Mathematical Biosciences 259 (2015) 43–54

Contents lists available at ScienceDirect

Mathematical Biosciences

journal homepage: www.elsevier.com/locate/mbs

Modeling the effect of insulin-like growth factor-1 on human cell growth

Gemma M.A. Phillips[a], Paul R. Shorten[b,d,1], Graeme C. Wake[a,d,*], Jian Guan[c,d,e,2]

[a] Institute of Natural and Mathematical Sciences, Massey University at Albany, Private Bag 102904, North Shore MC, Auckland, New Zealand
[b] AgResearch Ltd, Ruakura Research Centre, Private Bag 3123, Hamilton, New Zealand
[c] Liggins Institute, University of Auckland, Private Bag 92019, Auckland, New Zealand
[d] Gravida National Centre for Growth and Development, University of Auckland, Private Bag 92019, Auckland, New Zealand
[e] Centre for Brain Research, University of Auckland, Private Bag 92019, Auckland, New Zealand

ARTICLE INFO

Article history:
Received 27 January 2014
Revised 9 November 2014
Accepted 14 November 2014
Available online 26 November 2014

Keywords:
Simulation
Dynamic modeling
Insulin-like growth factor 1
Steady state analysis
Model testing

ABSTRACT

Insulin-like growth factor-1 (IGF-1) plays a key role in human growth and development. The interactions of IGF-1 with IGF-1 receptors and IGF-1 binding proteins (IGFBPs) regulate IGF-1 function. Recent research suggests that a metabolite of IGF-1, cyclo-glycyl-proline (cGP), has a role in regulating IGF-1 homeostasis. A component of this interaction is believed to be the competitive binding of IGF-1 and cGP to IGFBPs. In this paper we describe a mathematical model of the interaction between IGF-1 and cGP on human cell growth. The model can be used to understand the interaction between IGF-1, IGFBPs, cGP and IGF-1 receptors along with the kinetics of cell growth. An explicit model of the known interactions between IGF-1, cGP, IGFBPs, IGF-1 receptors explained a large portion of the variance in cell growth ($R^2 = 0.83$). An implicit model of the interactions between IGF-1, cGP, IGFBPs, IGF-1 receptors that included a hypothesized feedback of cGP on IGF-1 receptors explained nonlinear features of interaction between IGF-1 and cGP not described by the explicit model ($R^2 = 0.84$). The model also explained the effect of IGFBP antibody on the interaction between cGP and IGF-1 ($R^2 = 0.78$). This demonstrates that the competitive binding of IGF-1 and cGP to IGFBPs plays a large role in the interaction between IGF-1 and cGP, but that other factors potentially play a role in the interaction between cGP and IGF-1. These models can be used to predict the complex interaction between IGF-1 and cGP on human cell growth and form a basis for further research in this field.

1. Introduction

1.1. Biological background

Insulin-like growth factor 1 (IGF-1) plays a vital role in growth and development. The majority of IGF-1 is inactive in the body, bound to insulin-like growth factor 1 binding proteins (IGFBPs). These prolong the half life of IGF-1 and act as a transportation method to the receptors.

The biological function of IGF-1 is mediated through the activation of IGF-1 receptors, located on the surface of human cells. These receptors consist of two alpha subunits (extracellular) which bind with the ligands and two beta subunits which control whether certain cellular functions occur. IGF-1 function is dependent on the arrangement and concentration of these receptors. IGF-1 receptors have been found in many different tissues and cells indicating that there are a vast amount of variety in the effects IGF-1 can have in the body [1]. The binding proteins control the IGF-1 induced cell function by inducing or inhibiting the cell growth responses and metabolic activity [2].

The effective route of administration is problematic given the large size of IGF-1. The size restricts site specific treatment so administering IGF-1 or blocking IGF-1 function can potentially promote pathological growth.

Recent developments have indicated a metabolite of IGF-1 called cyclo-glycyl-proline (cGP), plays a role in regulating IGF-1 activity. This is mediated by competitive binding with IGF-1 for the binding proteins. Lower levels of cGP in the body indicate more binding proteins bound to IGF-1 and less free IGF-1 available for the receptors. Higher levels of cGP indicate a higher level of free IGF-1 (as the binding proteins are bound to cGP) and therefore more free IGF-1 available to be internalized by binding to the receptors. "cGP, a metabolite of IGF-1 can normalize IGF-1 function by showing its efficacy in improving the recovery from ischemic brain injury in rats and inhibiting the growth of lymphomic tumors in mice." [3].

* Corresponding author at: Institute of Natural and Mathematical Sciences, Massey University at Albany, Private Bag 102904, North Shore MC, Auckland, New Zealand. Tel.: +64 9 4140800; fax: +64 9 4418136.
E-mail addresses: gphi024@aucklanduni.ac.nz (G.M.A. Phillips), paul.shorten@agresearch.co.nz (P.R. Shorten), g.c.wake@massey.ac.nz (G.C. Wake), j.guan@auckland.ac.nz (J. Guan).
[1] Tel.: +64 7 8385068.
[2] Tel.: +64 9 9236134.

http://dx.doi.org/10.1016/j.mbs.2014.11.002
0025-5564/

1.2. Previous research

Previous model research in this area [4–6] simulated IGF-1 kinetics through *in vivo* experiments. We explore the model developed in Ref. [5] (model one) using a more mathematical approach. The previous model simulated IGF-1 interactions within the body by looking at the effects of infusing recombinant IGF-1 into human subjects. The research was aimed at showing that the binding proteins were what influenced IGF-1 via retaining IGF-1 in the vascular compartment or inhibiting their actions. The data used were obtained by infusing four healthy, adult, male volunteers for 3 h at a rate of 43.7 pmol min^{-1} kg^{-1}, with recombinant IGF-1. We produced analytical steady state solutions and response diagrams for this model. This resulted in an alteration of one of the equations (a decay term added into the second equation) to fit more accurately with the IGF-1 kinetics (model two). The research described IGF-1 kinetics but excluded an important metabolite (cyclic-gly-pro complex, cGP) which has been shown to regulate IGF-1 activity. This is the key difference between previous studies and the new modified models.

1.3. Recent developments

The new modified models investigate the interactions between IGF-1, IGFBPs, IGF-1 receptors and cGP in cell cultures. The third model involves implicitly representing the effects of cGP on IGF-1 through two nonlinear feedback terms. Model four explores the dynamics explicitly by showing the competitive binding between cGP and IGF-1 for IGFBPs in the equations. Using data from *in vitro* experiments, nonlinear optimization is used to produce comparative graphs of the data and simulated cell growth activity. The latest model is tested using an independent data set.

The *in vitro* data measured absorbance percentages, which is assumed to be proportional to the cell number used in the *in vitro* models. Four different treatments were used for parameter estimation. These include IGF-1 only, cGP only and two different combinations of IGF-1 and cGP treatments. The independent data used in testing the fourth model involved two sets of data, one was treated with antibodies and the other was not. Antibodies bind to the IGFBPs, therefore making IGFBPs less available for IGF-1 and cGP to bind to.

The model equations use the law of mass action, which states that the rate at which interacting compartments react is proportional to the product of concentration of their reactants.

2. Outline of the *in vivo* models

A detailed description of the data collection methods used in the *in vivo* experiments can be found in Ref. [5]. The first model in this section is a seven compartmental model which involves IGF-1 interactions with IGFBPs and IGF-1 receptors. Model two is an extension of this, which includes an important decay term in the differential equations. A glossary of variables and parameters for models one and two can be seen in Tables 1 and 2.

2.1. Method (in vivo Models)

A schematic diagram and equations for model two (an extension of model one) are shown in this section. The analytical steady state solutions of models one and two are calculated. From here a steady state analysis is performed to investigate the change in long term solutions in the system as the production rate parameters are changed. The goal of this analysis is to identify potential long term periodic solutions (*e.g.* Hopf bifurcations), which cannot be found by calculating the steady state solutions.

2.1.1. Introduction (in vivo models)

The model groups IGFBPs 1–6 (excluding 3) together in the free (q_1) and bound (q_3) form. While IGFBP-3 has its own compartment for its free (q_4) and bound (q_5) form since IGFBP-3 is the largest and most influential binding protein. The IGFBPs 1–6 (excluding 3) were taken as having 50 kDa molecular weight while IGFBP-3 was taken as having 150 kDa molecular weight. The inputs in Eq. (2) (R_a and $Infu$) are separated as they represent external input (infusion rate) and a measure of IGF-1 production within the body.

See Fig. 1 for a schematic diagram of models one and two from Ref. [5].

Table 1
Definitions of the state variables as in Eqs. (1)–(7) given in Ref. [5]. Where IGFBP-3 (in free and bound form) has a molecular weight of 150 kDa, IGFBPs 1–6 excluding 3 are grouped together with a molecular weight of 50 kDa (in free and bound form).

Variable	Definition
q_1	Molar mass of IGFBPs 1,2, 4, 5,6 50 kDa (nmol)
q_2	Molar mass of free IGF-1 in the plasma (nmol)
q_3	Molar mass of IGF-1/IGFBPs 1,2,4,5,6 50 kDa (nmol)
q_4	Molar mass of IGFBP-3, 150 kDa (nmol)
q_5	Molar mass of IGF-1/IGFBP-3, 150 kDa (nmol)
q_6	Molar mass of IGF-1 in interstitial fluid volume (nmol)
q_7	Receptor bound IGF-1 (nmol)

Table 2
Parameter definitions as given in Ref. [5]. Where IGFBP-3 (in free and bound form) has a molecular weight of 150 kDa, IGFBPs 1–6 excluding 3 are grouped together with a molecular weight of 50 kDa (in free and bound form).

Parameter	Definition
k_{ij}	Rate constant, to compartment i from j, where zero is outside the system (min^{-1})
k_{+1a}	Binding constant of IGFBPs 1,2, 4,5,6, 50 kDa ($nmol^{-1}$ min^{-1})
k_{+1b}	Binding constant of IGFBP-3, 150 kDa ($nmol^{-1}$ min^{-1})
k_{-1a}	Dissociation rate constant of IGFBPs 1,2,4,5,6, 50 kDa (min^{-1})
k_{-1b}	Dissociation rate constant of IGFBP-3, 150 kDa (min^{-1})
R	IGF-1 receptor number (nmol)
R_a	IGF-1 production rate (nmol min^{-1})
$R_{a,1}$	IGFBPs, 50 kDa production rate of IGFBPs 1,2,4,5,6 (nmol min^{-1})
$R_{a,2}$	IGFBPs, 150 kDa production rate of IGFBP-3 (nmol min^{-1})
$Infu$	IGF-1 infusion rate (nmol min^{-1})

2.1.2. Equations (in vivo models)

The first model of Ref. [5] considered the case $k_{02} = 0$ (model one), whereas we have now put k_{02} non-zero (model two). The rate equations for the biomasses in Table 1 are given by Eqs. (1)–(7):

$$\frac{dq_1}{dt} = -k_{+1a}q_1q_2 + k_{-1a}q_3 - k_{01}q_1 + R_{a,1}, \tag{1}$$

$$\frac{dq_2}{dt} = -k_{+1a}q_1q_2 + k_{-1a}q_3 - k_{+1b}q_4q_2 + k_{-1b}q_5 - k_{62}q_2 + k_{26}q_6 - k_{02}q_2 + R_a + Infu, \tag{2}$$

$$\frac{dq_3}{dt} = k_{+1a}q_1q_2 - k_{-1a}q_3, \tag{3}$$