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Molecular physiology of cellular glucose transport — a potential area for clinical studies in diabetes mellitus

Molekularna fizjologia dokomórkowego transportu glukozy — potencjalny obszar badań klinicznych dotyczących cukrzycy

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Abstract

The normalization of cellular glucose assimilation is the basic aim of metabolic therapy in type 2 diabetes mellitus (T2DM). It requires parallel changes in the process of cellular glucose transport (CGT).

This review presents the pathophysiological and clinical outlines of CGT. Sequentially, the advances in the mechanisms and classification of CGT and their physiological and molecular base are described. The role of CGT pathogenetic significance in diabetes mellitus is stressed. Finally, the opinion is expressed that the CGT study is a potentially important approach to clinical interpretation of glucose metabolism disturbances and their pharmacotherapy. **(Pol J Endocrinol 2010; 61 (3): 303–310)**

Key words: *cellular glucose transport, insulin, action-signalling pathway, diabetes mellitus*

Streszczenie

Podstawowym celem metabolicznego wyrównania cukrzycy typu 2 jest normalizacja komórkowego pobierania glukozy, która jest możliwa dzięki zmianom w procesie dokomórkowego transportu glukozy (CGT, *cellular glucose transport*).

W opracowaniu przedstawiono zarys patofizjologicznych i klinicznych problemów dokomórkowego transportu glukozy. Kolejno opisano postępy badań dotyczących mechanizmów i rodzajów CGT, ich molekularną fizjologię oraz potencjalną rolę CGT w patogenezie cukrzycy.

Wyrażono opinię, że badania CGT stanowią nowy, potencjalnie bardzo istotny sposób ujęcia zaburzeń metabolizmu glukozy oraz farmakoterapii. **(Endokrynol Pol 2010; 61 (3): 303–310)**

Słowa kluczowe: *dokomórkowy transport glukozy, insulina, szlak przekaźnictwa sygnału, cukrzyca*

Introduction

Cellular glucose transport (CGT) and the regulation of this process in the human organism are the subjects of many studies. The significance of the glucose transport studies does not result only from their cognitive values but also from the therapeutic benefits that they can uncover. In the pathogenesis of diabetes mellitus 2, metabolic syndrome, and other clinical conditions related to insulin resistance, disorders of cellular glucose transport play the most fundamental role.

In Poland, there is a historical tradition of studies in this area, which is also recognized throughout the world. In Warsaw and Łódź, the scientific basis for the studies of cellular glucose transport was created by the physiologist Mieczysław Wierzuchowski (1895–1967). He conducted studies on cellular glucose transport on the model of phlorizin diabetes. Phlorizin selectively inhibits glucose transport in the tubule cells of the nephrons. Therefore, Wierzuchowski's studies concerned the role of the kidneys in the shaping of glucose metabolism. For many years, particular problems in the area of cellular glucose transport have been a major area of research work in the centre which presents this review.

The dynamically increasing data in the area of cellular glucose transport have underlined the general significance of this process. For example, the disturbances may have an aetiological role in insulin resistance syndromes.

Molecular physiology of glucose transport

Almost all of the biological membrane transport processes employ specific membrane proteins, often in combination with the receptors or receptor domains

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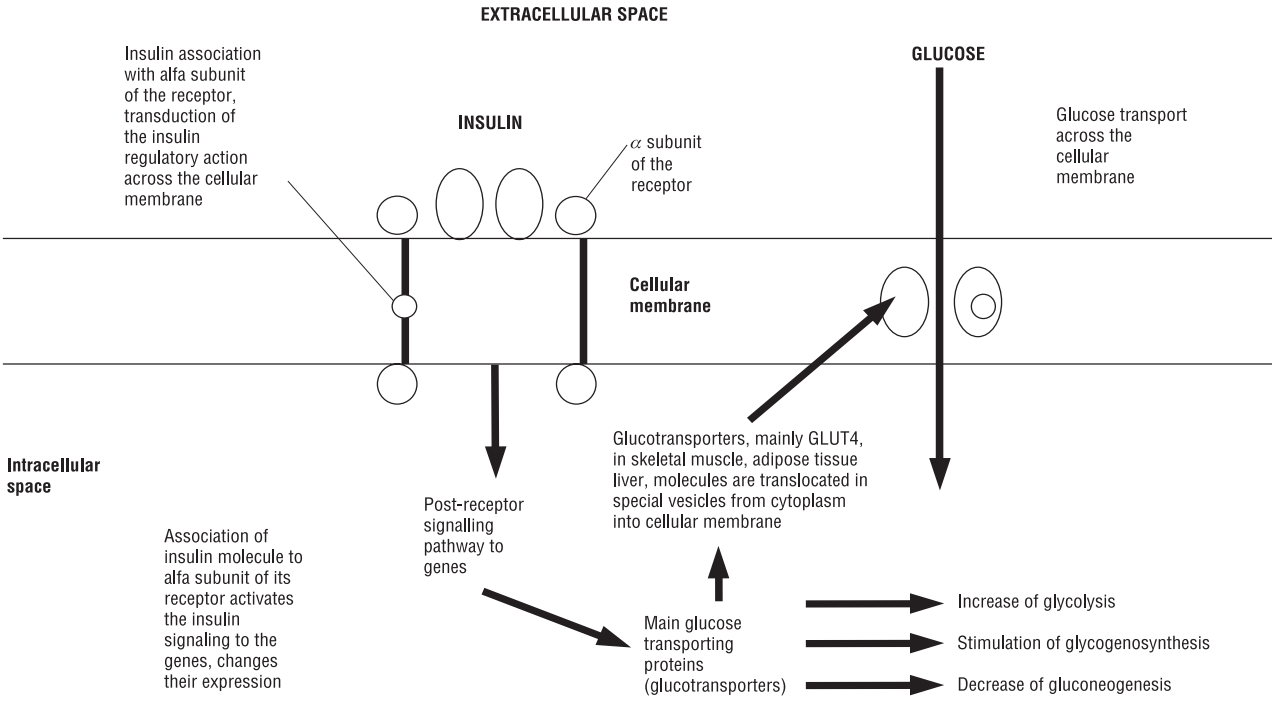

Figure 1. *Overview of the cellular transport of glucose*
Rycina 1. *Schemat dokomórkowego transportu glukozy*

located outside of the cytoplasm, as well as with the proteins or cytoplasmatic domains which play a regulatory role or supply energy [1]. Each of these systems of proteins or accompanying structures is called a transporter, transport system, or carrier. A transporter is, therefore, a protein or a system of proteins that catalyzes the directional reaction or movements of the molecule, *e.g.* glucose. These proteins can also catalyze another chemical reaction and electron transfer. Transport systems can be considered as proteins or protein complexes having catalytic properties analogous to enzymes or enzyme complexes [2].

Substance transport involving a specialized transporter can proceed in different, but interconnected, ways. The first way is a facilitated diffusion, a process that does not need energy. In biological systems, two kinds of facilitated diffusion have been detected: channel-type facilitated diffusion and carrier-type facilitated diffusion.

In channel-type facilitated diffusion, the substance goes through the membrane via a transmembrane channel formed by proteins (appropriately, hydrophilic for hydrophilic substances, hydrophobic for hydrophobic substances, and amphipathic for amphipathic substances). The structures of several such channel proteins have been studied and explained by means of X-ray crystallography [1, 2].

This biological interpretation of the cellular glucose transport is presented in Figure 1, 2, and Table I.

In the carrier-type facilitated diffusion, the transporter alters its conformation, allowing the transmembrane substrate to transport. However, this is only a theoretical discussion as none of the described carriers has been studied with the use of X-ray crystallography. With the help of computer software, a dimensional model of the glucotransporter GLUT 1 molecule has been created, allowing the reconstruction of the structure of the protein on the basis of its amino acid sequence and its similarity to already known molecules [3].

Substrate transport by the carrier is usually several times slower than the speed achieved by the channels. Additionally, in contrast to most of the channels, the carriers display specificity of dimensional structure of the substrate. All kinds of transporters can be characterized by saturation kinetics. Nevertheless, this feature is more characteristic for carriers. Very few of them display the ability to function by the same rules as channels, and among those that possess this ability, it occurs only after the covalent or noncovalent ligand binding or after a build-up of high membrane potential. Most of the channels exist in the form of oligomeric complexes, while most of the carriers can function in the form of monomeric proteins. Such observations lead to the conclusion that channels and carriers (and their functions) differ [4].

If, at the time of transmembrane transport of a substance (glucose), an expenditure of energy occurs, the system catalyzing such a reaction becomes an active

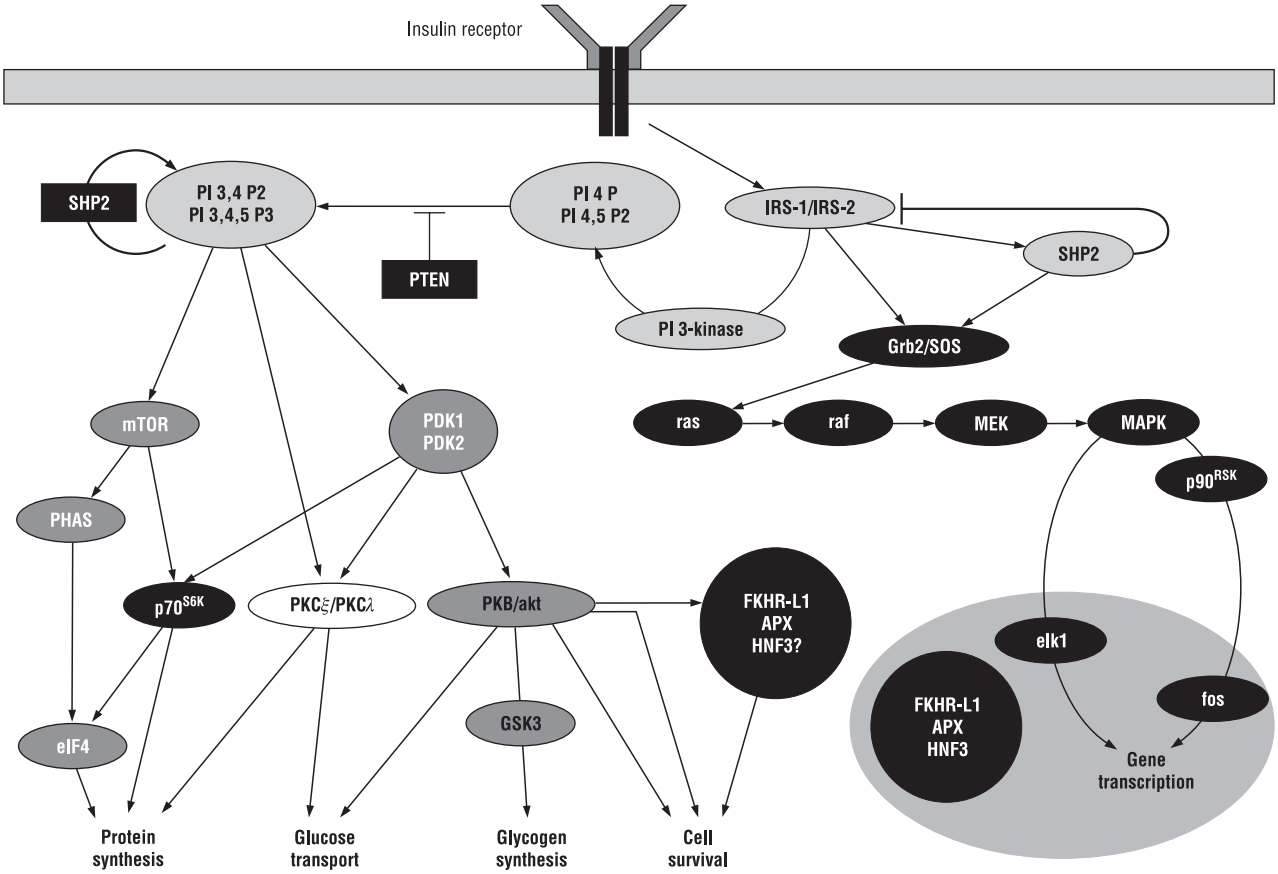

Fig. 2. *Insulin signalling pathways. The sequence of events starts with the binding of the insulin molecule to the α subunit of its receptor. This reaction activates signal proteins from the insulin receptor substrate (IRS) family. From this initial signalling event, further signals travel down the signalling pathway, are multiplied, and are directed toward different effectors — glucose transport, metabolic processes, and mitogenesis (acc. to 1)*

Rycina 2. *Przekazywanie sygnałów insulinowych. Sekwencja zdarzeń rozpoczyna się od przyłączenia cząsteczki insuliny do podjednostki α jej receptora. Ta reakcja aktywuje białka sygnałowe z rodziny substratów receptora insulinowego (IRS). W dalszej kolejności sygnały zostają przekazane dalej, wzdłuż szlaku sygnałowego, ulegają zwielokrotnieniu i powodują wiele różnych efektów, wpływają między innymi na transport glukozy, procesy metaboliczne oraz mitogenezę*

Table I. *Types of glucose transport in live organisms*
Tabela I. *Rodzaje transporu glukozy w organizmach żywych*

• **Physicochemical transport,** harmonious with the laws of diffusion, constitutes about 5% of transport necessary for the metabolism. This is so because of the lipid, structure of the cellular membrane, makes them practically impenetrable for glucose *Physicochemical cellular glucose transport = the difference of glucose concentrations on both sides of the cellular membrane x membrane penetrability*
• **Biological transport,** biological diffusion, and facilitated transport covers about 95% of cellular glucose transport necessary for metabolism. It is physiologically regulated. Its activity is specific to various types of cells and their functioning *Biological cellular glucose transport = the difference of glucose concentrations on both sides of the cellular membrane x biological activity of specific transport systems x availability of energy for the functions*

transporter. Primary active transport is such a system in which the energy is drawn from a primary source (*e.g.* chemical energy, photon energy, or the flow of electrons). In secondary active transport, the energy is taken from secondary sources, *e.g.* electrochemical ion gradient (protons: proton motive force — PMF, or sodium motive force — SMF). A secondary energy source comes into being using the energy from a primary source [4].

Active transporters can function on the basis of uniport, symport, and antiport. Uniporters catalyze the transport process of one type of molecule, so it is conducted independently of the movement of other molecules. Symporters, classically called cotransporters, catalyze the transport of molecules of two or more types in the same direction. Single-point mutation in the symporter can change such a carrier into a uniporter, which proves that these two types of carriers do not differ

much. Antiporters, also called counter-transporters or exchangers, catalyze the reaction of changing molecules of one or more types into different molecules [5].

In human cells there are two families of proteins which are responsible for cellular glucose transport.

These are:

— glucose transporter systems from the group of GLUT1–14 peptides (glucotransporters);
— sodium/glucose transporters (SGLT, Na^+/glucose cotransporters).

Expression of particular GLUT protein coding genes is specific for tissues and cells [6–11].

GLUT protein glucose transport corresponds to facilitated diffusion. SGLT protein cellular glucose transport is a secondary, active sodium transport combined process.

All the membrane transport systems were gathered and classified in the transporter classification, or TC. This classification system partially corresponds to the enzyme classification system, but in contrast to the latter, it is not based solely on the protein function but also on the phylogenesis. Transporters were grouped according to five criteria: V — transporter class, W — transporter subclass, X — transporter family or superfamily, Y — family or subfamily, and Z — substrate or range of substrates transported, direction of the transport (intra- or extracellular). Each transporter subclass has a two-digit number in the TC classification (V.W), and each family a three-digit number (V.W.X) [5].

As mentioned previously, glucose and other hexose transmembrane transport occurs thanks to proteins from two different families: GLUT and SGLT. Glucose transport harmonious with volume gradient, without energy, occurring due to the process of facilitated diffusion, takes place through the work of carriers belonging to the GLUT family transporters, which are present on the surface of all cells of an organism. Facilitated diffusion, which undergoes saturation, is stereoselective and is two-directional. The second family of transporters, represented by *e.g.* Na^+/glucose intestinal cotransporter (SGLT1), uses the electrochemical sodium ion gradient to transport glucose and galactose, contrary to their volume gradient. SGLT1 is responsible for the collection of glucose and galactose from nutrients found in the intestinal lumen as well as for re-absorption of these sugars from primary urine in the nephron. In the renal proximal tubule, two other transporters belonging to this family exist: SGLT2and SGLT3 [12–14].

The characteristics of these two types of glucose transporters are presented below.

Transporters from the GLUT family

Currently, 13 genes are known that code the homological but different proteins transporting glucose and other hexoses to cells with the use of facilitated diffusion. These genes, in accordance with the assumed nomenclature (HUGO Gene Nomenclature Committee), are described as SLC2A1-SLC2A13 (Solute Carrier Family 2A). Proteins coded by these genes are accordingly: GLUT1-GLUT12 and HMIT 1 [15].

In the literature concerning glucose transporters, there is considerable variety relating to the nomenclature of the genes and GLUT proteins coded by these genes. In this study, the nomenclature of genes and proteins (Tables II, III, and Fig. 3) proposed by Joost and Thorense has been assumed [15].

The first carrier that became a model for the studies of the structure and characteristics of glucose transporters in mammals was isolated from erythrocytes [16]. Purification and determination of the part of the amino acid sequence from human erythrocytes and the use of antibodies against these proteins allowed isolation of cDNA glucose transporter clones from human HepG2 cells and rat's brain [17, 18]. This protein, built from 492 amino acids of molecular mass of 45 or 55 kDa (depending on the level of glycolization) is currently called GLUT1. The dimensional orientation model of GLUT l in cellular membrane assumes the occurrence of 12 transmembrane segments with α-helix structure (TMH, transmembrane helices) and with N and C termini located intracellularly.

Apart from a large intracellular loop linking segments 6 and 7, and dividing the whole structure into two parts, the loops on the cytoplasmic surface are very short, amounting to 8-12 amino-acid residues. These short loops are a considerable limitation for tertiary protein configuration and cause a very tight packing of helical segments on the internal side of the membrane. The length of the loop on the external surface is larger than on the cytoplasmic surface, which results in a looser packing on the external side. Limitations resulting from the presence of short linking loops of the transporter occur between the 460^{th} and 480^{th} amino-acid residues. Substitution of the last 45 amino acids of GLUTl with the use of the appropriate region of GLUT2 protein caused the occurrence of chimeric protein of about four times larger K_m and V_{max} values. Since the substitution of C terminus of GLUTl protein by means of GLUT2 terminus caused the occurrence of a protein with kinetic characteristics similar to the ones possessed by GLUT2, it seems that C terminus is responsible, at least partially, for the characteristic features of a given isoform, probably through direct influence on the glucose binding site placed on the internal side of the membrane, which influences the speed of release of glucose from the internal binding site [19].

The results of studies of glucose transporters fully confirm the hypothesis that glucose transporters are

Table II. *List of mammalian glucose transporter proteins*
Tabela II. *Białka transporujące glukozę występujące u ssaków*

Isoform	Tissue distribution	Function
GLUT1	Widely distributed in foetal and adult tissues, abundant in human erythrocytes, placenta, microvasculature, immortalized cell lines	Basal glucose uptake; increased glucose for growing/dividing cells; upregulated in many tumours; uptake across blood-brain barrier and other barrier tissues
GLUT2	Hepatocytes, intestinal mucosa, renal tubules, brain	High-capacity, low-affinity transport system; transepithelial transport (basolateral membrane); often expressed in parallel with glucokinase; may be involved in glucose sensing
GLUT3	Widely distributed in foetal and adult tissues, restricted to brain in some other species	Basal glucose uptake in many human cells; uptake from cerebral fluid into brain parenchymal cells
GLUT4	Skeletal muscle, heart, adipocytes	Insulin-responsive glucose transport; important in whole-body glucose homeostasis
GLUT5	Jejunum, spermatozoa, adipose, muscle, brain, and kidney tissues	Fructose transport
GLUT6	Spleen, leukocytes, brain	Unknown
GLUT7	Unknown	Unknown
GLUT7	Testis, blastocyst, brain	Unknown
GLUT7	Liver, kidney	Unknown
GLUT7	Liver, pancreas	Unknown
GLUT7	Heart, skeletal muscle	Unknown
GLUT7	Heart, prostate	Unknown

Table III. *Characteristics of the GLUT family glucotransporters*
Tabela III. *Charakterystyka rodziny transporterów glukozy GLUT*

A group of specific, specialized, GLUT transporters:
• the group covers 14 peptide glucose transporters described as the GLUT family
• they create channels in the membranes, penetrable by glucose
• they undergo genetic, hormonal (insulin), and substrate regulation
• their function is correlated with the functional state of the cells
• they are specific for various types of cells
• disorders can cause pathological states
Molecular features of GLUT:
• molecules of the transporters from the GLUT family present themselves as polypeptic chains containing transmembrane domains, which means fragments of molecules penetrating cellular membranes, terminal residues — NH_3 and COOH. They can undergo glycolization in loop I or 9
• 14 isoforms of GLUT transporters have been identified in humans (GLUT1–GLUT12 and GLUT14 as well as the HMIT transporter)
• Their biosynthesis and action are regulated by SLC2A1––SLCA14 genes
• the amount of GLUT molecules is regulated by many factors: oncogenes, insulin, IGF-1 and IGF-2 growth factors as well as other growth factors, glucocorticosteroids and glycaemic unsteadiness
• regulation of glucose transporters is specific for every tissue

built from two major domains composed of a-helical segments: 1–6 (N terminus) and 7–12 (C terminus). Half of the protein plays a structural role and is essential for the proper build-in into the cellular membrane, while the half closer to the C terminus contains the region involved in glucose molecule transport. With this assumption, transmembrane segments 7–11 can create a part of the water channel through which glucose is transferred [20]. Segment 10 can also play a significant role in the glucose transport process, probably as the dynamic element, the movement of which allows the glucose binding structures to change places on the inside and outside. This region contains the conserved motif GPXPIP, which can supply this glucose transport fragment with a large degree of mobility and creates the possibility of conformative changes accompanying glucose molecule transport [21]. The intracellular segment on C terminus also plays an important role in the change of internal and external glucose binding sites, probably through direct interaction with the short intracellular segment which links TMH 10 and TMH 11 [22].

Transporters from the Sodium/Glucose Transporters — SGLT family

Proteins from the SGLT family take part in the secondary active transport of glucose. They draw their energy from the electrochemical Na^+ ion gradient, sustained

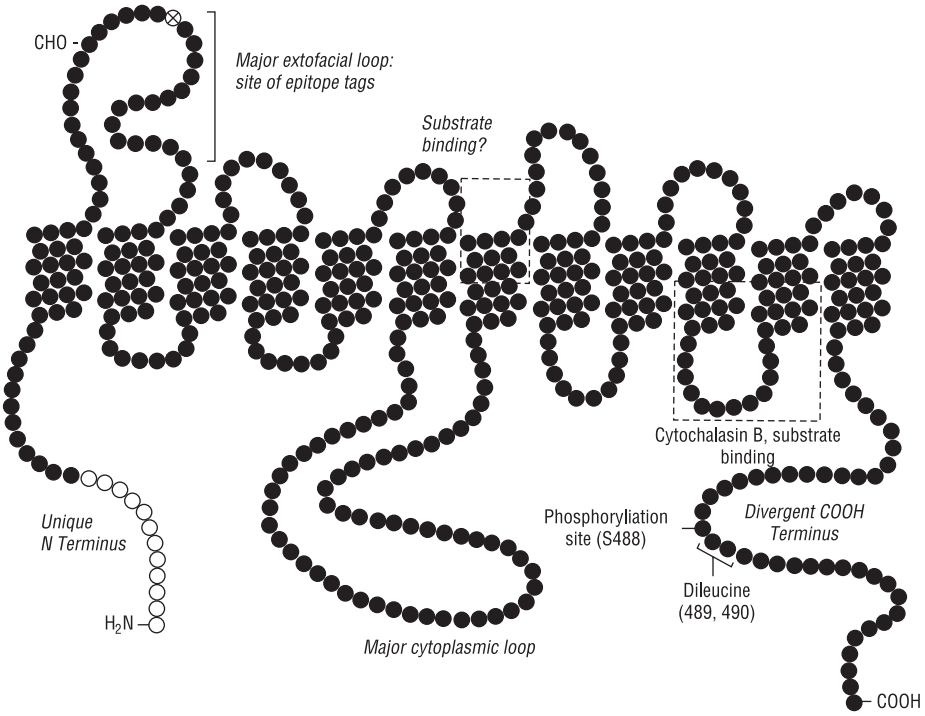

Figure 3. *Structure and function of the GLUT4 transporter.*
Rycina 3. *Budowa i czynność transportera GLUT4*

by Na^+/K^+-ATPase present in the peripheral basement membrane of epithelial cells. The activity of SGLT1 is proven by the fact that blockage of GLUT2 in the peripheral basement membrane of an intestinal epithelial cell causes a level of cytoplasm glucose concentration that is 30-fold higher [than what? than normal?]. SGLT in enterocytes occurs also on the membrane of cytoplasmic sacs. They can fuse with cellular membrane, which causes an increase of SGLT volume on the surface of the cell [23].

In the peptide structure of the sodium-glucose contransporters (SGLT), one may delineate 14 domains in the form of α-helisa positioned in the cellular membrane. The best known is the physiology of SGLT1 and SGLT2.

Transporters from the same family are also present in the kidney, and the glucose reabsorption model in the kidney resembles the one originally proposed for the small intestine. Glucose gathers inside epithelial cells thanks to the Na^+/glucose cotransporter present in the brush border membrane, and is then transported outside the cell by the GLUT2 uniporter located in the peripheral basement membrane. There is interesting genetic evidence proving that two types of SGLT are present in the human kidney. Patients with familial renal glucosuria do not display intestinal glucose absorption disorders, while patients with glucose-galactose malabsorption (CGM) display only slight renal glucosuria. This supports the claim that the major intestinal Na^+/glucose cotransporter plays only a small role in renal reabsorption of glucose. It is assumed that most of the filtered glucose undergoes reabsorption in the proximal convoluted tubule with the involvement of SGLT of low affinity and high capacity, described as SGLT2. The remaining glucose undergoes reabsorption by the symporter with a high affinity of SGLT1 [24].

Apart from SGLT l and SGLT 2, the SGLT family encompasses Na^+/glucose cotransporter with low affinity; — SGLT 3, inositol transporter — SMIT, iodide transporter — N1S, and vitamin transporter — SMVT (Tables IV and V).

Kinetic similarities between SGLTI, SGLT3, and other proteins from the SGLT l family (SMIT and NIS) point to a similar transport mechanism. Similar to the case of the GLUT family, transporters of compounds other than glucose are also a part of the SGLT family. Apart from those listed in the table, more than 50 proteins belonging to the SGLT family have been discovered occurring in different organisms,.

Human SGLTI was isolated for the first time from the intestinal cDNA library with the use of a rabbit SGLTI probe.

Northern blot analysis showed that the SGLT1 gene undergoes expression in the ileum as well as in the small intestine, renal cortex, and the external part of rabbit renal medulla. SGLT2 was isolated from the human re-

Table IV. *Biological characteristics of the SGLT transporters family (Sodium/Glucose Transporters)*

Tabela IV. *Biologiczne właściwości rodziny transporterów SGLT*

I. Sodium-glucose transporter 1 — SGLT1:
• protein molecule with a molecular weight of 52 Kd
• the value of Km is 0.35 mU
• the highest concentration exists in the heart, the next highest in cells of renal tubules and in enterocytes of the jejunum
• SGLT1 expression is regulated by the gene [correct?] located at chromosome 22q13.1
II. Sodium-glucose transporter 2 — SGLT2:
• protein molecule acting as transporter in renal tubules, enterocytes (jejunum), and myocytes of skeletal muscles
• the value of Km is 1.64 mU
• the deficit of SLGT1and SGLT2 action in nephrons causes the renal glucosuria. This is due to the decrease of glucose reabsorption
• this deficit in enterocytes (jejunum) contributes to glucose malabsorption

nal cDNA library. In humans, the gene of this transporter undergoes expression in the renal cortex and, to a significantly smaller extent, in the intestine. SGLT3 was isolated from a pig kidney epithelial cell line with the use of a rabbit SGLTI probe and was first named SAATl then, later on, pig SGLT2. Pig SGLT3 is expressed in the kidney, intestine, liver, and spleen. There is not much information on the translation of SGLT transporter mRNA in the human kidney because there are no proper antibodies to differentiate these three proteins [25].

Conclusions

The cellular membrane is built mainly from lipids. Due to this fact, it is almost nonpermeable for glucose on the basis of physicochemical mechanisms. The delivery of glucose from the extracellular space to the cell interior is adequate for the physiological needs. Its utilization is dependent on biological transport mechanisms. They are based on two systems of biological transporters: the group of glucotransporters GLUT, and the group of SLGT transporters. The cells of different tissues express the glucotransporter molecules in a way corresponding to their functional specialization.

They act in a special, functional way depending on genetic, substrate, and hormonal regulation. The disturbances in the glucose transporters may be the main cause for frequent and clinically important pathogenetic mechanisms like insulin resistance presenting diabetes mellitus, and in many other clinical insulin-resistant syndromes. Cellular glucose transport is also the target for pharmacotherapy. Research in this area is developing quickly.

Table V. *Physiology of transporters from the SGLT transporter family (Sodium/Glucose Transporters)*

Tabela V. *Fizjologia transporterów glukozy należących do rodziny SGLT*

Transporter	Substrate of the transport process	Localization in a human organism
SGLT1	Na^+/glucose	Small intestine and S3 segment of nephron
SGLT2	Na^+/glucose	S1 segment of nephron
SGLT3	Na^+/glucose	Kidney
SMIT	Na^+/myoinositol	Kidney
NIS	Na^+/iodide	Thyroid
SMVT	Pantothenic acid	?

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