Modeling the regulation of glucose absorption in intestinal cells

PhD project

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Abstract. Type 2 Diabetes (T2D) is the main epidemic of this century. A recent hypothesis of medical research is that an important cause of T2D may be the abnormal regulation of glucose absorption in the small intestine. Despite of many experimental observations, this question remains poorly investigated. The objective of the present project is to investigate the regulation of glucose absorption at the cellular level of the intestin. First, a simple model of glucose absorption regulation, based on existing ones and on new experimental data, will be proposed. The aim is to decypher the relative contribution of the two main glucose transporters SGLT1 and GLUT2. Second, a more detailed model will be proposed to study the cellular trafficking of glucose transporters and its impact on glucose absorption.

Scientific context

Type 2 Diabetes (T2D) is the main epidemic of this century: it affects nearly 400 million people worldwide raising highly pressing and costly healthcare challenges.

Since the discovery of insulin nearly 100 years ago, T2D was defined by its (physiopathological) effects: an increase of glycemia that comes with a decrease of the secretion of insulin in combination with insulin resistance (ie. muscle and fat tissues are less responsive to insulin signal to absorb the glucose and restore a normal glycemia). These effects are targeted by most drugs clinically available today. However, the causes of these effects are not cured nor well-understood. As a consequence, these treatments are not very efficient.

Growing evidence suggests the role of glucose absorption by the small intestine [2, 3] which abnormal functioning may significantly contribute to T2D. At the level of epithelial cells of the small intestine, glucose absorption through dedicated transporters is indeed highly regulated. The consumption of a diet rich in glucose leads to an increase of these transporters and in particular of a transporter called SGLT1 [4]. In patients with T2D, we observe a genetic over-expression of SGLT1. Moreover, mutations in the gene SGLT1 entail lower risk of glucose intolerance and obesity [5]. These indicate that SGLT1 may have a crucial role in the desease.

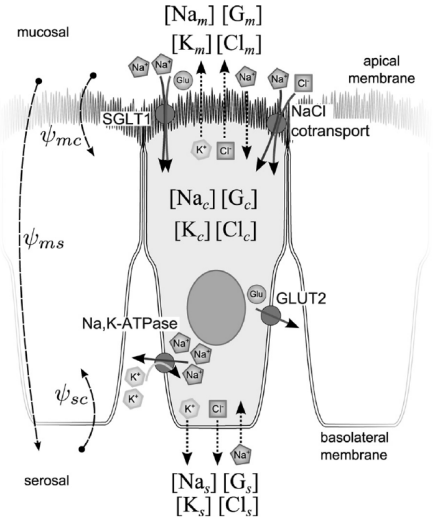

Fig. 1. Enterocytes regulation from [1].

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 epithenial cells of the intestin (called *enterocytes*). In [1], the authors propose a sophisticated mathematical model (defined in terms of ordinary differential equations (ODEs)) to study the interplay between glucose absorption (through SGLT1) and Na+/K+ homeostasis. In this model, glucose uptake is mainly driven by membrane potential maintained by active exchange of Na+ and K+ (through Na/K-ATPase pumps) and specific types of ion channels [6].

More recently, in [7], the previous model is extended to include the additional glucose transporter GLUT2 that was previously omitted. Still, this model ignores the dynamics of the transporters and considers them in constant number in the apical membrane.

There is a debate in the literature about the respective roles of transporters SGLT1 and GLUT2 in abnormal glucose absorption in diabetes. While some experimental works suggest that "SGLT1 is unequivocally the prime intestinal glucose transporter even at high luminal glucose concentration" [8], the model of [7], based on different experimental data, predicts that GLUT2 also plays a significant role in diabetic conditions. In addition, the cellular trafficking of these transporters are still poorly understood [9] and no computational model exists.

Existing models are based on ODEs, where the variables represent the time course concentration of the molecular species of interest. Numerical simulation is most often the only feasible approach for the analysis of these systems: even simple ODE systems rarely have known analytical solutions, therefore one has to resort to numerical integration. This requires the estimation of parameters from experimental data. This, however, is rarely feasible for all parameters. In addition, depending on the level of detail of the model and on the available observable quantities, parameter identifiability issues can arise, that are often unsolvable.

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Project work

In this PhD project, we propose to use reaction networks instead of ODE models. A reaction network is a system of chemical reactions made of reactants, products and a kinetics that specifies the rate of the reaction at any time point. The advantage of reaction networks is that, in addition to possibly derive ODE models if needed, they provide a structure that can be represented as a graph. Several qualitative analysis (ie. independantly of the parameter values) can then be used to make approximate predictions. In particular, abstract interpretation is one such interesting approach [10] that will be used and improved in this thesis. Based on this methodological approach, the modelling objectives are twofold.

On the relative contribution of SGLT1 and GLUT2 to intestinal absorption. (*first year*)

Facing food-derived high glucose luminal concentrations, *the intestine rapidly adapts its glucose absorption capacity through the recruitment of pending glucose transporters*. Rapid adjustment of SGLT1 abundance comes along with an additional pivotal mechanism of adaptation of GLUT2 abundance in the apical membrane. This complex dynamic process plays an important role in absorption and its modeling will surely contribute to understand how it can affect diabetes.

A *reaction network* model of cellular intestinal glucose absorption derived from the ODE model of [7] and extended with a simple regulation of transporter dynamics will be designed. In this first model, we will disregard sub-cellular transporter trafficking and make the amount of SGLT1 and GLUT2 in the apical membrane dependent on luminal glucose concentration. This model will be calibrated, fine-tuned and validated using our experimental data. The resulting model will be able to predict relative quantitative contribution of glucose transporters SGLT1 and GLUT2 to glucose absorption.

Modeling and analysis of sub-cellular SGLT1 and GLUT2 trafficking. (*second and third year*)

In response to food ingestion, a rapid adaptation of the activity of SGLT1 and GLUT2 is necessary. Short-term posttranslational regulation mechanisms are triggered to increase glucose absorption capabilities of enterocytes: this entails the fusion to the apical membrane of SGLT1-containing recycling endosomes and vesicles from the Golgi [9]; in addition, GLUT2 is rapidly translocated at the apical membrane from intracellular stores. Despite being pivotal to potentially address new drugs, the current knowledge on the involved pathways are still insufficient. Based on the new experimental findings that will be carried out in the UMR1011, the first formal (reaction network) model of transporter trafficking will be delivered which will improve the understanding of their regulation.

References

1. Thorsen, K. *et al.* Transepithelial glucose transport and Na+/K+ homeostasis in enterocytes: an integrative model. *American journal of physiology. Cell physiology* **307,** C320–37 (Aug. 2014).
2. Baud, G. *et al.* Bile Diversion in Roux-en-Y Gastric Bypass Modulates Sodium-Dependent Glucose Intestinal Uptake. *Cell Metabolism* **23,** 547–553 (2016).
3. Basu, S. *et al.* The Relationship of Sugar to Population-Level Diabetes Prevalence: An Econometric Analysis of Repeated Cross-Sectional Data. *PLOS ONE* **8,** 1–8 (Feb. 2013).
4. Ferraris, R. P. & Diamond, J. Regulation of intestinal sugar transport. *Physiological Reviews* **77.** PMID: 9016304, 257–302 (1997).
5. Seidelmann, S. B. *et al.* Genetic Variants in SGLT1, Glucose Tolerance, and Cardiometabolic Risk. *Journal of the American College of Cardiology* **72,** 1763–1773 (2018).
6. Schultz, S. G. *et al.* Electrophysiological studies of sodium cotransport in epithelia: toward a cellular model. *Ann. N. Y. Acad. Sci.* **456,** 127–135 (1985).
7. Afshar, N. *et al.* Computational Modeling of Glucose Uptake in the Enterocyte. *Frontiers in physiology* **10,** 380 (2019).
8. Röder, P. V. *et al.* The Role of SGLT1 and GLUT2 in Intestinal Glucose Transport and Sensing. *PLOS ONE* **9,** e89977 (2014).
9. Koepsell, H. The Na^+-D-glucose cotransporters SGLT1 and SGLT2 are targets for the treatment of diabetes and cancer. *Pharmacol. Ther.* **170,** 148–165 (Feb. 2017).
10. Niehren, J. *et al.* Predicting Changes of Reaction Networks with Partial Kinetic Information. *Biosystems. Selected Papers from the Computational Methods in Systems Biology 2015 Conference* **149,** 113–124 (Nov. 2016).