Model informed quantification of the feed-forward stimulation of growth hormone secretion in humans

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Systems Biomedicine and Pharmacology

INTRODUCTION

- Growth hormone (GH) secretion is pulsatile and the number of bursts, the amplitude, and the burst interval varies highly between individuals.
- To understand and ultimately predict GH secretion, it is important to delineate and quantify the variability in the biological processes underlying GH secretion between individuals.
- This study reports on the development of a physiologically based model for GH release, incorporating the feed-forward stimulation of GH by GH releasing hormone (GHRH).

RESEARCH OBJECTIVES

- **Quantify the variability in individual growth hormone kinetics and stimulated growth hormone response**
- **Develop a physiological model that can describe the key components of growth hormone secretion**
  - **Pituitary**
  - **Systemic circulation**
  - **Receptor activation**
  - **GHRH kinetics**

METHODS

Study population

- Healthy (n=8), upper (n=8) and lower (n=8) body obese women
  - Mean age = 37 years [IQR 33-43]

Study design

- Recombinant GH administration
  - 2.5h infusion of somatostatin
  - Recombinant GH infusion
    - 5 min. 100 mU
  - Dense sampling
  - Before and after weight loss
- GH stimulation
  - 100 µg GHRH
  - Dense sampling
  - Before and after weight loss

Physiological information

- Plasma volume
- Pituitary volume and blood flow
- Median eminence volume
- GHRH
  - Half-life
  - Volume of distribution

Model development and simulation

- Estimation of parameters
- Simulation to judge description of data
- Accuracy in parameter estimates
- Scaling to healthy men (n=6)
  - GHRH stimulation (1 µg/kg)
  - Two occasions
  - Mean age = 22 years [IQR 19-25]

Table 1) Parameter estimates of the physiologically based model for GH stimulation by GHRH. CL_{GH} equation = $CL_{GH\text{-}intercept}$ + $CL_{GH\text{-}slope}$ (weight-70), RSE=relative standard error, CV% = coefficient of variation, * indicate fixed parameter, CI = confidence interval.*

Parameter	Unit	Estimate [RSE%] (CV%)	Shrinkage (%)
Population parameters			
$CL_{GH\text{-}slope}$	L/h/kg	0.185 [6.1]	-
$CL_{GH\text{-}intercept}$	L/h	26.5 [3.65]	-
$V_{SAC\text{-}Fast}$	L	1.17 [29.4]	-
$Q_{SAC\text{-}Fast}$	L/h	10000*	-
$V_{SAC\text{-}Slow}$	L	2.29 [6.63]	-
$Q_{SAC\text{-}Slow}$	L/h	12.1 [11.4]	-
GH baseline secretion	µg/h	1.04 [9.49]	-
k_{act}	nmol/h	100*	-
k_{inact}	/h	1.46 [4.43]	-
GH-Release	mg/h	99.8 [14.9]	-
Inter-individual variability			
ω^2 CL_{GH}	-	0.0268 (16.5)	2.41
ω^2 $V_{SAC\text{-}Slow}$	-	0.0714 (27.2)	17.8
ω^2 GH baseline secretion	-	0.701 (101)	8.07
ω^2 GH-Release	-	0.59 (89.7)	< 0.01
Residual error structure			
σ^2 Proportional error GH kinetics	-	0.0415	7.64
σ^2 Proportional error GHRH stimulation	-	0.225	3

Future perspectives

- **This models sets the stage for physiologically based scaling and simulations to acromegaly patients, to better inform drug development.**
- **Additional data will inform the model on covariate relationships that may explain the variability in the response to GHRH stimulation.**
- **Endogenous GH secretion can be added to this model by the addition of a stochastic pulse generator**
- **Information on the variability in GH kinetics and the response to GHRH stimulation can now be used for clinical trial simulations.**

RESULTS

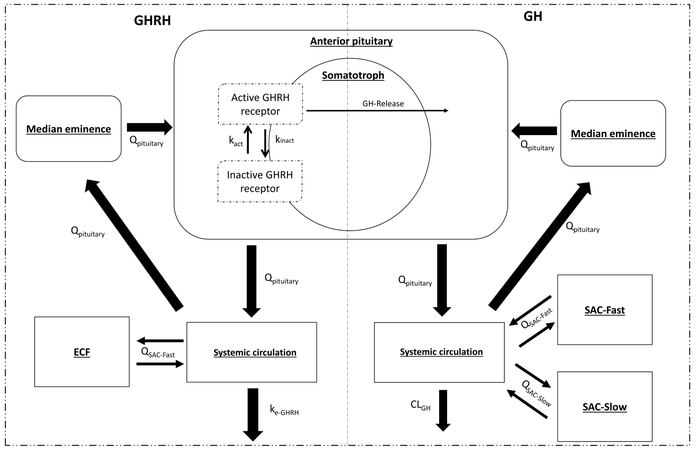

Figure 1) Model structure with the growth hormone releasing hormone (GHRH; left panel) and growth hormone (GH; right panel) kinetics. ECF = extracellular fluid, SAC = single adjusting compartment, Q = (blood) flow, k_e = elimination rate constant, CL = clearance, k_{act} = activation rate constant, k_{inact} = receptor inactivation rate constant.

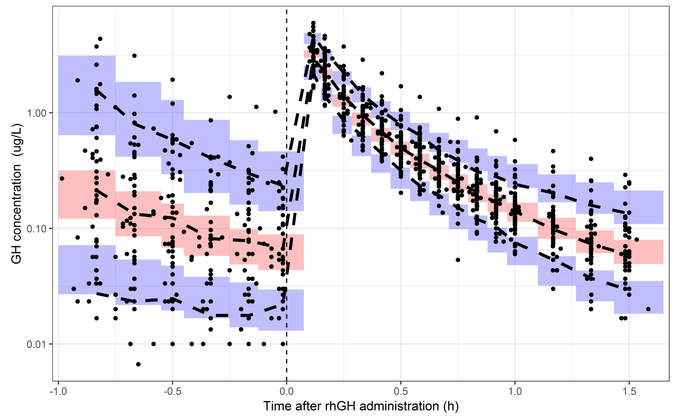

Figure 3) Black dots = observations, black dashed lines = 10 and 90th data percentiles and median of the observations, red shaded area = 95%-confidence interval of the median prediction, blue shaded area = 95%-CI of the 10 and 90th prediction percentiles, vertical dashed black line = time of rhGH administration.

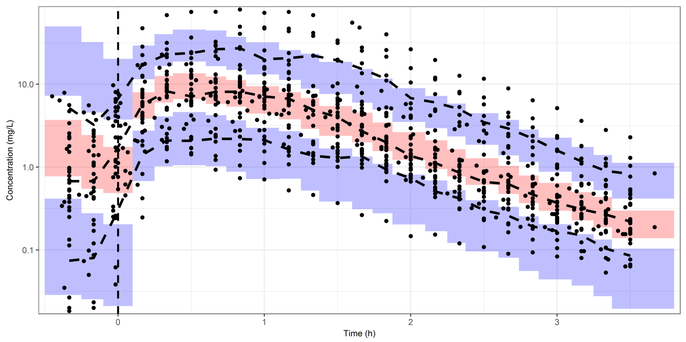

Figure 4) Black dots = observations, black dashed lines = 10 and 90th data percentiles and median of the observations, red shaded area = 95%-confidence interval of the median prediction, blue shaded area = 95%-CI of the 10 and 90th prediction percentiles, vertical dashed black line = time of GHRH administration.

Recombinant GH administration

- The pharmacokinetics of GH were best described using 2 peripheral compartments (Figure 1).
- A linear increase in GH clearance with body weight was identified **(Figure 2)**.
- Low levels of variability in the pharmacokinetics of GH was identified.
  - Parameter estimates were estimated with high precision (Table 1).
- The physiologically based model was able to adequately describe the GH administration **(Figure 3)**.

GH stimulation by GHRH

- A single dose of GHRH stimulated GH secretion up to 2.5 hours.
- High variability in the response to equal GHRH doses were observed.
- A fast onset of the effect was quantified.
- The developed model correctly captured the general trend and variability in this population **(Figure 4)**.

Scaling to men

- Estimation of GH secretion in men resulted in under prediction of the observations **(Figure 5A red line)**.
- Re-estimation of the parameters in men indicated a 40% increase in GHRH stimulated secretion.
- The age difference between men and women in this study may have caused the quantified difference.

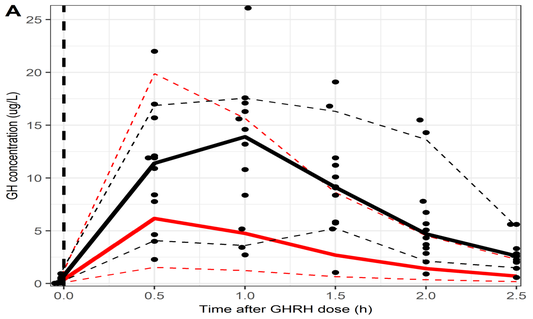

Figure 5) Simulated model predictions for the data in men. Red line = median simulation of model from women, red dashed lines = 80% simulated prediction interval, black line = median of data in men, black dashed line = 80% distribution of the data in men, black dots = observations, vertical dashed black line = time of GHRH administration.

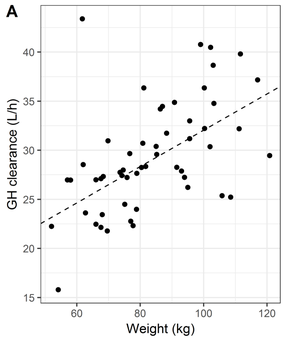

Figure 2) Estimated growth hormone clearance versus the weight of individual subjects. Dashed line indicates the linear covariate relationship.

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