Model-based Analysis of the GLP-1 Response Following an Oral Glucose Tolerance Test (OGTT)

Authors

1. **JB Møller**
Novo Nordisk A/S
Vandtårnsvej 114
Søborg, Denmark

2. **WJ Jusko**
Department of pharmaceutical sciences, State univ. of NY Buffalo, USA

3. **T Hansen**
Hagedorn Research Institute
Gentofte, Denmark

4. **O Pedersen**
Hagedorn Research Institute
Gentofte, Denmark

5. **JJ Holst**
Department of Medical Physiology
Panum Institute
University of Copenhagen

6. **RV Overgaard**
Novo Nordisk A/S
Vandtårnsvej 114
Søborg, Denmark

7. **H Madsen**
Department of Informatics and Mathematical Modelling, DTU
Lyngby, Denmark

8. **SH Ingwersen**
Novo Nordisk A/S
Vandtårnsvej 114
Søborg, Denmark

Objective

- To gain further insights into the pathophysiology of Type 2 diabetes, by providing description of the GLP-1 response following an oral glucose administration.

Background

- GLP-1 is known as an insulino-tropic hormone, meaning that the insulin response to elevated glucose levels is increased in the presence of this hormone [1].
- The GLP-1 response is increased in the presence of nutrients in the gastro-intestinal (GI) tract and thus also following intake of oral glucose.
- It is not clear how dynamics of such a response is changed under pathological conditions eg. in subjects with impaired glucose tolerance.
- Compared to a standard analysis (AUC and C_{max}), a PK/PD model of the response will provide more information regarding dynamics and can easily be used to detect the impact of demographic factors on these.

Methods

- In order to obtain such descriptive indices, a semi-mechanistic model for the GLP-1 response was built using glucose, insulin, and GLP-1 data [2].
- Initially, the glucose absorption rate was estimated only using glucose and insulin concentrations. The estimated glucose absorption rate was used as input to the GLP-1 model [3].

Table 1 Distribution of subjects and baseline values

Subjects	Normal	IFG-IGT-T2D	Total
Number	117	18	135
Age [yr]	41.77 (11.4)	45.56 (12.7)	42.27 (11.6)
Fasting plasma glucose [mg·dL^{-1}]	93.02 (8.1)	109.82 (13)	95.26 (10.5)
Fasting plasma insulin [pmol·L^{-1}]	5.43 (3.1)	11.66 (8.4)	6.26 (4.6)
Fasting plasma GLP-1(total) [pmol·L^{-1}]	5.35 (3.3)	4.61 (2.6)	5.26 (3.2)
GLP1 stimulation - S_4 [mg^{-1}]	13.54(13.23)	10.76(8.7)	13.16(12.7)

Table 1 : Mean (SD) of demographic factors and baseline characteristics. S_4 presents magnitude on slow GLP-1 response.

Figure 1 Model setup

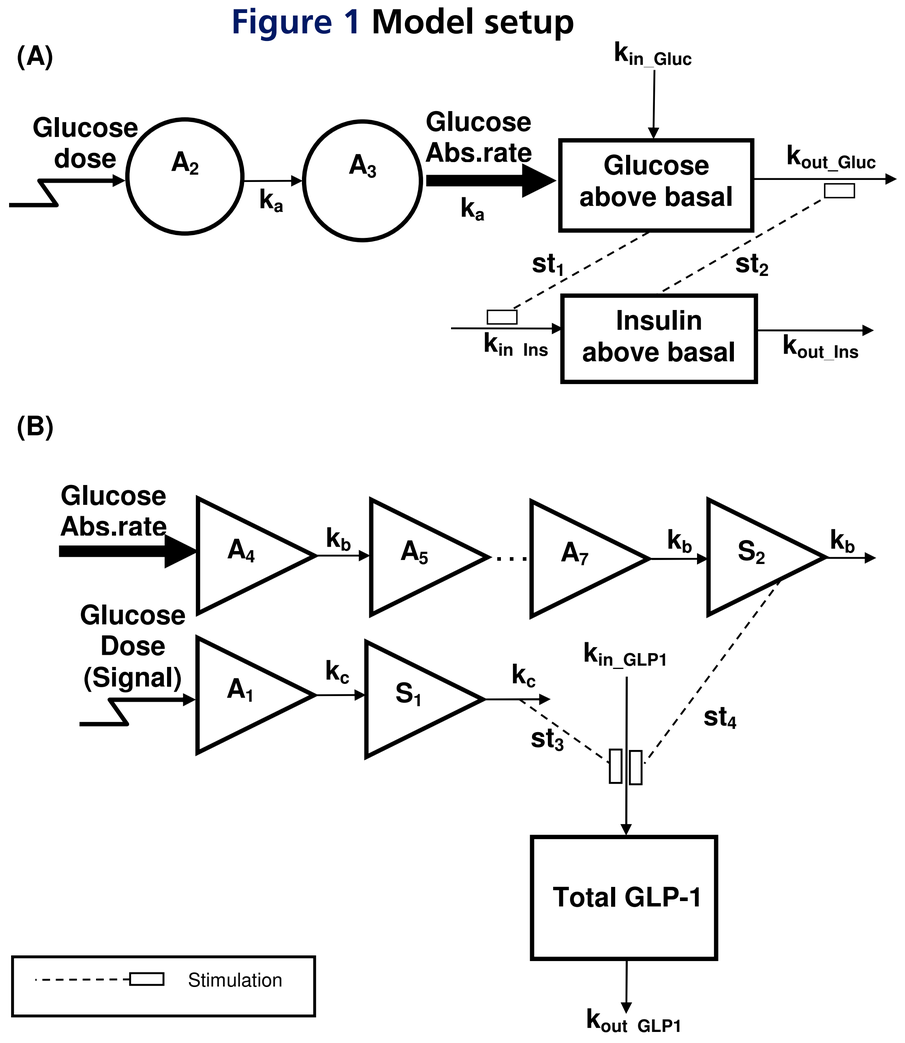

Figure 1 : (A) Indirect response model relating glucose and insulin dynamics applied for estimation of glucose absorption rate, (B) GLP-1 model using glucose absorption rate as input. Triangles present delay(transit) compartments.

Figure 2 Diagnostics

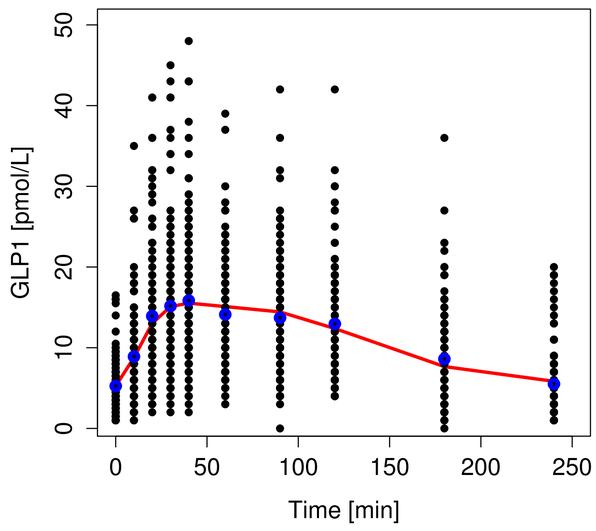

Figure 2: Black =Individual observations, Blue =Mean observations, Red =Population prediction.

Figure 3 Stimulation

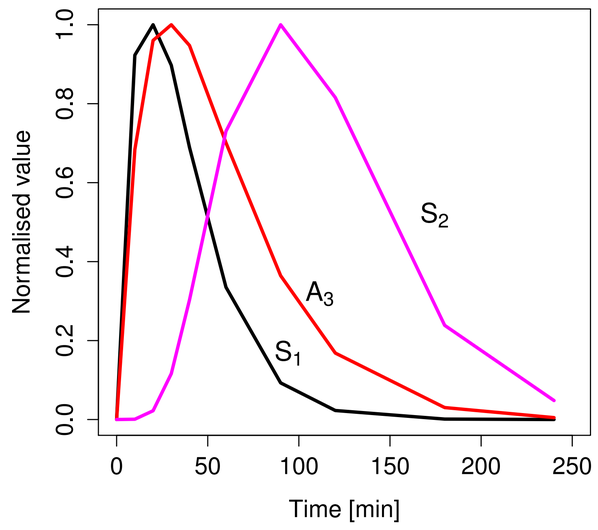

Figure 3 : S_1=Fast stimulation component, A_3=Glucose absorption rate, S_2=Slow stimulation component.

Results and conclusions

- The final indirect-response model obtained for GLP-1 production following an oral glucose tolerance test included two stimulation components on a zero-order production rate. (Fig. 1)
- The fast stimulation was estimated to arrive prior to glucose absorption, suggesting a neuro-endocrine loop, where nutrients in doudenum stimulates GLP-1 secretion from L-cells in the lower part of GI (ileum). (Fig. 3)

Conclusions

- A semi-mechanistic population model was successfully developed and applied to describe total GLP-1 concentrations over time observed after an OGTT
- The secretion of GLP-1 appears to be stimulated by glucose in two ways: by a fast mechanism driven by glucose dose in the GI and by a slower mechanism driven by glucose absorption rate.
- The model provides a good basis to study influence of demographic factors on individual GLP-1 secretion capabilities.

References

[1] Holst JJ 2007. The Physiology of Glucagon-like Peptide 1. Physiol Rev 87(4):1409-1439.

[2] Hansen T, Drivsholm T, Urhammer SA, Palacios RT, Vølund A, Borch-Johnsen K, Pedersen O 2007. The BIGTT Test. Diabetes Care 30(2):257-262.

[3] Jonas B. Møller, William J. Jusko, Wei Gao, Torben Hansen, Oluf Pedersen, Jens J. Holst, Rune V. Overgaard, Henrik Madsen, Steen H. Ingwersen. Mechanism-based population modelling for assessment of L-cell function based on total GLP-1 response following an oral glucose tolerance test. *Submitted to J.PK.PD*

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