Mathematical Modeling of Glucose Transporters in Intestinal Epithelial Cells

Master Project

Cédric Lhoussaine

October 2019

Context

Type 2 Diabetes (T2D) is the main epidemic of this century. Even though non-communicable, it affects nearly 400 million people worldwide of which more than 4 million are French, raising highly pressing and costly healthcare challenges.

From Effects to Causes. Since the discovery of insulin nearly 100 years ago, T2D was defined by its physiopathological effects: the increase of the blood glucose concentration that comes with a defect of insulin secretion in combination with insulin resistance. These effects are targeted by most drugs clinically available today, while the pathogenesis causing these effects is not cured (nor well-understood). As a consequence, these treatments are not very efficient: the risk of death today remains more than twice superior in T2D patients than in the general population.

Glucose Absorption in the Small Intestine. Growing evidence suggests the role of glucose absorption in the small intestine. First, there is the striking metabolic outcome induced in patients with T2D simply by altering the gastrointestinal anatomy by bariatric surgery (Baud et al. 2016). Second, available clinical data shows that the amount of ingested carbohydrates is associated with T2D (Basu 2013). Therefore abnormal glucose absorption may significantly contribute to T2D.

Regulation of Intestinal Absorption. Glucose absorption in the small intestine is highly regulated, and more specifically in the enterocytes which are intestinal epithelial cells. The consumption of a diet rich in glucose leads to an increase of expression of sodium-glucose cotransporter 1 (SGLT1) (Ferraris and Diamond 1997). The expression of SGLT1 is increased in patients with T2D and associated with early post load hyperglycemia (Fiorentino et al. 2017). Interestingly, it was shown that individuals with mutations in the gene SGLT1 had a lower risk of glucose intolerance and obesity (Seidelmann et al. 2018).

Problematic

Even though the inner molecular mechanisms are poorly understood, recent works have been done to model the regulation of glucose absorption at the level of enterocytes. In (Thorsen, Drengstig, and Ruoff 2014), the authors propose en sophisticated mathematical model to study the interplay between glucose absorption (through SGLT1) with Na+/K+ transport. In the even more recent contribution (Afshar et al. 2019), the previous model is extended with another glucose transporter that was omitted, namely GLUT2. The authors compare the relative contribution of glucose absorption through SGLT1 and GLUT2. Based, on simulations of their model, they postulate that at high concentrations of glucose, glucose absorption through SGLT1 is saturating contrary to the absorption through GLUT2. We believe that this conclusion is actually an artifact of their model that neglects the regulation of the transporters by assuming that their amount is constant over time. We actually know that those transporters are highly regulated and believe that this should have an effect on their absorption efficiency.

Project work

In this project, we want to test an extension of the model of (Afshar et al. 2019) with a simple regulation of the transporters. The student will have to

- read both papers (Thorsen, Drengstig, and Ruoff 2014) and (Afshar et al. 2019),
- download and study the implementation of the Matlab model of (Afshar et al. 2019),
- depending on the student knowledge, he will either directly work with Matlab or reimplement it in Python,
- extend the model (and its implementation) with the regulation of SGLT1 and GLUT2,
- confront, through simulations, the conclusions of (Afshar et al. 2019) paper with simulations of the new model.

Bibliographie

Afshar, Nima, Soroush Safaei, David P Nickerson, Peter J Hunter, and Vinod Suresh. 2019. "Computational Modeling of Glucose Uptake in the Enterocyte." *Frontiers in Physiology* 10: 380.

Basu, Paula AND Hills, Sanjay AND Yoffe. 2013. "The Relationship of Sugar to Population-Level Diabetes Prevalence: An Econometric Analysis of Repeated

Cross-Sectional Data." *PLOS ONE* 8 (2): 1–8. https://doi.org/10.1371/journal.pone.0057873.

Baud, Gregory, Mehdi Daoudi, Thomas Hubert, Violeta Raverdy, Marie Pigeyre, Erik Hervieux, Magalie Devienne, et al. 2016. "Bile Diversion in Roux-En-Y Gastric Bypass Modulates Sodium-Dependent Glucose Intestinal Uptake." *Cell Metabolism* 23 (3): 547–53. https://doi.org/https://doi.org/10.1016/j.cmet.2016.01.018.

Ferraris, R. P., and J. Diamond. 1997. "Regulation of Intestinal Sugar Transport." *Physiological Reviews* 77 (1): 257–302. https://doi.org/10.1152/physrev.1997.77.1.257.

Fiorentino, Teresa Vanessa, Evelina Suraci, Gaetano Paride Arcidiacono, Antonio Cimellaro, Chiara Mignogna, Ivan Presta, Francesco Andreozzi, et al. 2017. "Duodenal Sodium/Glucose Cotransporter 1 Expression Under Fasting Conditions Is Associated with Postload Hyperglycemia." *The Journal of Clinical Endocrinology & Metabolism* 102 (11): 3979–89. https://doi.org/10.1210/jc.2017-00348.

Seidelmann, Sara B., Elena Feofanova, Bing Yu, Nora Franceschini, Brian Claggett, Mikko Kuokkanen, Hannu Puolijoki, et al. 2018. "Genetic Variants in Sglt1, Glucose Tolerance, and Cardiometabolic Risk." *Journal of the American College of Cardiology* 72 (15): 1763–73. https://doi.org/10.1016/j.jacc.2018.07.061.

Thorsen, Kristian, Tormod Drengstig, and Peter Ruoff. 2014. "Transepithelial glucose transport and Na+/K+ homeostasis in enterocytes: an integrative model." *American Journal of Physiology. Cell Physiology* 307 (4): C320–37.