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Modelling the hepatic glucose production in Type 1 Diabetes during aerobic exercise

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Abstract: Mathematical models of the glucose-insulin metabolism are a powerful tool to improve blood glucose control in type 1 diabetes. A high model accuracy is essential. This work investigates whether the hepatic glucose production submodel and the glucagon subsystem of the Lunze model, which was developed for the resting state, remain valid during aerobic exercise. Experimental data of 5 dogs is used for the evaluation. Results show, that the behavior of both the hepatic glucose production submodel and the glucagon subsystem is similar, though not identical, to experimental data during aerobic exercise.

I. Introduction

Blood glucose (BG) control of patients with Diabetes mellitus type 1 is malfunctioning, as patients do not produce the BG lowering hormone insulin. BG levels of patients with type 1 diabetes are controlled by insulin injections. BG control is challenging due to many disturbances and the delayed effect of subcutaneously injected insulin. Mathematical models of the glucose-insulin metabolism are a powerful tool to improve BG control. The accuracy of these models is of high importance. Aerobic exercise (AE) causes several changes in the body, e.g. an increased insulin sensitivity, and is considered as a major challenge in BG control. In healthy subjects, the response to AE includes a reduced insulin concentration and an increased concentration of glucagon, i.e. a BG increasing hormone. This work focuses on the AE-related increase in hepatic glucose production (HGP). The hormone response of healthy subjects to AE indirectly leads to an HGP increase (see Fig. 1) [1]. Other mechanisms, e.g. adrenaline or an increased supply in gluconeogenic precursors [2], might be involved in increasing HGP during AE, but to the best of authors' knowledge, there is currently no consensus on the significance of these mechanisms.

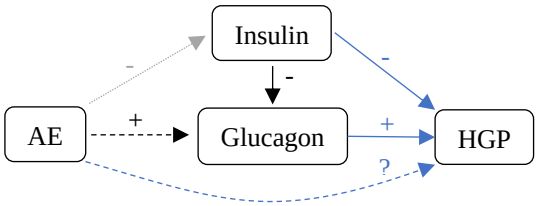

Figure 1: HGP is regulated by insulin and glucagon concentrations, which in turn are impacted by AE and by each other. Glucagon concentration and HGP are moreover influenced by BG (not shown).

Only some models considering the impact of AE on the glucose-insulin metabolism explicitly describe the HGP increase. Changes in HGP are usually directly modelled in terms of exercise intensity. The impact of changes in glucagon and particularly insulin concentration during AE on HGP are often not considered in model development [3, 4]. In this work, the Lunze model describing the metabolism in resting state is used [5]. The aim of this work is to investigate whether the hormone-induced impacts (solid lines in Fig. 1) on HGP and glucagon concentration, which are currently included in the Lunze model, are sufficient to describe changes during AE, or whether the model needs to be extended by directly AE-induced (dashed lines in Fig. 1) impacts.

II. Material and Methods

Two simulation studies are performed and results are compared to experimental data. In experiment 1, the HGP submodel is evaluated (blue arrows in Fig. 1), while experiment 2 is designed to investigate the glucagon submodel (black arrows in Fig. 1).

II.I. Experimental Data

In a study by Wasserman and colleagues [6], 5 dogs performed 150 minutes of moderate exercise on a treadmill twice, respecitvely. Endogenous insulin and glucagon secretion were suppressed by somatostatin. Before exercise, the dogs received intraportal replacements of glucagon (fixed rate) and insulin (rate required to keep BG stable). In one protocol, the glucagon infusion during AE and recovery was set to mimic the normal exercise-induced response, while the basal glucagon level was maintained in the other protocol. The insulin infusion during AE and recovery was chosen to mimic the normal exercise-induced response. Additionally, glucose was infused to mimic BG levels observed in control experiments. Before, during and after AE, Wasserman et al. determined HGP, BG and glucagon and insulin concentrations.

II.II. Lunze Model

The Lunze model [5] is a compartment model of the glucose-insulin metabolism in resting state. Concentrations of glucose, insulin and glucagon in different parts of the

body are described and substrate mass fluxes, sources and sinks are modelled (see Fig. 2).

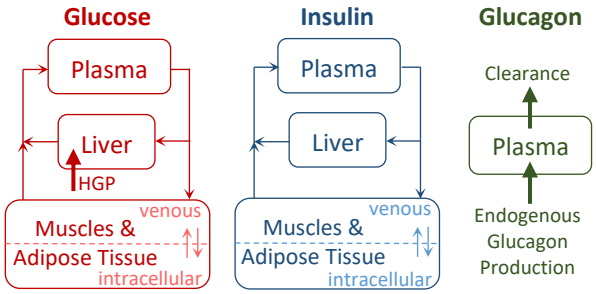

Figure 2: Lunze model of the glucose-insulin metabolism. Only relevant sources and sinks are shown for clarity.

Here, only two submodels are considered. Inputs to the HGP submodel (experiment 1) are BG, insulin and glucagon concentration. Inputs to the glucagon submodel, which includes endogenous glucagon production and clearance (experiment 2), are BG and insulin concentration.

II.III. Simulations

Both submodels are initialized to the basal state occurring 40 min before the onset of exercise. The individualizable model parameters representing the individual basal BG and insulin concentration are set to the basal values observed in the experimental data. The basal values from clinical data are also used to normalize measured glucagon levels and HGP. These were the only individualized adaptions of the model parameters to the experiment, all other parameters were set to their nominal values [7]. For experiment 1, measured BG, insulin and glucagon concentrations are fed into the HGP submodel. Experiment 1 is performed twice, i.e. once for the mimicked glucagon exercise-response and once for basal levels. For experiment 2, measured insulin and BG concentrations are fed into the glucagon submodel. Only the data of the protocol with a mimicked glucagon exercise-response is used.

III. Results and Discussion

The characteristics of simulated and measured HGP are similar (see Fig. 3), i.e. a significant difference between both protocols, a slight increase in the basal glucagon protocol and an up to ca. 3-fold increase in the exercise-response protocol. However, absolute values differ as only 50% (exercise-response) and 85% (basal) of simulated values during AE are within mean ± standard error (SE) of measured values.

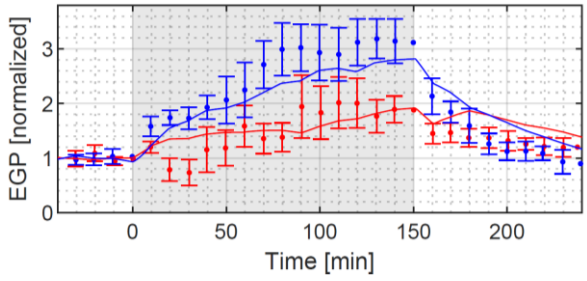

Figure 3: Measured vs. simulated HGP. Red: protocol with basal glucagon concentration. Blue: protocol with mimicked glucagon exercise-response. Points with errorbars: measured HGP (mean ± SE) [6]. Solid lines: simulated HGP. Grey area indicates AE.

Measured and simulated glucagon levels also share basic characteristics, i.e. a rise during AE and a decline after the cessation of AE (see Fig. 4). Again, there are differences in absolute values. Only 71% of simulated values during AE are within mean ± SE of measured values.

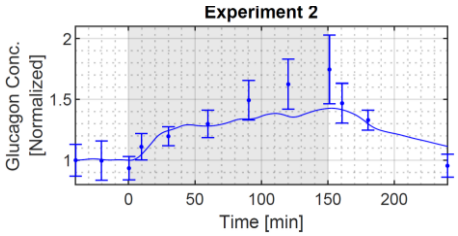

Figure 4:Measured vs. simulated glucagon concentration. Points with errorbars: measured (mean ± SE) [6]. Solid lines: simulated. Grey area indicates AE.

Results suggest that the HGP and the glucagon submodel are able to describe the major part of the changes occurring during AE. Incorporating direct AE-induced impacts could enhance simulation accuracy, but precise information or data about the involved processes are barely available.

This study possesses some limitations. Clinical data was measured in dogs, data of individual subjects was not available, the number of subjects was small, and only data from moderate-intense AE of medium duration was used. Moreover, results cannot be directly transferred to most other models due to different model structures.

It should moreover be noted, that the choice of individual model parameters, i.e. the individual basal BG, insulin and glucagon concentration, has a significant impact on HGP and glucagon exercise-response.

IV. Conclusion

Results suggest that considering only hormone-induced impacts but not directly AE-induced impacts in the HGP and the glucagon submodel causes a similar, though not identical, AE-response compared to experimental data.

Author's Statement

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References

[1] J. J. Grimm, "Exercise in Type 1 Diabetes," in *Exercise and Sport in Diabetes*, D. Nagi, Ed. W. Sussex, John Wiley & Sons, pp. 25-43, 2005.
[2] D. H. Wassermann, "Four grams of glucose," in *Am. J. Physiol. Endocrinol.*, vol. 296, no. 1, pp. E11-E21, 2009.
[3] S. Frank *et al.*, "Modeling the acute effects of exercise on glucose dynamics in healthy nondiabetic subjects," in *J Pharmacokinet. Pharmacodyn.*, vol. 48, no. 2, p. 225-239, 2021.
[4] P. Lenart *et al.*, "Modeling exercise effects in type I diabetic patients," in *IFAC Proc. Vol.*, vol. 35, no. 1, pp. 247-252, 2002.
[5] K. Lunze *et al.*, " Modeling of glucose-insulin system dynamics in diabetic Goettingen minipigs," in *IFAC Proc. Vol.*, vol. 45, no. 18, pp. 414-419, 2012.
[6] D. H. Wassermann *et al.*, "Glucagon is a primary controller of hepatic glycogenolysis and gluconeogenesis during muscular work," in *Am. J. Physiol. Endocrinol.*, vol. 257, no. 1, pp. E108-E117, 1989.
[7] J. T. Sorensen, "A physiologic model of glucose metabolism in man and its use to design and assess improved insulin therapies for diabetes," Doctoral Dissertation, Massachusetts Institute of Technology, 1985.