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PRACE POGLĄDOWE • REVIEWS

Kidneys function in glucose homeostasis regulation and its therapeutic implications

Funkcja nerek w regulacji homeostazy glukozy i jej terapeutyczne implikacje

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A – Study Design, **B** – Data Collection, **C** – Statistical Analysis, **D** – Data Interpretation, **E** – Manuscript Preparation, **F** – Literature Search, **G** – Funds Collection

Summary In the postabsorptive state, glucose must be continuously delivered into the circulation in order to meet energy requirements of tissues such as brain cells, which use glucose as their main fuel. Only liver and kidney are able to release glucose into the circulation. Release of glucose into the circulation occurs via two processes: gluconeogenesis, the *de novo* synthesis of glucose from non-glucose precursors; and glycogenolysis, the breakdown of glycogen. The kidneys play a major role in the regulation of glucose in humans, reabsorbing 99% of the plasma glucose that filters through the renal glomeruli tubules. The glucose reabsorption system in the kidney is mediated by sodium-dependent glucose cotransporters (SGLTs). This reabsorption is effected by two sodium-dependent glucose cotransporter proteins. Cotransporter SGLT2, situated in the S1 segment, and SGLT1, situated in the S3 segment. Expression and activity of SGLT2 are increased in diabetes. A higher than normal amount of glucose is reabsorbed, thereby contributing to maintaining hyperglycemia. Chronically elevated plasma glucose levels exacerbate insulin resistance and ß cell dysfunction, contributing to the abnormal glucose homeostasis. Blocking sodium-glucose cotransporters (SGLTs) to decrease the reabsorption of glucose, and thus increase renal glucose excretion. This represents a novel therapeutic approach to diabetes that is independent of insulin secretion or action. Initial clinical data are promising and suggest that SGLT2 inhibitors may be a new therapeutic option for treating type 2 diabetes mellitus.
Key words: gluconeogenesis, glycogenolysis, glucose reabsorption, sodium-dependent glucose cotransporters (SGLTs), SGLT2 cotransporter inhibitors.

Streszczenie W okresie poposiłkowym krążenie wymaga stałego dopływu glukozy, będącej zasadniczym źródłem energii dla tkanek, takich jak komórki mózgowe. Tylko wątroba i nerki mogą dostarczać glukozę do krążenia, wytworzoną w dwóch procesach: glukoneogenezy, czyli syntezy glukozy *de novo* z nieglukozowych substratów, oraz glikogenolizy, czyli rozkładu zmagazynowanego glikogenu. Nerki odgrywają główną rolę w regulacji glukozy u ludzi – reabsorbują 99% przefiltrowanej glukozy w kanalikach nerkowych. Proces ten mediowany jest przez dwa sodozależne kotransportery glukozy (SGLTs): kotransporter SGLT2 usytuowany jest w segmencie S1, kotransporter SGLT1 – w segmencie S3. Ekspresja i aktywność SGLT2 są zwiększone w przebiegu cukrzycy, co prowadzi do zwiększonej reabsorpcji glukozy i tym samym – do wzrostu hiperglikemii. Przewlekle podwyższone stężenie glukozy w osoczu może nasilać insulinooporność i ß-dysfunkcją komórek, przyczyniając się do zaburzenia homeostazy glukozy. Blokowanie SGLTs obniża reabsorpcję glukozy i zwiększa wydalanie glukozy przez nerki. To reprezentuje nowe terapeutyczne podejście do cukrzycy, które jest niezależne od jej wydzielania lub działania. Wstępne dane kliniczne są obiecujące i sugerują, że inhibitory SGLT2 mogą być nową opcją terapeutyczną w leczeniu cukrzycy typu 2.
Słowa kluczowe: glukoneogeneza, glikogenoliza, reabsorpcia glukozy, sodozależne kotransportery (SGLTs), inhibitory kotransportera SGLT2.

Background

Glucose homeostasis depends on glucose inflow to blood and tissue utilisation. Plasma glucose concentrations are normally maintained within a narrow range. Such tight regulation is critical for organs such as the brain, which utilizes glucose almost exclusively as its energy source. Glucose present in circulation comes from two main sources [1–4].

One is alimentary tract, where glucose is obtained from food, and subsequently is partially metabolised in glycolysis to cover current body requirements, and partially stored as glycogen in liver and skeletal muscles. The other source is glucose produced in glycogenolysis meaning glycogen break down, and produced *de novo* in gluconeogenesis.

Key enzymes in glycolysis process are hexokinase, phosphofructokinase, pyruvate kinase located in renal medulla cells. Enzymes located mostly in renal cortex, like pyruvate carboxylase, phosphoenolopyruvate carboxykinase, fructose-1,6-bisphosphatase and glucose-6-phosphatase, are engaged in gluconeogenesis process. Gluconeogenesis enables transformation of some non-sugar compounds, such as amino acids or glycerol, into glucose.

Only two organs have adequate enzymatic activity to lead glucose synthesis in gluconeogenesis process [5].

Since renal glucose release is almost exclusively due to gluconeogenesis, it seems that the kidney is as important gluconeogenic organ as the liver. The most important renal gluconeogenic precursors appear to be lactate, glutamine and glycerol.

The process undergoes multiple regulations – hormone, neural and metabolic control.

Main substrates for glucose synthesis in liver are alanine and lactate. Transformation is performed in lactic acid cycle (Cori cycle) and in glucose-alanine cycle.

Main substrate for glucose synthesis in kidneys is lactate glutamine and glycerol, and the process is performed in glucose-glutamine cycle [6]. Gluconeogenesis depends on current blood glucose concentration, substrate inflow and hormone control [7].

Kidneys function in glucose homeostasis

Research on kidneys function in glucose homeostasis maintain has long-term history. First studies were published in 1938–1941 [8].

Kidneys have an important influence on maintaining body metabolic glucose homeostasis both in physiologic, and pathologic conditions [2, 9, 10].

Kidneys not only take part in glycolysis and gluconeogenesis, but also perform essential functions of glucose filtration in glomeruli, and reabsorption in tubules.

In these processes two types of transporters are involved. GLUTs (*glucose transporters*), which are glucose specific protein carriers, and SGLTs (*sodium-dependent glucose cotransporters*), which require sodium ions for work [11–13].

First reports concerning sodium-dependent glucose cotransporters are dated 60s of previous century. In following years knowledge on SGLTs role expanded [13].

Gluconeogenesis

Insulin is a hormone inhibiting gluconeogenesis process. Other hormones action on kidney gluconeogenesis was investigated mostly in animals, and is less recognized in human.

Most important substrates for human gluconeogenesis are lactate, glutamine, alanine and glycerol, of which, as fore mentioned, glutamine is the main substrate for kidney gluconeogenesis. Significant kidneys role in glucose homeostasis maintaining is pointed by the fact that about 25% of total body glucose production is renal synthesis, and kidneys use up to 20% of total body glucose utilisation. During starvation, gluconeogenesis is responsible for production of about 55% of total body glucose pool, of which about half is synthesized in kidneys. During hypoglycemia kidney gluconeogenesis rate is increased, which lessens glucose concentration drop. This fact leads to a conclusion that kidneys play an important role in counterregulation process during hypoglycemia [5].

Glucose filtration and reabsorption

Glucose particles are moved from intracellular space to bloodstream by SGLT2 glucose transporter located in basal region of cells of renal tubules. About 90% of glucose filtered in glomeruli is later absorbed in tubules [14]. Glomeruli glucose filtration and tubular glucose reabsorption are mediated by sodium-dependent glucose cotransporters (SGLTs) [5, 10–12, 15–20]. Two main sodium-dependent glucose cotransporters are distinguished. SGLT2 cotransporter is a protein compose of 672 amino acids, located in S1 segment of proximal renal tubule, and is responsible for reabsorption of 90% of filtered glucose. SGLT2 plays a major role in renal glucose reabsorption. SGLT1 cotransporter, located in small intestine and most distant S3 segment of proximal renal tubule, is responsible for reabsorption of 10% of filtered glucose [8]. Probably there exists the third cotransporter SGLT3 involved in glucose reabsorption, but up to now its function was assessed in experimental studies. Tubular glucose reabsorption rate depends on numerous factors. In physiologic conditions all glucose is absorbed in proximal tubules. Even though the most common glycosuria cause is excessive blood glucose concentration, glucose presence in urine may be observed in normoglycemia during conditions, when proximal tubules function is deprived. In these cases processes described before may be disturbed, which leads to renal glycosuria. Genetic defects of SGLT cotransporters may be responsible for signs in familial renal glycosuria (FGR) [21–24]. Conditions caused by genes mutations require further studies [24].

Diabetes influence on kidney glucose metabolism

As mentioned before, kidneys participate in glucose homeostasis maintaining by taking part in gluconeogenesis, glucose filtration, reabsorption and utilization [9]. Every of these processes may be disturbed in diabetes.

Perspectives of sodium-dependent cotransporters modulation use in diabetes therapy

Role of SGLT2 genetic variation in the regulation of glucose homeostasis and promote pharmacogenomic studies to clarify the efficacy of antidiabetic treatment by SGLT2 inhibitors. Expression and activity of SGLT2 are increased in type 2 diabetes. A higher than normal amount of glucose is reabsorbed, thereby contributing to maintaining hyperglycemia. Chronically elevated plasma glucose levels exacerbate insulin resistance and ß cell dysfunction, contributing to the abnormal glucose homeostasis. Recovery of glucose from the glomerular filtrate is executed principally by the type 2 sodium-glucose cotransporter (SGLT2). Inhibition of SGLT2 promotes glucose excretion and normalizes glycemia in animal models. First reports of specifically designed SGLT2 inhibitors began to appear in the second half of the 1990s. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are the first agents to exploit excreting glucose as a target of therapy. Most of studies concern attempts of SGLT2 function inhibition, which may lead to glycosuria increase, and subsequent drop of blood glucose concentration, which gives hope of better metabolic control of diabetes [14, 15, 18–20, 25–36].

According to latest results, SGLT2 inhibitors allow safe reduction of glucose reabsorption rate leading to decreased excursions, with no risk of hypoglycemia, loss of body mass, and blood pressure, by mild osmotic diuresis [30]. The potency and positioning of SGLT2 inhibitors as an antidiabetic drug are dependent on their characteristic profile, which induces selectivity, efficacy, pharmacokinetics, and safety. Hence, these agents should be considered as alternatives to the second-line diabetes therapies in patients with inadequately controlled glycemia treated with monotherapy.

Blocking sodium-glucose cotransporters (SGLTs) to decrease the reabsorption of glucose – and thus increase renal glucose excretion – represents a novel therapeutic approach to diabetes that is independent of insulin secretion or action [37].

Initial clinical data are promising and suggest that SGLT2 inhibitors may be a new therapeutic option for treating type 2 diabetes mellitus [26].

Human studies have confirmed the efficacy of SLGT2 inhibitors in improving glucose control and reducing the A1c. Because the mechanism of SGLT2 inhibition is independent of circulating insulin levels or insulin sensitivity, these agents can be combined with all other antidiabetic classes, including exogenous insulin. Although the long-term efficacy and safety of SGLT2 inhibitors remain under study, the class represents a novel therapeutic approach with potential for the treatment of both type 2 and 1 diabetes [38].

However, still there are many doubts, requiring explanation in experimental studies [18, 39–43].

Most of studies on therapeutic use of SGLT inhibitors were carries on type 2 diabetes patients groups.

Selective inhibitors of SGLT2 reduce glucose reabsorption, causing excess glucose to be eliminated in the urine; this decreases plasma glucose. In T2DM, the glucosuria produced by SGLT2 inhibitors is associated with weight loss, and mild osmotic diuresis might assist a reduction in blood pressure. The mechanism is independent of insulin and carries a low risk of hypoglycaemia [39].

Because the action of SGLT2 inhibitors is independent of insulin, they to be potential also to combined with exogenous insulin as adjunctive therapy for type 1 diabetes. Further investigations on possibilities of such therapy use in both type 1 diabetes, and metabolic syndrome patients are still necessary [18].

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