Virtual Liver
HepatoSys

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Blood Glucose Control by the Human Hepatocyte

Berlin: Modelling
Kinetic Modell of the Hepatocyte

Matthias König, Sascha Bulik & Hermann-Georg Holzhütter
Institute of Biochemistry, Charité - Universitätsmedizin Berlin, Seestr. 73, 13347 Berlin, Germany

Introduction

Plasma glucose levels are tightly controlled to ensure a constant glucose supply and to avoid toxic effects of hyperglycemic conditions. The liver is the central organ of glucose homeostasis and the main glucose producer (**hepatic glucose production HGP**), but also utilizes glucose for biosyntheses and storage in fatty acids (**hepatic glucose utilization HGU**).

Results

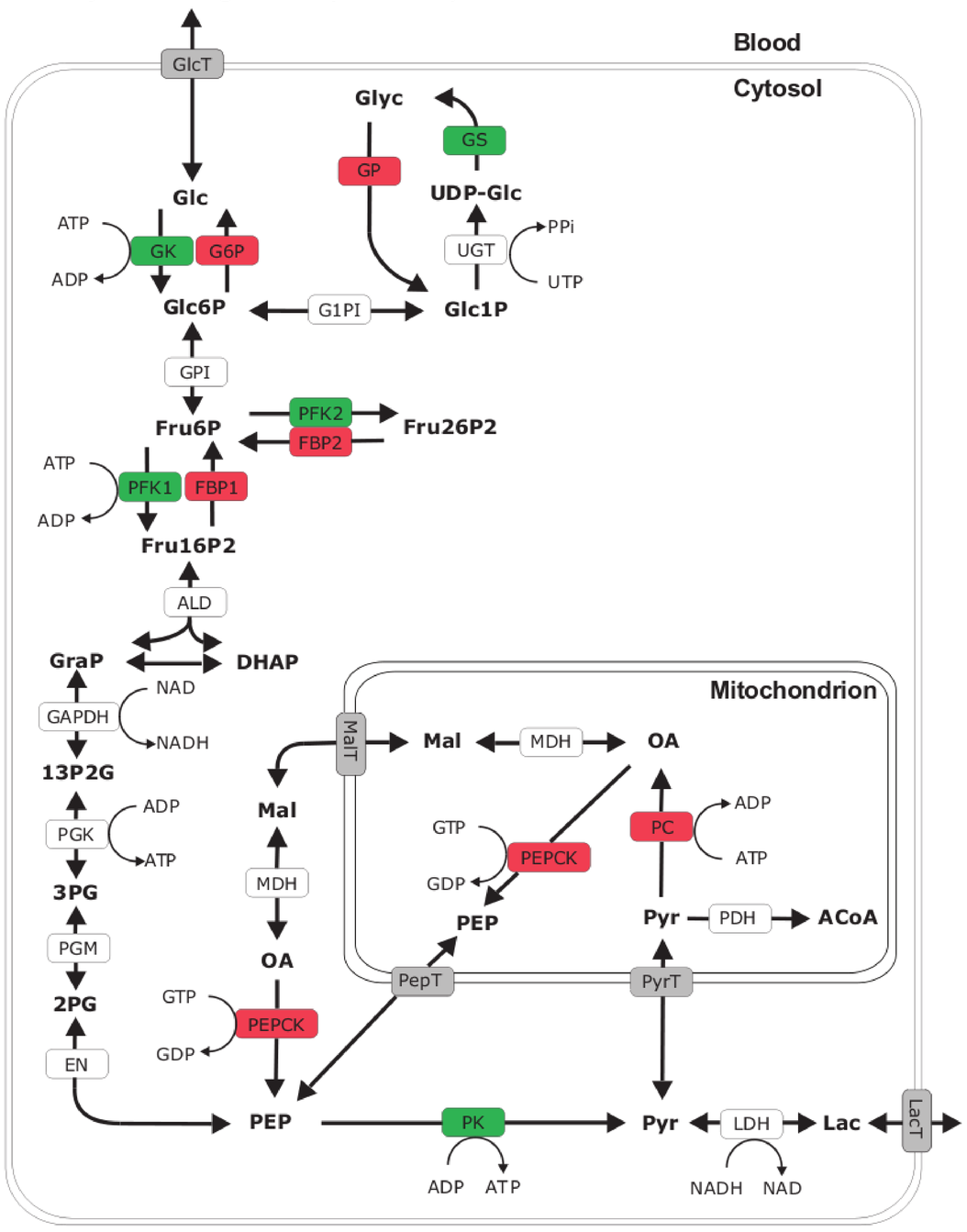
We present the first detailed kinetic model of the human hepatocyte glucose metabolism [Fig.1] which comprises allosteric regulation as well as hormonal regulation by insulin and glucagon via inter-convertible enzymes [Fig.2]. The model reproduces fundamental features of hepatic glucose metabolism like

- glucose dependent **switch between HGP and HGU** [Fig.3]
- **observed changes** in glucose homeostasis **in diabetes II** [Fig.4]
- **dependency** of HGP **on gluconeogenic substrates** (lactate)

Outlook

Possible future applications of the model are

- analysis of hepatic effects of various diabetic treatments
- simulations of the influence of temporary changes in the gene expression on the glucose homeostasis (for example circadian rhythms of gene expression)



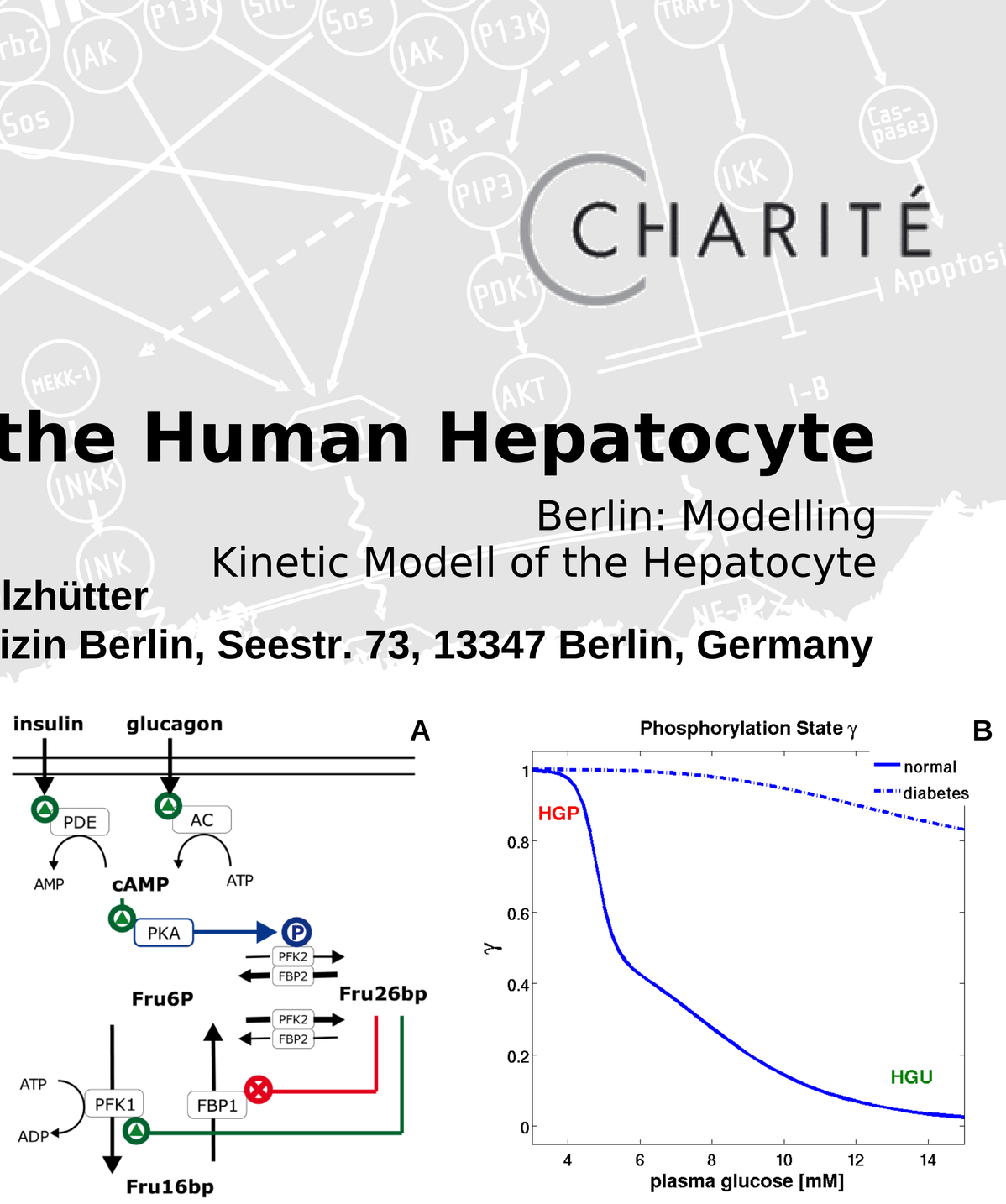


Fig.2: [A] Insulin and glucagon signal cascade to key enzymes of the HGU and HGP (PFK1 and FBP1) Example of the PFK1 and FBP1 regulation by PFK2/FBP2 and allosteric effector fru26bp.
[B] Changes in phosphorylation state of key enzymes depending on blood glucose concentration. With increasing blood glucose concentration the phosphorylation state of key interconvertible enzymes decreases.

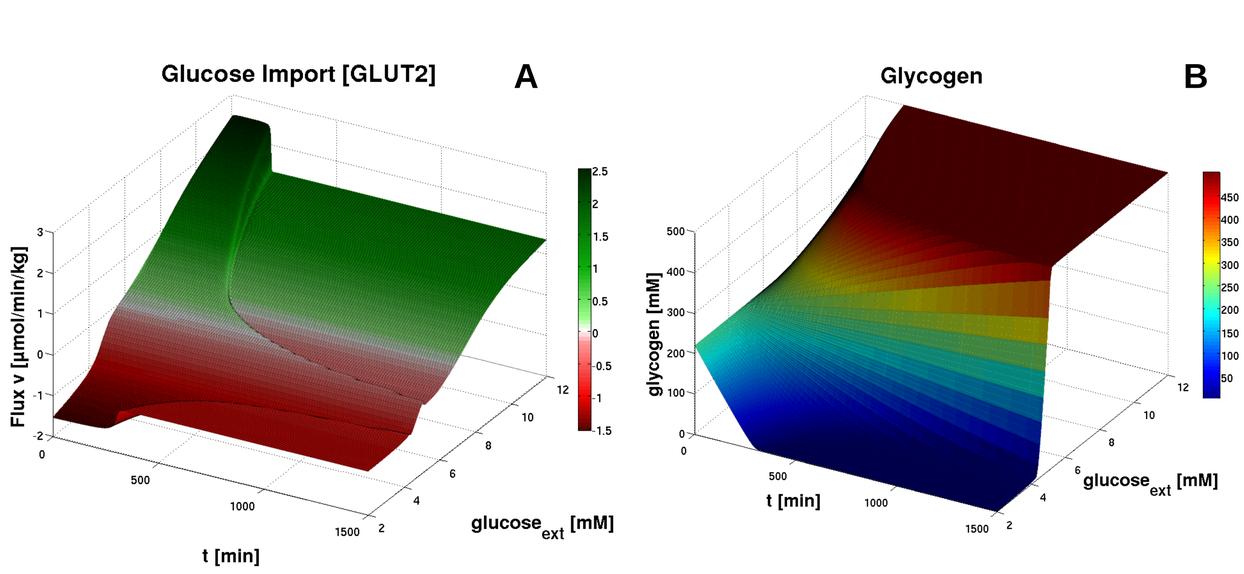


Fig.3 Switch between HGU and HGP depending on the blood glucose concentration. [A] Glucose import and [B] glycogen content of the hepatocyte depending on blood glucose concentration and time. Under hypoglycaemic conditions the glycogen store is emptied, the hepatocyte perfoms HGP.

Under hyperglycaemic conditions the glycogen stores are filled, HGU is observed.

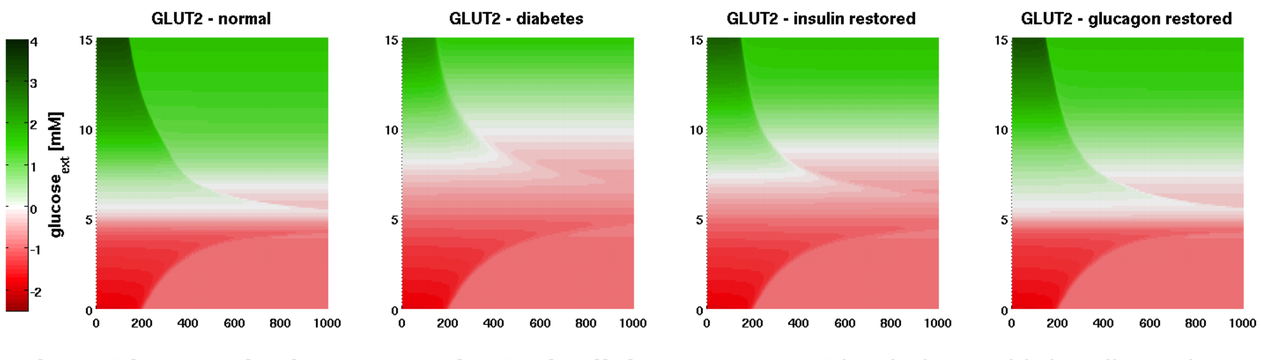


Fig.4: Changes in the HGU and HGP in diabetes type II. Simulations with insulin and glucagon response curves observed in diabetes type II shift the switch point to higher blood glucose. HGU is decreased, HGP increased. Restoration of insulin and glucagon response curve lead to an shift of the switch point to lower glucose concentration compared to diabetes phaenotype. Glucagon restoration is more effective than insulin.

< Fig.1: Overview kinetic network of human hepatocyte glucose metabolism (36 reactions, 49 metabolites, 3 compartments) including glycolysis, gluconeogenesis and glycogen metabolism. HGU reactions are depicted in green, HGP in red. Model is a detailled ODE model which includes allosteric regulations and hormonal regulations based on interconvertible enzymes.

Contact:
Matthias König
Charité - Universitätsmedizin Berlin
Institute of Biochemistry
Phone.: +49 30 450-528-396
Fax.: + 49 30 450-528-937
E-Mail: matthias.koenig@charite.de

Federal Ministry
of Education
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