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Thiamine transporters and hyperglycaemia-induced damage in human retinal cells

Author Block: E. Beltramo, A. Mazzeo, M. Porta;
Dept Internal Medicine, University of Turin, Torino, Italy.

Abstract:

Background and aims: Thiamine, a co-factor for transketolase and other glycolytic enzymes, counteracts high glucose-induced damage in microvascular cells in vitro and prevents progression of retinopathy and nephropathy in diabetic animals. Impaired thiamine availability may facilitate metabolic damage, and diabetes might be considered a thiamine-deficient state, if not in absolute terms, at least relative to the increased requirements deriving from accelerated glucose metabolism in non-insulin dependent tissues prone to complications. Renal loss via proximal tubules, resulting in reduced thiamine/transketolase activity, has been described in diabetic patients. We previously described 2 single nucleotide polymorphisms (SNPs), rs12694743 and rs6713116, located in the SLC19A3 gene encoding for the thiamine transporter THTR2, and associated with resistance to development of proliferative diabetic retinopathy and end-stage renal disease in type 1 diabetic subjects. The protective effects of these SNPs may work either through loss of function, decreasing the discharge of thiamine, or gain of function, by increasing its uptake in target tissues. The objective of this work was to investigate if, in human retinal cells, a diabetic-like microenvironment is able to modulate the expression of the two thiamine transporters THTR1 and THTR2 and their transcription factor Sp1.

Materials and methods: Human retinal pericytes (HRP), human microvascular endothelial cells (HMEC) and human Mueller cells (MIO-M1) were cultivated for 8 days in physiological glucose (NG), stable high glucose (HG) or intermittent physiological/high glucose conditions (IntHG) (n=6). To investigate substrate influence on the expression of transporters, cells were also cultured in thiamine-deficient medium (noT) or in high thiamine conditions (50μmol/l, HT) (n=6). THTR1, THTR2 and Sp1 mRNA expression was checked by relative quantitative RT-PCR and protein expression by Western blotting.

Results: Our results show that both transporters and Sp1 are expressed in HRP, HMEC and MIO-M1, THTR1 being more expressed than THTR2 in all cases. THTR2 and Sp1 mRNA expression decreased in HRP cultured in HG and IntHG (THTR2: -20.8 and -36.1% respectively, p<0.05 vs NG; Sp1: -17.1 and -19.9%, p<0.05), while THTR1 expression was unchanged. On the contrary, THTR2 mRNA expression increased in HMEC (+29.7%, p<0.05) and MIO-M1 cells cultured in IntHG (+36.4%, p<0.05). Protein expression checked by Western blotting confirmed these results. Different thiamine concentrations did not influence THTR1, THTR2 or Sp1 expression.

Conclusion: Diabetic-like conditions are able to modulate the expression of thiamine transporters in retinal cells. However, THTR2, which appears to be the most affected, is regulated in opposite directions in pericytes on one side, and endothelial and Muller cells on the other. Pericytes are the
first cells to be affected by early diabetic retinopathy; therefore, decreased expression of THTR2 in these cells may lead to reduced intracellular availability of thiamine, with consequent metabolic damage due to accumulation of toxic metabolites. On the contrary, increased expression of THTR2 in the surrounding cells may be interpreted as an attempt to counteract glucose-induced damage, by stimulating thiamine uptake.

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**European Association for the Study of Diabetes (EASD)**
Rheindorfer Weg 3
D-40591 Düsseldorf - Germany
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