Dynamical Modelling of the effect of Insulin-like Growth Factor 1 on Human Cell Growth

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Abstract

Insulin-like Growth Factor-1 (IGF-1) plays a vital role in human growth and development. Interactions with IGF-1 receptors and IGF-1 binding proteins (IGFBPs) regulate IGF-1 function. Boroujerdi et al. (1997) published a mathematical model describing dynamic regulation of IGF-1. We extended the Boroujerdi et al. (1997) model to evaluate the role of cyclic Gly-Pro (CGP) in dynamic regulation of IGF-1 function. Recent research from the Liggins Institute suggests that a metabolite of IGF-1, CGP, may have a role in regulating IGF-1 homeostasis, possibly through competitive binding to IGFBPs.

The goal of the research was to understand the kinetics of IGF-1, IGFBPs and CGP, along with their interactions with IGF-1 receptors. This goal and an understanding of how the kinetics mediate IGF-1 function was achieved through consideration of the nonlinear dynamics of the physiology using a modelling approach.

The resulting models were directly focused on three central theories. The first is that CGP can either inhibit, stimulate or maintain IGF-1 function based on the extent of receptor binding. The other theories are that CGP regulates IGF-1 through competitive binding to IGFBPs and that CGP does not directly interact with the IGF-1 receptors.

Four *in vitro* models were developed and fitted to experimental data. These included two implicit models which relied on two feedback terms in the equations. The second model was an alteration of the first to produce a reduction in cell number levels for high doses of CGP added to the system. The other two models were explicit models, the first of which could not express the IGF-1 dynamics well (it showed no CGP response). Although the models incorporated these theories, there are other mechanisms influencing the system which will have an effect on the data. Therefore the fourth model was introduced as a simplified version of the third. This was aimed at resembling cell culture situations more closely and was designed to have the receptor bound IGF-1 dependent on IGF-1 and CGP production rates.

The models can be used to predict cellular response in an *in vitro* situation, or as a basis for further research in this field.

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Abbreviations

BSA	Bovine serum albumin
CGP	Cyclo-glycyl-proline or Cyclic Gly-Pro
DE	Differential equation
DKP	Diketopiperazine
EDTA	Ethylenediaminetetraacetic acid
GPE	Glycine-proline-glutamate
IGF-1	Insulin-like Growth Factor 1
IGF-1R	Insulin-like Growth Factor 1 Receptor
IGFBP	Insulin-like Growth Factor Binding Proteins
kDa	Kilo Dalton (Dalton is a unit of mass based on molecular mass)
nM	nmol L^{-1}
ODE	Ordinary Differential Equation
PBS	Phosphate Buffered Solution
PDE	Partial Differential Equation
RK4	Runge Kutta fourth order method
SDS	Sodium Dodecyl Sulfate
SSE	Sum of Squares of Errors
WST-1	Water Soluble Tetrazolium Salt-1

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