The role of iron and zinc in retinal physiology and disease: Development of a metabolic systems model

Eva Caamaño Gutiérrez

Introduction

- **Diabetic retinopathy** (DR):
  - Leading cause of blindness in working-age individuals in developed countries.
  - Microcirculatory disease of the retina due to the deleterious metabolic effects of hyperglycemia typical of diabetic patients [1].
- **Main cause of pathogenesis**: variations contributing to oxidative stress and biochemical imbalances.
  - Iron misbalance → Reactive oxygen species (ROS) [2].
  - Zinc → role in functioning of the retina and essential for antioxidant defence mechanisms [2].
  - Zn and Fe have similar properties and compete for ligands. It is very important to maintain their homeostasis.
- **The problem:** DR often has no early warning signs and evaluating the risk status of the diabetic is extremely complex.
- **The aim:** Creation of a mathematical model which will provide deeper scientific understanding of the process. It might be also useful to predict the damage caused by misregulation of metal ions.

The model

- Built using Simbiology® (Matlab®) which uses the System Biology Markup Language. As input, chemical reactions which describe the process described in figure 1, were used.
- Concentration of zinc and iron modulates the expression of the transferrin receptor, transferrin and ferritin and they were taken into account.
- Assuming the differential equations formalism: variables evolve continuously and in deterministic way; a model with 16 variables and 26 parameters was created.
- Population of the model with parameter values and initial values of concentration variables obtained through extensive literature review.
- Three situations were simulated in order to spot the changes in the homeostasis
  - Normal individual (taken as normal literature values).
  - High levels of iron (e.g. diabetic patients [3]).
  - Low levels of zinc.

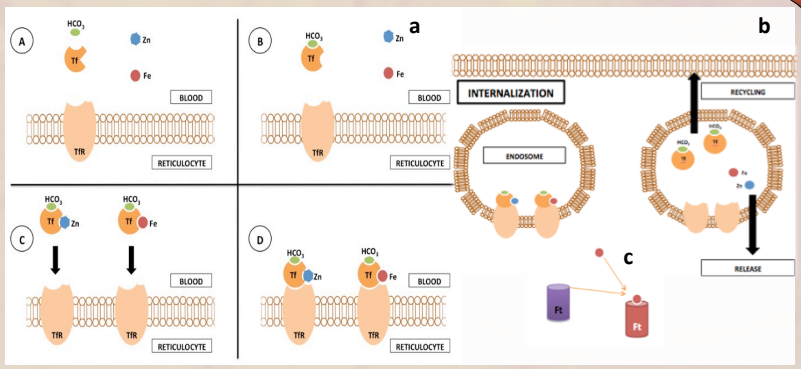

Figure 1: Biological process: (**a**) Binding to the transferrin receptor:(A) Free transferrin (Tf) is inefficient in the binding of metallic ions until (B) HCO3 is bound to it. Once the complex *Tf-HCO3* is formed, *Fe* and *Zn* can bind to it (C and D) although Tf has higher affinity for iron. (**b**) Transport of iron and zinc: endosome internalization and recycling of transferrin and transferrin receptor (*TfR*). (**c**) Storage of iron in ferritin (*Ft-Fei*).

Simulation results

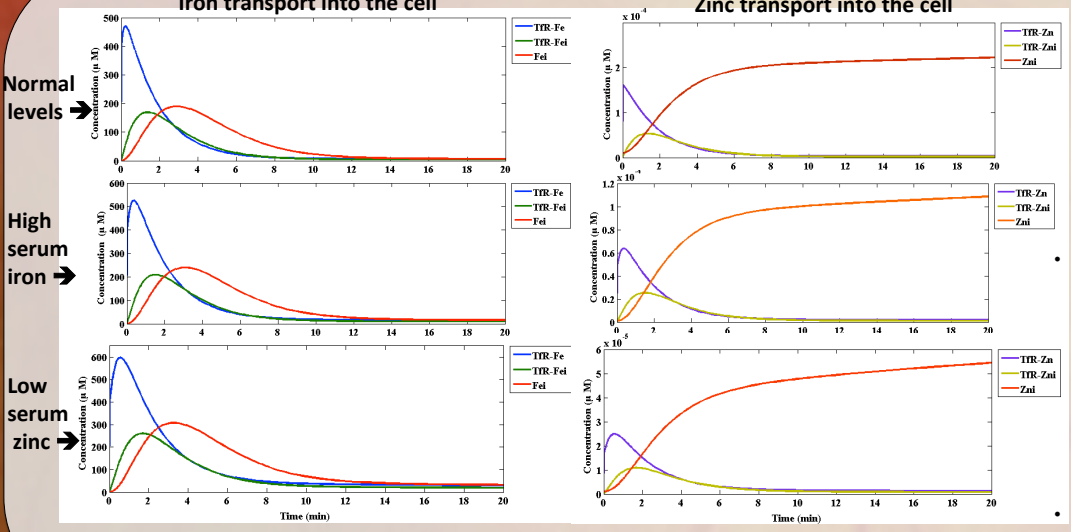

Figure 2: Iron and zinc transports through the transferrin receptor (*TfR*). Note that the small 'i' means inside the cell.

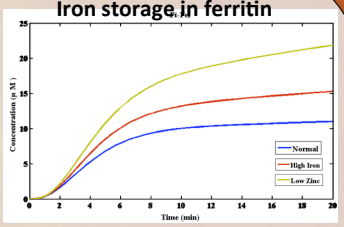

Figure 3: Ferritin storage of iron .

- Lower levels of zinc provoke an increase in the rate of production of the transferrin receptor but, as the affinity of iron by transferrin is much higher than the one of zinc, there is more iron-transferrin complex available to bind to the receptor and ultimately the concentration of iron increases inside the cell as a consequence of a decrease in the serum concentration of zinc. Proportionally the ferritin bound to iron increases as well (fig. 3).
- Higher levels of iron displace zinc whilst binding transferrin (fig. 2) and provoke a higher internalization of iron than zinc.

Conclusions and future work

- Simulations show from the equilibrium levels reached that the model qualitatively reflects the characterized mechanism, as the machinery determined by the transferrin receptor allows to adapt the internal state of the cell to changes in the external and internal levels of iron and/or zinc.
- The study of the disease situations manifest the delicate homeostasis of the process and how the imbalance of one of the metallic ions studied would destabilize the system. This is of great importance as little is known about the role of micronutrients (e.g. iron and zinc) in relation to type 2 diabetes risk [4].
- Future work:
  - To improve the power of the model: design experiments to obtain specific variables and parameters values for the tissue studied (e.g. retina) in order to homogenize the data from the literature review.
  - To improve the diagnosis and risk evaluation accuracy of the model:
    - Obtain values of metallic concentrations in the different layers of the retina as it is stratified.
    - Obtain data from different cohorts of individuals classify in genders and ages as the metal distribution varies among these categories.

References

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