CONGENITAL HYPERINSULINISM CAUSED BY A COMBINATION OF NOVEL HETEROZYGOUS ABCC8 AND KCNJ11 MUTATIONS

Klara Rozenkova¹, Azizun Nessa², Barbora Obergmannova, Lenka Dusatkova, Petra Dusatkova, Zdenek Sumnik, Ondrej Cinek, Jan Lebl, Khalid Hussain²-3, Stepanka Pruhova¹

¹Department of Paediatrics, 2nd Faculty of Medicine, Charles University in Prague and University Hospital Motol, Prague, Czech Republic
²Genetics and Epigenetics in Health and Disease, Genetics and Genomic Medicine Programme, Institute of Child Health, University College London, London, UK
³Department of Paediatric Endocrinology, Great Ormond Street Hospital for Children NHS Trust, London, UK

Background

- Congenital Hyperinsulinism (CHI) is a common cause of persistent hypoglycaemia in the neonatal and infant period. It is most commonly caused by mutations in one of the K<sub>ATP</sub> channel subunits, either SUR1 encoded by the gene ABCC8 or Kir6.2 encoded by the gene KCNJ11. Patients carrying mutations in the ABCC8 and KCNJ11 genes simultaneously have not been reported yet.

Objective and Hypothesis

- Our aim was to perform in-vitro functional analysis of a combination of novel heterozygous ABCC8 (Y1293D) and KCNJ11 (R50W) mutations found in one Czech patient with CHI in order to clarify the pathogenic effect on the pancreatic β-cell function.

Methods

- Novel heterozygous ABCC8 (Y1293D) and KCNJ11 (R50W) mutations were created in-vitro using site-directed mutagenesis. The functional analysis using radioactive Rubidium (⁸⁶Rb) was performed in HEK293 cell cultures transfected with a combination of these novel heterozygous ABCC8 and KCNJ11 genes mutations. Mutant and wild type (WT) channels were exposed to different drug conditions: control (DMSO), 100µM diazoxide, 100µM diazoxide and 10µM glibenclamide, 2.5mM NaCN and 20mM 2-deoxy-D-glucose and 2.5mM NaCN, 20mM 2-deoxy-D-glucose and 10µM glibenclamide. ⁸⁶Rb efflux was measured in a liquid scintillation counter using Cherenkov radiation.

Results

- The functional study of this unique heterozygous combination of ABCC8 (Y1293D) and KCNJ11 (R50W) mutations revealed that the activation by diazoxide in mutated K<sub>ATP</sub> channels was decreased by 60.1% when compared to WT channels.

Conclusion

- We report for the first time a patient with CHI caused by a combination of novel heterozygous mutations in both of the genes (ABCC8 and KCNJ11) encoding the K<sub>ATP</sub> channel subunits. We have proved a pathogenic effect on the pancreatic β-cell function of this combination of mutations by an in-vitro functional study.

Supported by a grant from the Czech Ministry of Health (NT11402), by the Grant Agency of Charles University (GAUK 248 213) and ESPE Short-term Research Fellowship for Klara Rozenkova.

klara.rozenkova@fmotol.cz