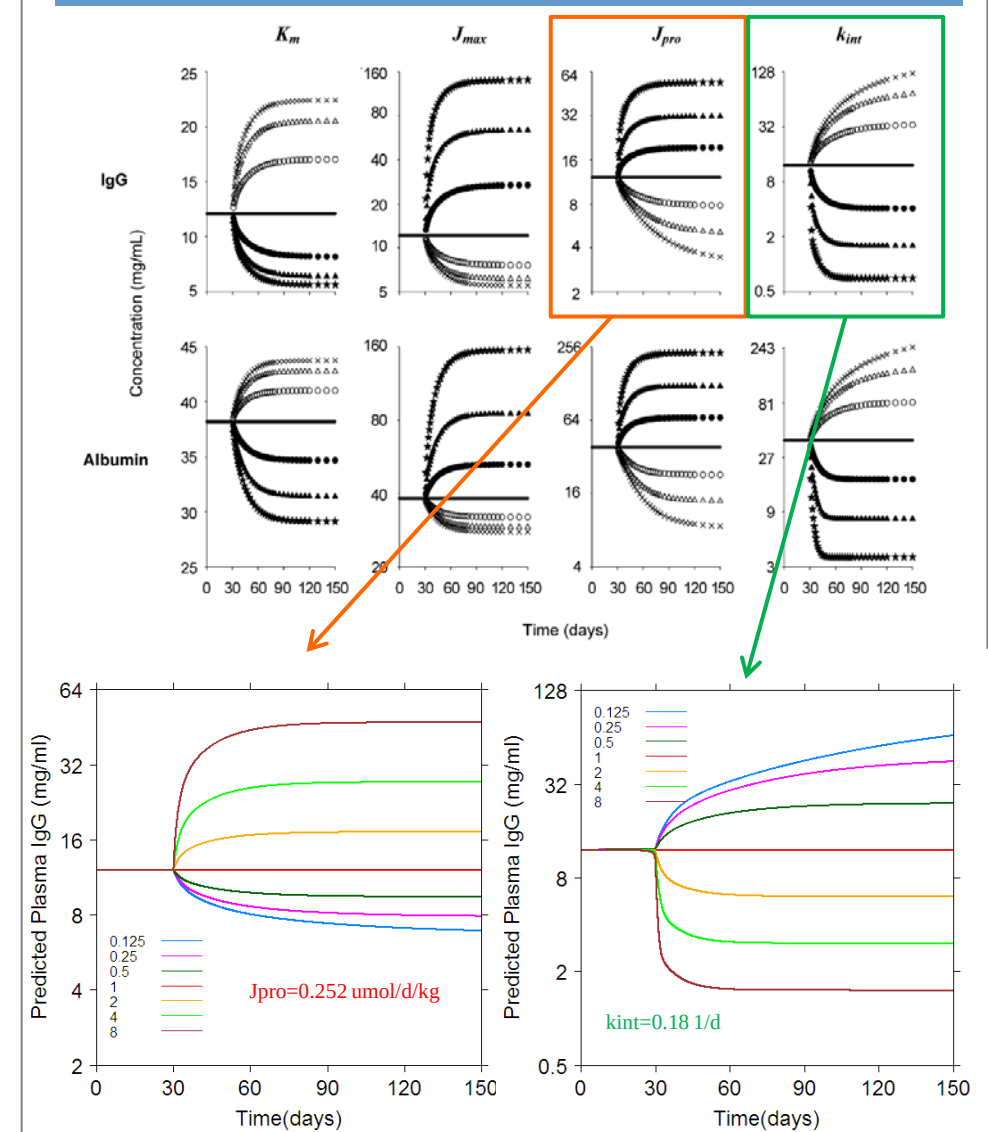
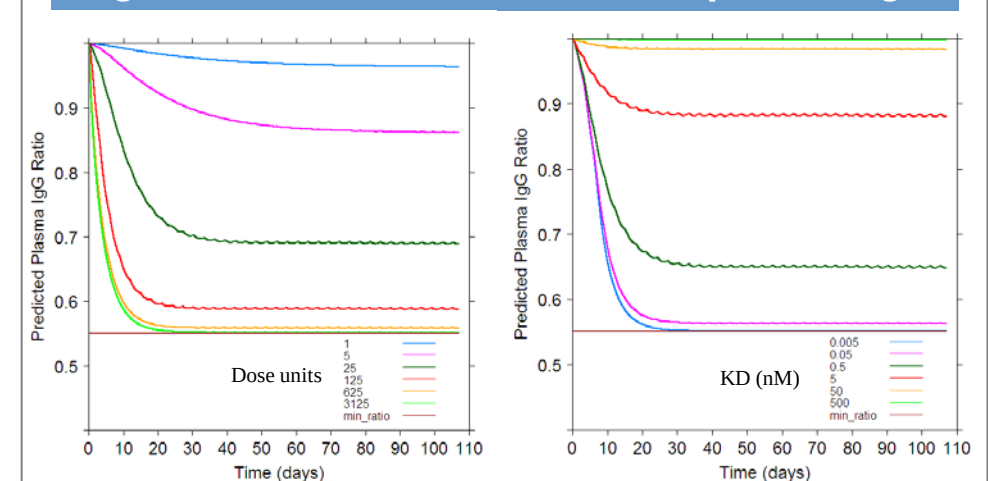


Figure 6: maximal reduction of plasma IgG



Conclusions

We have used literature findings to construct a versatile model to describe the FcRn involvement in the disposition of IgG in human. Emerging results showed that the model could successfully reproduce the change in blood IgG during several types of system perturbation. Upon further development, the model can potentially be used to evaluate the pharmacological potential of certain therapeutic approaches.

References

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