DIABETES-LINKED DEFICIENCY OF TRANSCRIPTION FACTOR HNF4A RESULTS IN IMPAIRED METABOLISM OF ASYMMETRIC DIMETHYLARGININE AND BETA-AMINOISOBUTIRIC ACID - A NOVEL MECHANISM OF CARDIOVASCULAR COMPLICATIONS IN METABOLIC SYNDROME?

R.N. Rodionov[1], D.V. Burdin[2], A.A. Kolobov[3], C. Brocker[4], A.A. Soshnev[5], N. Samusik[6], A.V. Demyanov[2], S. Brilloff[1], N. Jarzebska[1], J. Martens-Lobenhoffer[7], M. Mieth[8], R. Maas[8], S. Bode-Böger[7], F. Gonzalez[4], S.R. Bornstein[9], N. Weiss[1]

[1]*University Center for Vascular Medicine, University Hospital Carl Gustav Carus, Technische Universität Dresden, Germany*

[2]*Department of Physiology, Saint-Petersburg State University, Russia*

[3]*Department of Biochemistry, Saint-Petersburg State University, Russia*

[4]*Center for Cancer Research, National Cancer Institute, USA*

[5]*Laboratory of Chromatin Biology and Epigenetics, The Rockefeller University, USA*

[6]*Department of Microbiology and Immunology, Stanford University School of Medicine, USA*

[7]*Institute of Clinical Pharmacology, Otto-von-Guericke University, Germany*

[8]*Institute of Experimental and Clinical Pharmacology and Toxicology, Friedrich-Alexander-University Erlangen-Nürnberg (FAU), Germany*

[9]*Department of Internal Medicine III, University Hospital Carl Gustav Carus, Technische Universität Dresden, Germany*

Background: Alanine-glyoxylate aminotransferase 2 (AGXT2) regulates nitric oxide (NO) bioavailability by metabolizing an endogenous inhibitor of NO synthases asymmetric dimethylarginine (ADMA). An alternative substrate of AGXT2, beta-aminoisobutyric acid (BAIBA), is an important regulator of lipid metabolism. Using bioinformatic approach we identified a highly conserved putative binding site for the diabetes-associated transcription factor hepatic nuclear factor 4 alpha (HNF4A) in the mammalian AGXT2 promoter. In this study we tested the hypothesis that HNF4a is the major regulator of AGXT2 expression and activity. Methods and results: Direct binding of HNF4A to the *Agxt2* promoter region in murine hepatic cell line Hepa 1-6 was demonstrated using chromatin immunoprecipitation assay. Mutations of the predicted HNF4A binding site in the Agxt2 core promoter caused a decrease in the promoter activity as assessed by luciferase reporter assay. siRNA-mediated knockdown of HNF4a led to reduction of *Agxt2* expression level in the Hepa 1-6 cells. Liver-specific *Hnf4a* knockout in mice resulted in significantly reduced liver *Agxt2* mRNA levels, decreased liver AGXT2 activity and increased plasma levels of ADMA and BAIBA. Conclusions: In this study we identified HNF4a as the major regulator of AGXT2 expression. These results suggest that diabetic patients with HNF4A deficiency might have a unique mechanism for development of cardiovascular complications via AGXT2-dependent impairment of lipid metabolism and ADMA-mediated vascular dysfunction. Our findings are especially intriguing, because the specific product of ADMA metabolism by AGXT2 asymmetric dimethylguanidino valeric acid (ADGV) has just been identified as predictor of future diabetes mellitus in the Framingham offspring cohort.