The significance of solute carrier group of genes in the pathogenesis and treatment of diabetic microvascular complications

K. Singh, T. Yuzvenko

Ukrainian centre for endocrine surgery and organ transplantation of endocrine organs and tissues, MOH of Ukraine, Kyiv

Abstract

Aim- To study the impact of the solute carrier group of genes on the mechanisms involved in hyperglycemia induced tissue damage and its implication on the treatment of diabetic microvascular complications.

Introduction – the estimated figure of people suffering from diabetes worldwide in 2019 was 9.3% (463 million people) and the projected estimates for 2030 is an alarming figure of approximately 578 million people [1]. Various pathological processes are responsible for the development of diabetes, the irreversible factor is the destruction of β-cells in the pancreas leading to insulin insufficiency, or other factors such as obesity and abnormal carbohydrate and fat metabolism which leads to insulin resistance and diminished tissue response to insulin. Defects in insulin secretion and insulin action frequently coexist in diabetics [2].

The damaging effects of hyperglycemia are classified into microvascular complications - diabetic retinopathy, neuropathy and nephropathy, and macrovascular complications - coronary artery disease, peripheral artery disease and stroke [3]. The effects
of hyperglycemia are not seen in all cells of the body, but are distinct only in certain types of cells: neurons and Schwann cells in peripheral nerves, capillary endothelial cells, mesencephalic cells in the renal glomerulus due to their inability to effectively maintain a constant level of glucose, in contrast most cells are able to reduce the transport of glucose when exposed to hyperglycemia [4, 5, 6].

Key words: solute carrier family; transketolase; PPP; thiamine transporter; diabetic peripheral neuropathy.

Hyperglycemia and microvascular complications

The pathobiology of diabetic complications as a unifying mechanism has been explained by Brownlee M in 2005. Hyperglycemia induced mitochondrial superoxide production activates the four damaging pathways by inhibiting GAPDH which leads to microvascular diabetic complications [7]. The polyol pathway activation caused by the increased flux of glucose, causes sorbitol accumulation in cells. Increased sorbitol is considered as the underlying mechanism in the development of diabetic microvascular complications [7, 8]. The hexosamine pathway where fructose-6 phosphate is converted by the enzyme GFAT to UDP–N-acetylglucosamine (UDP-GlcNAc) [7], which results in increased expression of TGF β1 and plasminogen activator inhibitor-1 [9]. The protein kinase C (PKC) pathway is activated as GADPH activity is inhibited it leads to the increase in glyceraldehyde-3 phosphate which is a precursor to diacylglycerol [7]. And the advanced glycation end products pathway leads to the increase of the major intracellular AGE precursor methylglyoxal [7], these substances have been linked with the formation of microaneurysms and pericyte loss [8].

When the increased superoxide inhibits GAPDH activity in glycolysis, the glycolytic intermediates above the enzyme i.e. glyceraldehyde-3-phosphate, fructose-6-phosphate and glucose -6-phosphate and glucose accumulate and are then shunted into the four pathways of hyperglycemic damage stated above. Two of these glycolytic intermediates glyceraldehyde-3-phosphate and fructose-6-phosphate are also metabolites of the non oxidative arm of the pentose phosphate pathway which is a parallel metabolic pathway to glycolysis. The main function of the non-oxidative arm of the PPP is to generate pentose phosphates for ribonucleotide synthesis in a series of reversible reactions. Depending on cellular metabolic needs fructose-6-phosphate can be converted back to glucose-6-phosphate to replenish oxidative arm of pentose phosphate pathway to generate additional NADPH [10]. The rate limiting factor in the non oxidative arm of PPP is the enzyme transketolase [11].
The PPP is generally considered as going from pentose phosphates to glycolytic intermediates, but the fact is that it can go in the opposite direction from glycolysis steps to pentose phosphates: ribose 5-phosphate (R5P) is used in the synthesis of nucleotides and nucleic acids and erythrose 4-phosphate (E4P) used in the synthesis of aromatic amino acids. The level of activity of the process depends upon the concentrations of substrate presented to transketolase [7, 10]. The enzyme transketolase requires a co factor thiamine for activation.

**Role of solute carrier family in activating PPP**

The solute carrier (SLC) group of membrane transport proteins include over 400 members organized into 65 families [12, 13]. Most members of the SLC group are located in the cell membrane, but some are located in the mitochondria. The SLC gene nomenclature system was originally proposed by the HUGO Gene Nomenclature Committee (HGNC) and is the basis for the official HGNC names of the genes that encode these transporters. The SLC mediate the exchange of various molecules such as sugars, amino acids, nucleotides, inorganic ions, and drugs over the cell membrane. The SLC families include genes that encode passive transporters, ion transporters, and exchangers. The different SLC families are functionally related to each other and generally rely on an ion gradient over the cell membrane as the driving force for transportation, but with a few exceptions [14]. Given the immense number of proteins within this family, only some of the transporters that are responsible for carrying thiamine will be discussed which are a part of the complex large family.

**SLC19: the folate/thiamine transporter family**- consists of three transporter proteins with significant structural similarity but transporting substrates with different structure and ionic charge. The three members of this gene family are expressed ubiquitously and participate in the transport of two important water-soluble vitamins, folate and thiamine. The concentrative transport of substrates mediated by the members of this gene family is energized by transcellular H(+)OH(-) gradient [15]. SLC19A1 is expressed at highest levels in absorptive cells where it is located in a polarized manner either in the apical or basal membrane, depending on the cell type. It mediates the transport of reduced folate and its analogs [16]. The other two transport proteins, SLC19A2 (THTR1) and SLC19A3 (THTR2), associated with the plasma membrane, are each able to mediate the transport of extracellular thiamin into the cytosol. In the body, both transporters are widely distributed, and both are abundant in kidney and intestinal epithelia, consistent with their involvement in thiamin uptake under physiological conditions [17]. The level of thiamine uptake in the intestine is
adaptively regulated by the level of vitamin in the diet of a person, but the molecular mechanism involved is not fully understood. This adaptive regulatory response is associated with a higher level of mRNA expression of thiamine transporter-2 (THTR-2), but not thiamine transporter-1 (THTR-1) and a higher level of promoter activity of gene encoding THTR-2 (SLC19A3) in thiamine deficient conditions [17]. In humans thiamine uptake in the intestine is adaptively regulated by the extracellular substrate level via transcriptional regulation of the THTR-2 system, and SP1 transcriptional factor is involved in this regulation [17].

Little data is available about the mechanism by which thiamin, once taken up by epithelial cells in the intestine and kidney, is released from these cells into the blood. THTR-2 transporter plays a significant role in carrier-mediated thiamine uptake in the human intestine. As thiamine is carried into the cell, in the cytosol.

Cytosolic thiamin pyrophosphokinase (TPK1) catalyzes the reaction of thiamine and ATP to form thiamine diphosphate (ThDP) and ADP. Thiamine diphosphate (ThDP), is the coenzyme for five key metabolic enzymes: mitochondrial pyruvate dehydrogenase complexes (PDHC), oxoglutarate dehydrogenase complexes (OGDHC), 2 branched-chain acid dehydrogenase (BCODC) complexes, 2-Hydroxyacyl-CoA Lyase 1(HACL1) as well as the cytosolic transketolase (TK).

Conclusion:
As cytosolic TKT needs its co-factor thiamine for activation, and as the glycolytic intermediates can also flow from glycolysis metabolic pathway to pentose phosphates pathway, depending on the concentrations of substrate presented to the transketolase enzyme, further study is needed to understand the expression of SLC19A3 in diabetic patients with polyneuropathy, and as its adaptively regulatory expression response in the treatment of DPN. We have been studying the correlation between the gene expression and its interconnection in treating diabetic polyneuropathy in various stages. The detailed description of the study is out of scope of this article, and will be presented in consequent articles.

Authors’ contributions- K Singh and Yuzvenko T participated in the conception and design of the study. All authors took part in the collection and analyses of the data. K Singh drafted the initial manuscript and Yuzvenko T revised the manuscript. All authors read and approved the final manuscript.

Acknowledgments – not applicable.

Competing interests- the authors declare that they have no competing interests.
Ethics approval and consent to participate - This study conformed to the guidelines of the Declaration of Helsinki, and the study procedures were reviewed and approved by the medical research ethics committee. Each patient agreed to participate and signed the informed consent form.

Funding - The study was self-funded.

References

1. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition, Pouya Saeedi Inga Petersohn, Paraskevi Salpea, Dominic Bright, Rhys Williams. Diabetes research and clinical practice 157 (2019) 107843. DOI: https://doi.org/10.1016/j.diabres.2019.107843.

2. Diagnosis and Classification of Diabetes Mellitus, American Diabetes Association, Diabetes Care 2009 Jan; 32(Supplement 1): S62-S67. https://doi.org/10.2337/dc09-S062.

3. Microvascular and Macrovascular Complications of Diabetes, Michael J. Fowler, MD, Clinical Diabetes 2008 Apr; 26(2): 77-82. https://doi.org/10.2337/diaclin.26.2.77

4. Kaiser N, Sasson S, Feener EP, Boukobza-Vardi N, Higashi S, Moller DE, Davidheiser S, Przybylski RJ, King GL: Differential regulation of glucose transport and transporters by glucose in vascular endothelial and smooth muscle cells. Diabetes 42:80–89, 1993. DOI:10.2337/diab.42.1.80

5. Heilig CW, Concepcion LA, Riser BL, Freytag SO, Zhu M, Cortes P: Overexpression of glucose transporters in rat mesangial cells cultured in a normal glucose milieu mimics the diabetic phenotype. J Clin Invest 96:1802–1814, 1995. DOI:10.1172/JCI118226

6. Alkayyali, S., Lyssenko, V. Genetics of diabetes complications. Mamm Genome 25, 384–400, 2014. https://doi.org/10.1007/s00335-014-9543-x

7. Brownlee M. The pathobiology of diabetic complications, a unifying mechanism. Diabetes June 2005 vol. 54 no. 6 1615-1625. DOI:10.2337/diabetes.54.6.1615

8. Microvascular and Macrovascular Complications of Diabetes, Michael J. Fowler, MD, Clinical Diabetes 2008 Apr; 26(2): 77-82. DOI: 10.2337/diaclin.26.2.77

9. Du XL, Edelstein D, Rossetti L, Fantus IG, Goldberg H, Ziyadeh F, Wu J, Brownlee M: Hyperglycemia-induced mitochondrial superoxide overproduction activates the hexosamine pathway and induces plasminogen activator inhibitor-1 expression by increasing
Sp1 glycosylation. Proc Natl Acad Sci U S A 97:12222–12226, 2000. DOI:10.1073/pnas.97.22.12222.

10. Boros LG, Lee PW, Brandes JL, Cascante M, Muscarella P, Schirmer WJ, et al. Nonoxidative pentose phosphate pathways and their direct role in ribose synthesis in tumors: is cancer a disease of cellular glucose metabolism? Med Hypotheses (1998) 50:55–9. doi:10.1016/S0306-9877(98)90178-5.

11. Hammes HP, Du X, Edelstein D, Taguchi T, Matsumura T, Ju Q, Lin J, Bierhaus A, Nawroth P, Hannak D, Neumaier M, Bergfeld R, Giardino I, Brownlee M: Benfotiamine blocks three major pathways of hyperglycemic damage and prevents experimental diabetic retinopathy. Nat Med 9:294–299, 2003. DOI:10.1038/nm834

12. Hediger MA, Romero MF, Peng JB, Rolfs A, Takanaga H, Bruford EA (February 2004). "The ABCs of solute carriers: physiological, pathological and therapeutic implications of human membrane transport proteinsIntroduction". Pflügers Archiv. 447 (5): 465–8. doi:10.1007/s00424-003-1192-

13. Perland E, Fredriksson R (March 2017). "Classification Systems of Secondary Active Transporters". Trends in Pharmacological Sciences. 38 (3): 305–315. doi:10.1016/j.tips.2016.11.008

14. The Solute Carrier Families Have a Remarkably Long Evolutionary History with the Majority of the Human Families Present before Divergence of Bilaterian Species Pär J. Höglund, Karl J.V. Nordström, Helgi B. Schiöth, Robert Fredriksson. Molecular Biology and Evolution, Volume 28, Issue 4, April 2011, Pages 1531–1541, https://doi.org/10.1093/molbev/msq350.

15. SLC19: the folate/thiamine transporter family. Ganapathy V1, Smith SB, Prasad PD. Pflugers Arch. 2004 Feb;447(5):641–6.DOI: 10.1007/s00424-003-1068-1

16. Subramanian VS, Marchant JS, Said HM. 2006b. Targeting and trafficking of the human thiamine transporter-2 in epithelial cells. J Biol Chem 281: 5233–5245. DOI: 10.1074/jbc.M512765200.

17. Adaptive regulation of human intestinal thiamine uptake by extracellular substrate level: a role for THTR-2 transcriptional regulation. Svetlana M. Nabokina, Veedamali S. Subramanian, Judith E. Valle, and Hamid M. Said. Am J Physiol Gastrointest Liver Physiol. 2013 Oct 15; 305(8): G593–G599. doi: 10.1152/ajpgi.00237.2013.