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

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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, mesengeal 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

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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.

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