Mechanistic modeling approach for explanation of metabolic memory phenomena among diabetic patients

Veronika Voronova, Kirill Zhudenkov

M&S decisions LLC, Moscow, Russia

EXECUTIVE SUMMARY

- Relations between hyperglycemia, oxidative stress and diabetic complications is widely discussed. Main observations from experiments are following: (1) preservation of oxidative stress after glucose normalization; (2) more crucial effect of instable glucose versus constant high glucose on living systems;
- A semi-mechanistic model explaining effect of hyperglycemia on *in vitro* ROS production was proposed and verified against the published data;
- The model is able to reproduce the experimental data and was used to better understand the relationship between glucose and oxidative stress.

INTRODUCTION

Diabetes mellitus is associated with increased plasma glucose level also known as hyperglycemia. Daily plasma glucose profiles in patients are determined by numerous factors and some of them are associated with higher risk of vascular complications. Oxidative stress is a key mechanism linking hyperglycemia with vascular endothelial cell abnormalities [1].

Effect of different glucose patterns on reactive oxygen species (ROS) generation was studied *in vitro*. The experiments demonstrate sophisticated glucose effect on ROS [2-10]. Metabolic memory (MM) (preservation of oxidative stress after glucose normalization) and a more deleterious effect of oscillating comparing to constant high glucose on oxidative stress are such examples [1-10].

OBJECTIVES

The objective of the current study was to explain mechanisms and provide a quantitative description of glucose effect on ROS dynamics with respect to several hypotheses proposed in the literature [1].

METHODS

- The model represents ordinary differential equation (ODE) system programmed in the Matlab based package IQM Tools (replacing the SBTOOLBOX2 - http://www.intiquan.com/). Parameters estimation was performed in the Monolix software by Lixoft (http://lixoft.com/products/monolix/);
- Metabolic memory effect is implemented as a positive feedback between ROS (ROS variable) and ROS-induced cell damages (MM variable) [1]. AD variable denotes sum of adaptation mechanisms, which decreases glucose impact on ROS synthesis;
- Data from numerous published experiments were used to verify the parameters [2-12];
- ROS generation experiments by HUVEC cultures were reproduced in the model implying exposure either to constant high (CG) or to oscillating between normal and high glucose over fixed time intervals (OG).

Figure 1. The model scheme

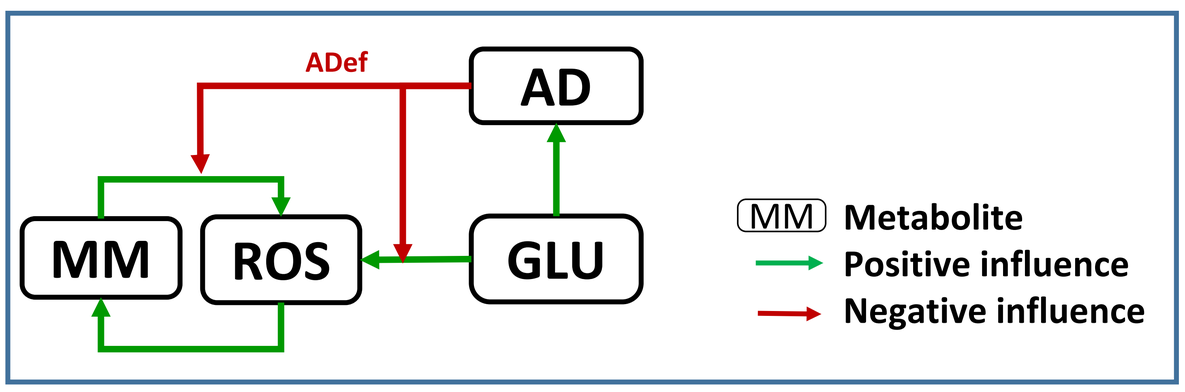
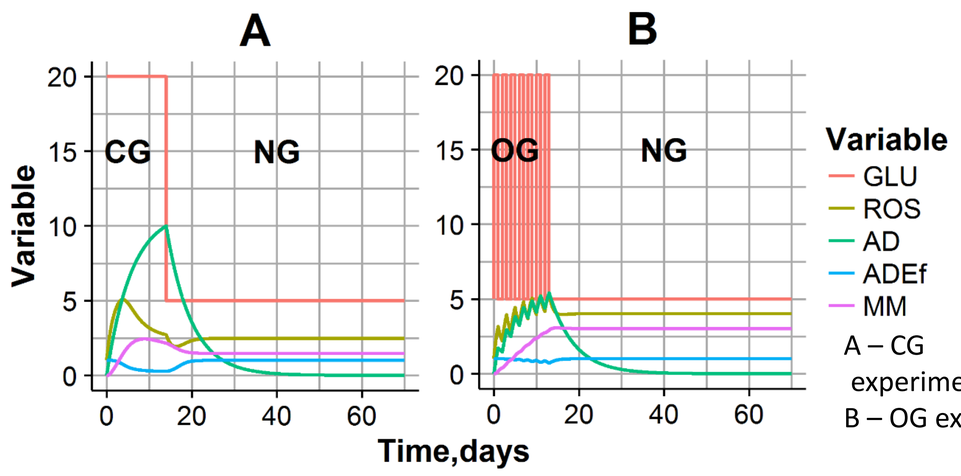


Figure 2. Metabolite dynamics in a typical experiment



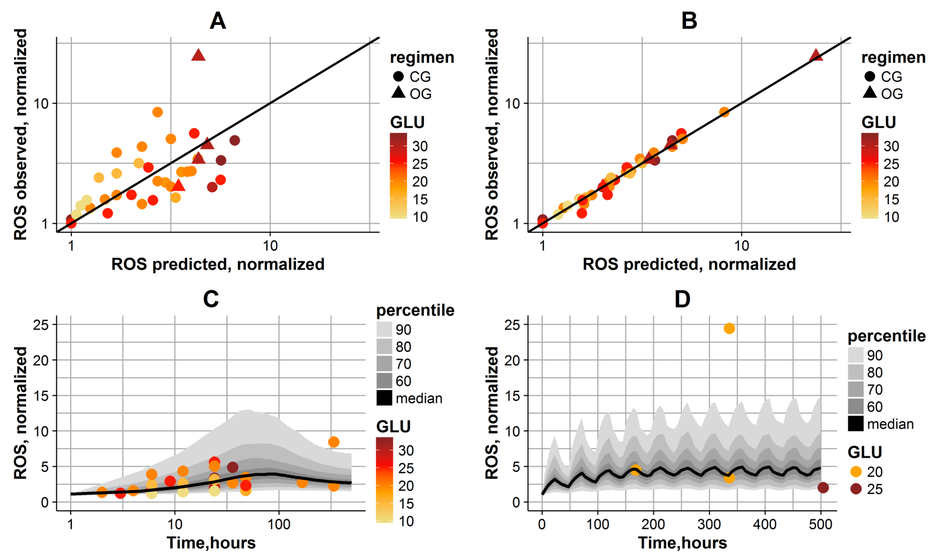
A – CG experiment;
B – OG experiment.

- Increased ROS level is supported in the model after glucose normalization (fig. 2);
- Accumulation of adaptation is stronger in CG experiment in comparison to OG experiment (fig. 2).

RESULTS

Quality of experimental data reproduction by the model

Figure 3. The goodness of fit plots for the ROS levels



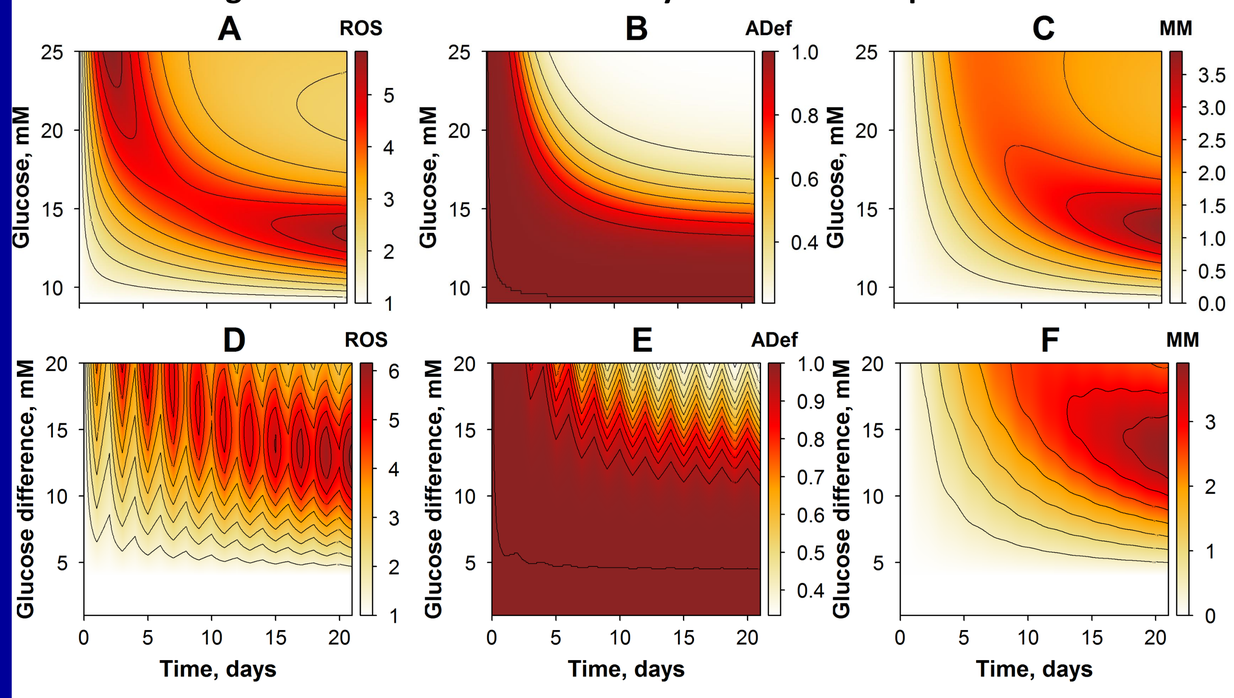
Data were taken from studies [2-10].

A. Observed vs predicted; population fit
B. Observed vs predicted, individual fit;
C. ROS dynamics in CG experiments;
D. ROS dynamics in OG experiments.

- High between-study variability is covered by random effects for two parameters, responsible for ROS turnover and glucose effect on ROS generation. Other parameters are the same for all experiments (fig. 3A, B);
- The bell-shaped ROS dynamics is observed in CG experiments with maximum ROS level at the second day of the experiment (fig. 3C);
- Oscillating ROS dynamics is observed in OG experiments with gradual increase of mean ROS level. ROS does not return to basal level during periods of glucose normalization (fig. 3D).

Model predictions

Figure 4. Predicted metabolite dynamics in the experiments



A, B, C – CG;
D, E, F – OG;

A, D – ROS;
B, E – Adaptation effect on ROS;
C, F – MM.

- Positive dose-dependent glucose effect on ROS within a first few days of the experiment for CG (fig. 4A) and during the whole period for OG experiments (fig. 4D). Positive correlation between amplitude of glucose oscillations and ROS production (fig. 4D);
- The bell-shaped ROS dynamics with time can be observed for cells exposed to higher glucose levels in CG experiments (fig. 4A). This can be explained by the influence of adaptation on ROS production (fig. 4B);
- MM behavior is similar to ROS behavior in CG and OG experiments but amplitude of MM oscillations in OG experiments is small (fig. 4A, C, D, F). This can be explained by longer MM variable half-life (4 days);
- No cell adaptation to OG with amplitude of oscillations less than 10 mM (fig. 4E).

CONCLUSIONS

- The proposed model quantitatively describes glucose-dependent ROS production and illustrates metabolic memory phenomenon;
- Metabolic memory phenomenon can be explained by the system of positive feedback between reactive oxygen species (ROS) and cell alterations, such as mitochondrial protein damage;
- More pronounced effect of instable glucose comparing to constant glucose on oxidative stress can be explained by insufficient cell adaptation to variable environment.

REFERENCES

1. Schisano B et al. Diabetologia. 2011 May;54(5):1219–26;
2. Ho FM et al. Circulation. 2000 Jun 6;101(22):2618–24;
3. Wang L et al. Nan Da Xue Xue Bao Yi Xue Ban. 2014 Dec;39(12):1253–8;
4. Meng X et al. Clin Exp Med. 2008 Mar;8(1):43–9;
5. Quagliaro et al. Diabetes. 2003 Nov;52(11):2795–804;
6. Quagliaro L et al. Atherosclerosis. 2005 Dec;183(2):259–67;
7. Wu QD et al. Am J Physiol. 1999 Dec;277(6 Pt 1):C1229–38;
8. Patel H et al. Cardiovasc Diabetol. 2013;12:142;
9. La Sala L et al. Acta Diabetol. 2015 Jun;52(3):505–12;
10. Hou Q et al. Cardiovasc Toxicol. 2015 Apr;15(2):140–6;
11. Lipsky NG et al. J Biol Chem. 1981 Aug 25;256(16):8652–7;
12. Schisano B et al. Diabetologia. 2011 May;54(5):1219–26.

AKNOWLEDGEMENTS

We would like to thank Kirill Peskov from M&S Decisions LLC and Tatiana Karelina from ISB Moscow for their contribution to the modeling discussions.

CONTACTS

Veronika Voronova e-mail:
Veronika.Voronova@msdecisions.ru.