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Insulin as the main regulator of cellular glucose utilization — aetiological aspects of insulin resistance

Insulina jako główny regulator komórkowej utylizacji glukozy — etiologiczne aspekty insulinooporności

Jan Tatoń, Anna Czech, Paweł Piątkiewicz

Chair and Department of Internal Diseases and Diabetology, II Medical Faculty, Warsaw Medical University, Brodnowski Hospital, Warsaw, Poland

Abstract

This review presents the advances in the molecular biology and the pathophysiology of insulin resistance with emphasis on disturbances in cellular glucose transport. New scientific information about the structure and function of glucotransporters from the GLUT4 and SLGT families underline their significance in endocrinopathies and metabolic disease pathogenesis as related to insulin resistance. The new discoveries in this area also contribute to a better understanding of the regulation of insulin receptor and post-receptor reactivity by hormones and by drugs. They refer to the regulation of glycaemia and to its disturbances in diabetes mellitus, particularly of type 2, to metabolic syndrome, and, in general, to the pathogenesis of many syndromes and clinical disturbances caused by insulin resistance. Impairment of cellular glucose transport may be one of the primary aetiological factors in this respect. Therefore, studies of cellular glucotransporters expression and function promise new clinical and pharmacotherapeutic developments. Progress in this area has already been transformed into many practical proposals which are improving clinical practice. **(Pol J Endocrinol 2010; 61 (4): 388–394)**

Key words: *cellular glucose transport, glucotransporters, expression and action of glucotransporters, insulin, diabetes mellitus, insulin resistance*

Streszczenie

W opracowaniu przedstawiono postępy biologii molekularnej oraz patofizjologię insulinooporności w aspekcie zaburzeń dokomórkowego transportu glukozy. Najnowsze doniesienia naukowe dotyczące struktury i funkcji transporterów glukozy z rodziny GLUT oraz SGLT podkreślają ich rolę w patogenezie insulinooporności prowadzącej do powstania endokrynopatii oraz chorób metabolicznych.
Nowe odkrycia w tej dziedzinie przyczyniają się również do lepszego zrozumienia wielopoziomowego działania insuliny, a także patogenezy cukrzycy typu 2, zespołu metabolicznego oraz wielu schorzeń spowodowanych insulinoopornością.
Upośledzenie dokomórkowego transportu glukozy może być jednym z podstawowych czynników etiologicznych insulinooporności. W związku z powyższym badania ekspresji i funkcji glukotransporterów zapowiadają nowe osiągnięcia kliniczne i farmakoterapeutyczne. Postęp w tym zakresie przyczynił się już do powstania wielu praktycznych rozwiązań, które poprawiają praktykę kliniczną.
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Słowa kluczowe: *dokomórkowy transport glukozy, glukotransportery, ekspresja i działanie glukotransporterów, insulina, cukrzyca, insulinooporność*

Insulin intracellular signal transduction: from the receptor to genes

Insulin regulatory action involves the basic life processes of cells, tissues, and whole organisms. It is multifactorial, perfectly organized, and functionally integrated into successive biochemical steps and biological events governing intracellular regulation. The primary signal resulting from the association of the insulin molecule with the alfa subunit of its specific receptor is transducted by the whole system of mediating molecules and transcriptional factors to over 100 genes [1–3]. The final result is changes in gene expression, which are followed by adaptive changes in the activity of different biochemical effectors - metabolic and proliferative enzymes [4–6] (Fig. 1).

In this way insulin unique, pan-metabolic hormone and drug - preserves the homeostasis of the cells and the organism as a whole [3]. The outlines of this system are presented in Table I.

The intracellular post-receptor regulatory influences of insulin – also, for didactic purposes - can be divided into three "arms" or directions [7–9].

They are:

— regulation (enhancement) of the cellular glucose transport molecular system;
— adaptive changes in gene expression, with the respective changes in the biosynthesis and actions of the enzymes preserving metabolic homeostasis;
— stimulation of genes increasing the pro-mitotic, proliferative, and anti-apoptotic activity of the cells [6].

Prof. Jan Tatoń M.D., Chair and Department of Internal Diseases and Diabetology, II Medical Faculty, Warsaw Medical University, Brodnowski Hospital, Kondratowicza St. 8, 03–242 Warszawa, tel./fax: +48 22 326 58 17, e-mail: diabetologia@wum.edu.pl

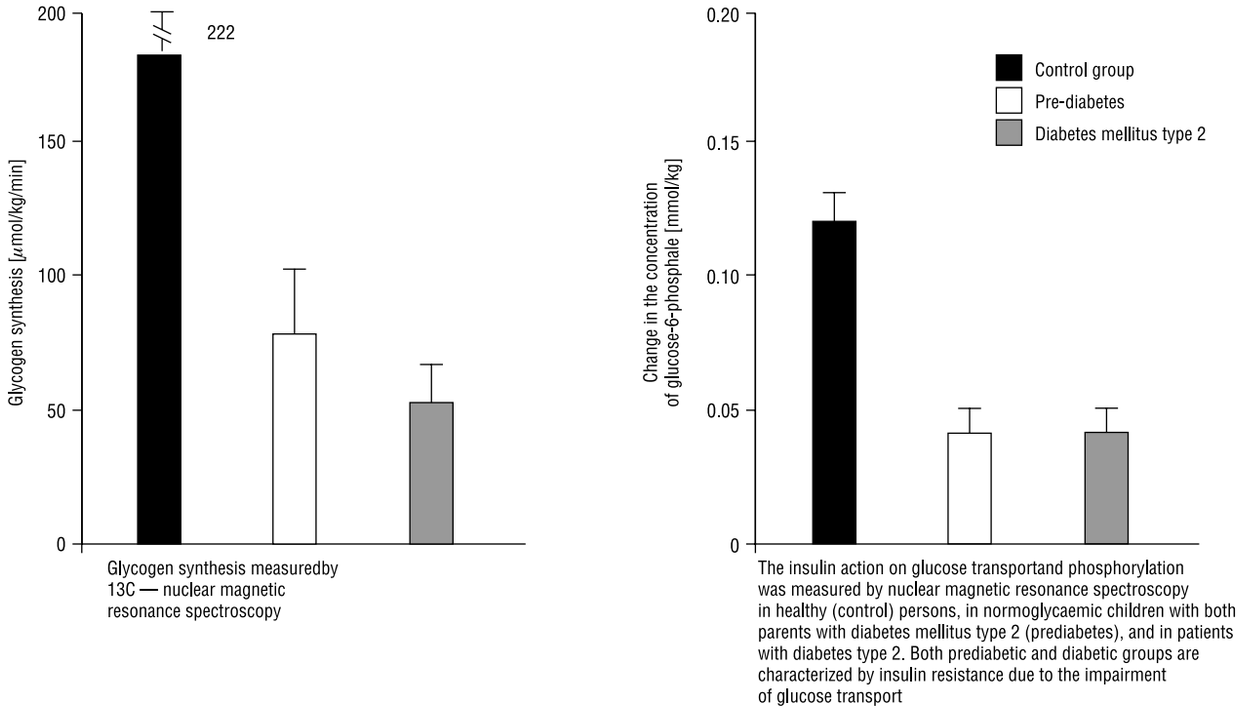

Figure 1. *Insulin resistance in children with parents with diabetes mellitus type 2 (adapted: Rothman D.L. et al., Proc. Natl. Acad. Sci. USA; 1995, 92: 983–987)*

Rycina 1. *Insulinooporność u dzieci osób chorych na cukrzycę typu 2 (na podstawie: Rothman D.L. et al., Proc. Natl. Acad. Sci. USA; 1995, 92: 983–987)*

Table I. ***Outline of the insulin signalling system [6–8]***
Tabela I. ***System przekazywania sygnałów insulinowych [6–8]***

Level 1	**Mediator**
Generation of mediator molecules	— glucoprotein molecule of the insulin receptor — Insulin Receptor — Substrates IRS 1, 2, 3, 4 — Phosphatydylinozytol-3 kinase (PI-3k) — Proteins ras (H-ras, k-ras, n-ras = 21 ras) — GRB-2
Level 2	**Protein kinases cascade**
Functional transduction of signals to the executive genes and enzymes	— Acetylo-CoA-carboxylase — ATP-citric liase — MAP-kinases — Kinases rat 1 — Kinases Ribosomal S6 kinases — Glycogen synthase — Pyruvate dehydrogenase — Triacylglycerol lipase — Phosporylases

The diminished reactivity to insulin in any of the above described "arms" of its regulatory action, or in all of them together, is called insulin resistance [4]. It may play an aetiological role in many clinical conditions (Table II).

The practical testing of these disturbances is outlined in Table III.

It should be emphasized that insulin resistance as a clinical syndrome may refer to one, two, or many specific steps and molecules of insulin regulatory influence, and to one or more tissues and organs. The impairment of the insulin action caused by its functional deficit or by cellular resistance to insulin due to abnormalities in the structure and function of the intracellular insulin signal transducting molecules and the transcriptional factors are the main pathogenetic promoter of diabetes mellitus type 2 and metabolic syndrome [3, 10].

It should also be underlined that the primary genetic abnormalities that cause insulin resistance in clinical conditions are not well known. Experimental data based on studies of "knock-out" animals are presented in Table IV [1, 11].

Post-receptor insulin signalling pathway as the potential aetiological site of insulin resistance.

Table II. *Cellular glucose transport and insulin resistance in clinical syndromes GLUT4 [6–8]*
Tabela II. *Dokomórkowy transport glukozy i insulinooporność w różnych klinicznych zespołach GLUT4 [6–8]*

Pathophysiological type of insulin resistance		
Primary insulin resistance	Secondary insulin resistance	Insulin resistance connected with genetic syndromes
Diabetes mellitus type 2	Obesity	Progeria syndrome (Werner Syndrome)
Metabolic syndrome	Diabetes mellitus type 1 and 2	
Gestational diabetes mellitus	Hyperlipidaemia	Down, Turner, Klinefelter syndrome
Lipodystrophic diabetes mellitus	Pregnancy	
	Trauma, stress	[Ataxia-teleangactosia ?? –telangiectasia??] Syndrome
Leprechaunism	Cushing Syndrome	
Rabson-Mendenhall Syndrome	Pheochromocytoma	Friedreich ataxia
	Acromegaly	Alström Syndrome
Arterial hypertension	Thyroid hyperfunction	Laurence-Moon-Biedl Syndrome
Atherosclerosis	Liver cirrhosis	
Polycystic Ovary Syndrome	Renal insufficiency	Neuro-muscular dystrophy

Table III. *Techniques for the assessment of insulin action (insulin resistance)* **in vivo**
Tabela III. *Metody oceny działania insuliny (insulinooporności)* **in vivo**

Dynamic techniques — endogenous insulin
Oral glucose tolerance test
Intravenous glucose tolerance test
Dynamic techniques — exogenous insulin
Insulin tolerance test
Incremental insulin infusion
Mathematical modelling techniques
Minimal model (of Bergman)
Homeostasis model assessment
Continuous infusion of glucose with model assessment
Steady-state open-loop techniques
Insulin suppression test
Euglycaemic hyperinsulinaemic glucose clamp

Studies of the molecular aspects of insulin resistance start with insulin receptors.

The molecules of cellular insulin receptors are present in all types of cells of vertebrates, including humans. However, their numbers expressed on cells differ in an important fashion. It could be 40–100 receptors on red blood cells, and 200,000 or more on hepatocytes and adipocytes [6, 7, 9]. An insulin receptor molecule has the structure of glycoprotein. It is composed of two extracellular alfa subunits which are responsible for the active, specific binding of the insulin molecules. The insulin receptor structure also contains two other beta subunits which act as the catalytic protein kinases using the ATP for autophosphorylation of the tyrosine residue within the beta subunit [11–14].

From this reaction, the multistep, functionally interrelated pathway of signalling develops. It has many directions.

The first step of the insulin action signalling is the phosphorylation of the family of glycoproteins, which are defined as the Insulin Receptor Substrate or IRS, with different, specific subtypes (Fig. 2, 3).

Starting from the IRS point, insulin regulatory actions can be divided into [6, 20–22]:
— formation and functional stimulation of cellular glucose transport by the specific glucotransporter family molecules of GLUT;
— changing the expression of genes regulating the metabolic processes;
— modifying the expression of genes promoting cell proliferation and resistance to apoptosis (MAP kinases).

The removal of protein IRS in "knocked-out" mice causes the appearance of the experimental metabolic syndrome associated with hyperinsulinaemia [1, 10, 11]. The phosphorylated IRS molecules associate, in their SH_2 domains (homology with Sre 2), molecules of successive signals [21]. For this reason they are called "docking" proteins. They "dock" the phosphatydylinositol-3-kinase (PK-3K), the molecules of protein associating the growth factor 2 (GRB-2), tyrosine phosphatase containing the SH_2 groups (SHP-2), and other signal molecules [1, 6].

Disturbances of cellular glucose transport as a candidate for the aetiological mechanism of insulin resistance

The stimulation of the GLUT4 function results from the translocation of the signal between IRS and the Akt molecule [11]

The direct relation between the activity of Akt and, stimulated by insulin, the functional translocation of

Table IV. *Summary of key knockout mouse models [1, 11]*

Tabela IV. *Zestawienia najważniejszych modeli zaburzeń chorobowych z wykorzystaniem modyfikowanych genetycznie myszy (knock out) [1, 11]*

Mutant	Phenotype
Insulin receptor knockouts	
Complete	Normal intrauterine growth and development Severe hyperglycaemia and hyperketonaemia develops shortly after birth, leading to death after 48–72 h
Muscle	Elevated fat mass, serum triglycerides and free fatty acids- (FFA) Normal blood glucose, serum insulin, and glucose tolerance Insulin resistance, severe glucose intolerance, insulin fails to suppress hepatic glucose output
Liver	Marked hyperinsulinaemia caused by increased insulin secretion/decreased insulin clearance Metabolic phenotype improves with ageing Reduced insulin secretion in response to glucose
β-cell	Progressive impairment of glucose tolerance and mild obesity Development of diet-sensitive obesity and insulin resistance Hyperinsulinaemia and hypertriglyceridaemia
Brain	Impaired spermatogenesis and ovarian follicle maturation
IGF-1 receptor knockout	
Complete	Lethal at birth owing to respiratory failure Severe growth deficiency and widespread developmental defects
IRS protein knockouts	
IRS-1	Significant growth inhibition Mild insulin resistance and glucose intolerance but diabetes does not develop owing to compensatory hyperinsulinaemia
IRS-2	Insulin resistance in muscle and liver coupled with abnormal β-cell function lead to diabetes Males develop dehydration and hyperosmolar coma leading to death Body weight and plasma glucose/insulin levels comparable to wild type
IRS-3	Insulin-stimulated glucose uptake in adipocytes from IRS-3 knockout mice similar to wild type Mild defects in growth in male mice
IRS-4	Mild defects in reproduction and slight impairments in glucose homeostasis
Glucose transporter knockouts	
GLUT4	Insulin resistance with mild impairment of glucose tolerance, growth retardation, and decreased fat tissue deposition Hyperinsulinaemia, cardiac hypertrophy, decreased levels of lactate and FFA
GLUT4	Insulin resistant, fasting hyperglycaemia, glucose intolerance — effects more severe than in muscle-specific insulin receptor knockout
GLUT4 (Adipose)	Markedly impaired insulin-stimulated glucose uptake in adipocytes Insulin resistance in muscle and liver leading to glucose intolerance and hyperinsulinaemia
Insulin/IGF-1 signalling protein knockout	
Knockout of PI 3-kinase	Increased insulin sensitivity, hypoglycaemia, and increased glucose transport caused by switch to alternative pathway (p50)
p85 regulatory subunit	Demonstrates role for PI 3-kinase in glucose homeostasis
Akt/PKB+2 (Complete)	Insulin resistance in muscle and liver coupled with increased pancreatic islet mass Glucose intolerant and hyperinsulinaemia

GLUT4 is very marked. PI-3K constitutes the necessary decisive step in the regulation of the GLUT4 translocation in adipocytes. It does not, however, participate in the GLUT4 translocation in the striated muscle contraction. Therefore, an additional signalling pathway exists, also regulated by the insulin receptor. This is the pathway involving the protein CAP and Cbl molecules. The exact mechanism of these reactions is not well

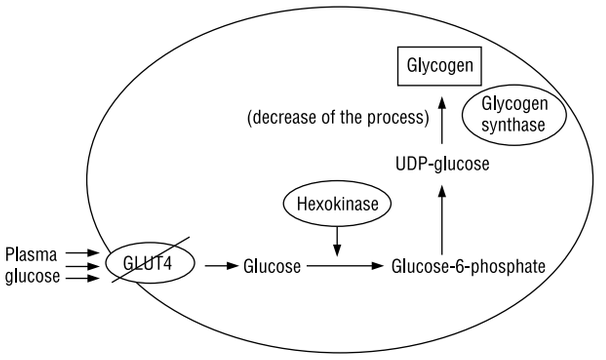

Figure 2. *Impairment of cellular glucose transport is the rate-controlling step responsiblefor reduced muscle glycogen synthesis in patients with type 2 diabetes mellitus (adapted, Shulman G.I.: Clin Invest 2000; 106: 171–176*

Rycina 2. *Upośledzenie dokomórkowego transportu glukozy jest głównym czynnikiem powodującym zmniejszenie syntezy glikogenu w mięśniach u chorych na cukrzycę typu 2 (na podstawie: Shulman GI. Clin Invest 2000; 106: 171–176*

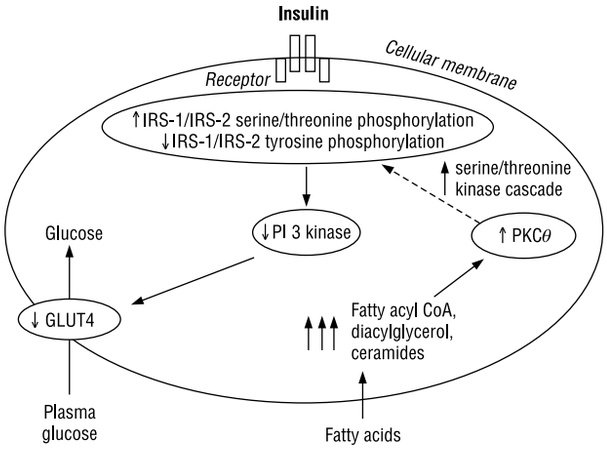

Figure 3. *Proposed mechanism for fatty acids-induced insulin resistance in human skeletal muscle (adapted: Shulman GI. J Clin Invest 2000; 106: 171–176)*

Rycina 3. *Mechanizm rozwoju insulinooporności indukowanej przez wolne kwasy tłuszczowe w ludzkim mięśniu szkieletowym (na podstawie: Shulman GI. J Clin Invest 2000; 106: 171–176)*

known. It is known that the specialized "cavities" covered with clathrine and the additional molecular regulator-dopamine participate in these actions. Cells with low specialization are characterized by the predominance of GLUTl expression. Interestingly, β-cells of pancreatic islets and hepatocytes present significant GLUT2 expression. This transporter has relatively low transport capacity. The influence of insulin on GLUT4 activity is based mainly on the activation of PI-3K, which is much faster and more efficient. It is assumed that in glucose transport, two speed levels can be distinguished. The first speed relates to the metabolism of glucose in preprandial circumstances, without insulin stimulation - mainly GLUT1 and 2. The second level is due to the significant and fast glucose absorption caused by the rise of insulin secretion and concentration in postprandial conditions. This is mainly the case of GLUT4. Both GLUT1 and GLUT4 glucotransporters exhibit similar turnover rates, about 20,000 molecules per minute. Km for GLUT4 glucose is, however, lower (2–7 mmol) than for GLUTl (20–23 mmol). In insulin-sensitive tissues GLUT4 dominates in terms of quantity and activity [30–32]. It can be inhibited by cytochalasin and bis-mannose analogues.

The increase of cellular glucose transport determines the rate of delivery of the glucose as the specific substrate for metabolic utilization. The stimulation of the cellular glucose transport system by insulin is harmonized with the increase in intracellular glucose utilization for anabolic and energy production, biochemical transformations, and for inhibition of catabolic processes like glucogenolysis and gluconeogenesis and for augmentation of the biosynthesis of proteins and triglycerides [12]. It is instantly reflected by the extracellular glucose concentration within its homeostatic, normoglycaemic level (Fig. 4, 5). Besides the metabolic effects, insulin, by stimulating the mitogen activated protein kinases (MAP kinases), is promoting the cells' survival and proliferation [13, 15].

In this particular mitogenic process, additional regulatory mechanisms may increase the action of insulin. Human cells expose the specific receptors for insulin-like growth factor-1 (IGF-1) [16]. This receptor, in its domain of tyrosine kinase located in beta-subunits, shows an amino acid structure the same as the insulin receptor in 80% of cases. Insulin (mainly hyperinsulinaemic states) may stimulate the IGF-1 receptor and vice-versa. This regulatory interchange plays an important role in foetal development. It could also be responsible for the increased risk of neoplastic proliferation in adults, mainly in diabetes mellitus type 2, connected with insulin resistance and hyperinsulinaemia [17–19].

The metabolic effects of insulin differ with respect to the functional specialization of the cells. They are dependent on the actions of molecules mediating the insulin signal transduction to the specific genes in striated muscle cells and in adipocytes [22–25]. PI-3K increases the cellular glucose utilization primarily by stimulating the formation and function of the glucotransporters GLUT4 and GLUT1. In this way the cells increase the glycogenogenesis (muscle) and lipidogenesis (adipocytes) [23–25]. At the same time, PI-3K increases the vitality of cells. The PI-3K mediated stimulation of the molecules mTOR (rapamycin dependent molecule) augments the synthesis of proteins. The molecule GRB-2 stimulates the mitogen activated kinases (MAPK) and the transcription of respective genes [16].

Table V. *Insulin regulatory actions on metabolic processes — the role of GLUT4 [28–31]*
Tabela V. *Regulacja procesów metabolicznych przez insulinę — rola GLUT4 [28–31]*

• The intake of glucose by the cells increases — predominantly by the striated muscle, and adipose tissue is strictly coordinated with the decrease of glucose production and release from the liver. This is also the effect of exogenous insulin;
• At the same time, resulting from the action of insulin, the increase of the production of alfa-glycerolphosphate facilitates the re-esterification of free fatty acids and inhibits the ketogenesis;
• in the striated muscle and adipose tissue cells, insulin causes the redistribution (translocation) of the glucose transporters, mainly GLUT4, to the cellular membrane;
• transmembrane glucose transport from the extracellular space to the interior of the cells, and the glucose utilization is increased

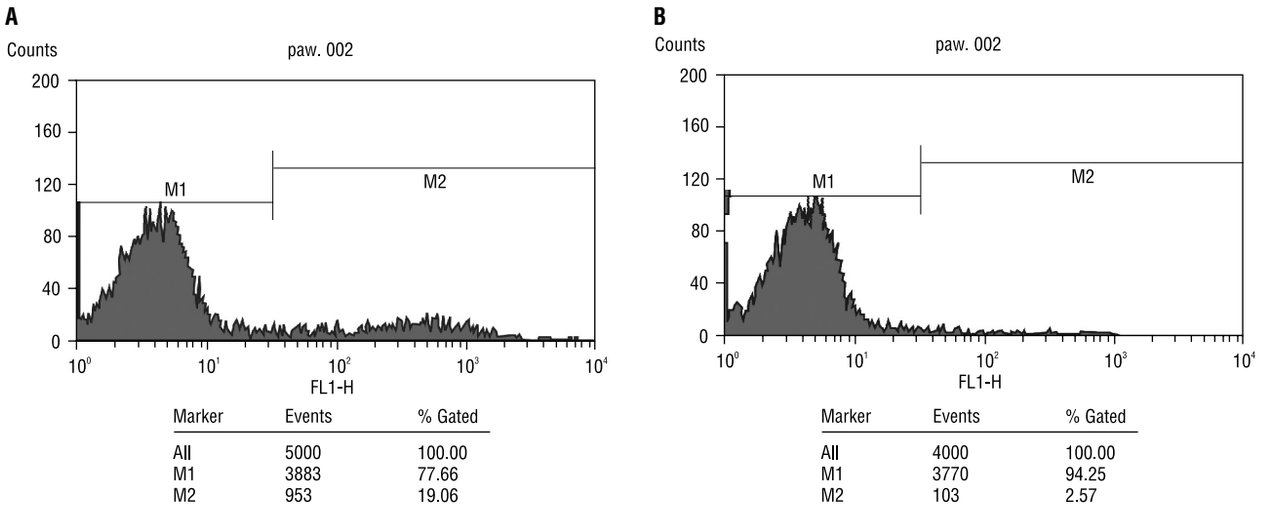

Figure 4. ***A****. Typical example of the GLUT4 expression assessment in lymphocytes of the peripheral blood with flow cytometry in the case of diabetes mellitus type 2: R.W., male, aged 58 years, HbA_{1C} 8.9%, 17.38% of lymphocytes expressed the GLUT4;* ***B****. After 12 weeks of diabetes mellitus type 2 therapy, in this case with diet and sulphonylurea,a significant decrease of the GLUT4 expression from 17.38% to 2.57% was observed.This phenomenon was connected with adecrease of HbA1C below 6.5%*

Rycina 4. ***A****.Typowy przykład oceny ekspresji GLUT4 w limfocytach krwi obwodowej metodą cytometrii przepływowej u chorego na cukrzycę typu 2: R.W., mężczyzna, wiek 58 lat, HbA_{1C} — 8,9%, ekspresja GLUT4 w 17,38% limfocytów;* ***B.*** *Ten sam chory; po 12 tygodniach leczenia dietą i pochodną sulfonylomocznika stwierdzono istotne zmniejszenie ekspresji GLUT4 z 17,38% do 2,57%. Jednocześnie nastąpiło obniżenie HbA_{1C} poniżej 6,5%*

Based on the examples described above, it can be stated that the structural (genetic) or functional (related to environment) changes in any of the signal molecules may limit the signalling process and cause resistance to insulin [5, 6, 26]. This can be observed in clinical conditions as the result of the signalling defects in the liver, striated muscle, and adipocytes as well as in pancreatic beta cells [22–27]. In this area, many interesting studies have proved the primary significance of the GLUT4 formation and function. It could be limited, for example, to making only the striated muscle cells insulin resistant. The reason for such perturbation is the intracellular hyper accumulation of free fatty acids, DAG, and other lipids, depressing the action of the different signalling molecules (IRS-1, PI-3K) and the increase of activity of the protein kinases C family. These abnormalities inhibit the translocation of GLUT4 in striated muscle and slow down the transport of glucose to the cells [28] (Table V, Fig. 4).

The role of intracellular hexokinase and glucokinase

The glucose molecules, after being transported through the cellular membrane, immediately enter the metabolic pathways. The first, regulatory step is the phosphorylation of glucose. This reaction is catalysed by two similar enzymes: hexokinase and glucokinase. The product of this reaction (the glucose-6 phosphate) enters the glycolysis metabolic pathway. In this way it regulates the intensity of the process depending on the glycolysis pathway as the tricarboxylic acid cycle in the mitochondrial matrix and inner mitochondrial membrane [12]. Free glucose is almost nonexistent in intracellular

space. These metabolic processes keep the difference in concentration of glucose in extracellular and in intracellular space and stimulate, in a secondary way, cellular glucose transport.

Conclusions

The resistance of the cell to insulin and the consequent impairment of cellular glucose utilization should be regarded as an important and frequent pathogenetic mechanism of several clinical symptomatic syndromes including, in the first place, type 2 diabetes mellitus. It may also play a role as a risk factor coexisting with other morbid influences, as in atherosclerosis first of all. For these reasons, diagnostic and specific therapy of insulin resistance is developing dynamically.

Resistance to insulin is primarily connected with a decrease of cellular glucose transport and is related, in a more or less specific way, to the structural and functional disturbances of the specific molecules forming the signalling pathway for insulin action from its receptor downstream to expression of more than 100 genes. On the basis of new research and data, it is now possible to diagnose resistance to insulin as resulting from the abnormalities in the specific molecules of the insulin signalling pathway. They may have a more general character, involving the whole organism, or may be limited to one organ or to one or more metabolic or proliferative processes. In addition, the molecular aetiology of resistance to insulin may have different mechanisms: genetic, metabolic, endocrine, pharmacological, or toxic. The aetiological and clinical classification of insulin resistance is therefore pending.

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