The full significance of the kidney’s role in glucose homeostasis is now well recognized. For example, it is now known that renal gluconeogenesis contributes substantially to total-body glucose release in the postabsorptive state. The kidney contributes to glucose homeostasis by filtering and reabsorbing glucose. Under normal circumstances, glucose filtered by glomeruli is completely reabsorbed, but glucosuria may occur under conditions of hyperglycemia or reduced reabsorptive capacity. The sodium-glucose cotransporter SGLT2 (encoded by the SLC5A2 gene), which is expressed almost exclusively in proximal tubules, mediates approximately 90% of active renal glucose reabsorption. This transporter can be blocked by SGLT2 inhibitors, a class of compound that may prove effective in managing type 2 diabetes. The glucosuria induced by these compounds has a naturally occurring parallel in familial renal glucosuria (FRG), a condition in which SGLT2 mutations reduce renal reabsorptive capacity. Interestingly, the chronic glucosuria of patients with FRG does not appear to be associated with other pathological changes, and patients with FRG are mostly asymptomatic. This suggests that glucosuria is not intrinsically detrimental. Selective SGLT2 inhibitors are currently in clinical trials.


INDEX WORDS: Glucose metabolism; renal glucose excretion; sodium glucose cotransporter (SGLT); type 2 diabetes.

The importance of the kidney in normal glucose homeostasis is now well recognized. Unlike most other tissues involved in glycemic control, the kidney’s contribution to glucose homeostasis is not limited to glucose uptake and release, but also includes its filtration and subsequent reabsorption or excretion. Improved understanding of the renal pathways active in the maintenance of glucose homeostasis, including glucose reabsorption, has prompted the development of pharmacological agents that have the potential to reduce hyperglycemia in patients with diabetes by promoting glucosuria. The objective of this report is to review the role of the kidney in glucose homeostasis and clarify its position as a potentially important new target in the management of diabetes.

THE ROLE OF THE KIDNEY IN GLUCOSE HOMEOSTASIS

Despite wide variations in food intake and activity level, plasma glucose levels are maintained at all times within a range of approximately 70 to 160 mg/dL in healthy individuals. This close control is achieved by a well-regulated homeostatic system that balances glucose production, reabsorption, and use in peripheral tissues through a network of hormones, neural pathways, and glucose transport proteins. The diet normally is the body’s major source of glucose. Between meals or during fasting, plasma glucose levels are maintained by the breakdown of glycogen (glycogenolysis) and gluconeogenesis. Of organs capable of gluconeogenesis, only the liver and kidney are capable of generating sufficient glucose to release it into the circulation. Until recently, it was believed that the liver was solely responsible for gluconeogenesis under normal physiological conditions and that renal synthesis of glucose became significant only during prolonged fasting or acidosis. However, it is now recognized that the kidney has a significant role in glucose homeostasis under both physiological and pathological conditions. Gluconeogenesis and reabsorption of filtered glucose are the major renal mechanisms affecting glucose metabolism.

Gluconeogenesis in the Kidney

Early studies showed little or no difference between arterial and venous glucose levels in kidneys of nondiabetic fasting individuals, and these data were taken as evidence that renal...
Gluconeogenesis was inconsequential in the normal postabsorptive state. However, it is now clear that the kidney both takes up and releases glucose, although these 2 processes occur in different parts of the organ. Cells of the renal medulla, which are incapable of gluconeogenesis, are predominantly responsible for renal glucose use. In contrast, studies of humans and animals indicate that the proximal tubule (which lies within the renal cortex) is the only nephron segment that contains the key gluconeogenic enzymes (glucose 6-phosphatase, fructose 1,6-diphosphatase, and phosphoenolpyruvate carboxykinase) and thus is the only segment capable of synthesizing glucose. Recent work implies that these 3 enzymes are active along the entire length of the proximal tubule. Gluconeogenesis in the kidney involves the de novo synthesis of glucose from such noncarbohydrate precursors as lactate, glutamine, alanine, and glycerol. The proximal tubule does not produce glucose from endogenous substrates in the absence of glutamine and lactate, consistent with the very low glycogen content of these cells in healthy individuals.

It is not easy to determine the magnitude of renal glucose release in humans, and widely differing conclusions regarding the contribution of the kidney to total-body glucose release have been published. One technique commonly used is the combined isotopic–net renal balance approach. This involves calculating both net renal arteriovenous glucose balance and renal glucose uptake and using these data to determine total renal glucose release. In 2001, Gerich et al averaged results of 10 studies that used this approach and concluded that the renal contribution to total-body glucose release in the postabsorptive state is approximately 20%. Assuming that gluconeogenesis accounts for approximately half of all glucose release into the circulation in fasting humans, this suggests that renal gluconeogenesis is responsible for approximately 40% of all gluconeogenesis. Moreover, there is evidence that renal glucose release is increased in both the postprandial and postabsorptive states in patients with type 2 diabetes. The kidney thus contributes to the hyperglycemia that characterizes this condition. In 1 study, renal glucose release showed a 3-fold increase in patients with diabetes compared with nondiabetic controls. In contrast, hepatic glucose release increased by only 30%.

**Glucose Reabsorption in the Kidney**

In addition to its important role in gluconeogenesis, the kidney contributes to glucose homeostasis by filtering and reabsorbing glucose. Under normal circumstances, glomeruli filter from plasma approximately 180 g/d of D-glucose, all of which is reabsorbed through glucose transporter proteins that are present in membranes of cells in the proximal tubules. It is only when the capacity of these transporters is exceeded that glucose appears in urine. This maximum capacity, known as the tubular maximum for glucose (TmG), ranges from 260 to 350 mg/min/1.73 m² in healthy human adults and children and corresponds to a plasma glucose level of approximately 200 mg/dL (Fig 1). Small differences between individual nephrons and the imprecise nature of biological systems means the concentration/reabsorption curve is not entirely linear, showing a splay from the theoretical as the TmG is approached. This means that as blood glucose levels increase, glucosuria can start to occur slightly before one might expect based on the TmG, and the degree of glucosuria may be slightly less than expected when the theoretical capacity of the transporters starts to be exceeded. The correlation between degree of hyperglycemia...
mia and degree of glucosuria becomes linear only when blood glucose concentrations have increased beyond this splay region of the curve (Fig 1). In patients with diabetes, glucose concentration in renal tubules is high and transporters are unable to reabsorb all the glucose, resulting in glucosuria. A direct regulatory relationship between renal glucose reabsorption and renal gluconeogenesis has not been shown.

**RENAL GLUCOSE TRANSPORTERS**

The presence of membrane-associated carrier proteins is necessary to transport glucose, a polar compound, into and across cells. Mediation of glucose transport within the body involves transporters in 2 gene families, the facilitated glucose transporters (GLUTs) and the sodium-coupled glucose cotransporters (SGLTs). These transporters control glucose transport and reabsorption in several tissue types, including the proximal renal tubule, small intestine, blood-brain barrier, and peripheral tissues.

GLUTs mediate the passive transport of glucose across cell membranes and thus facilitate the downhill movement of this molecule as it equilibrates across a membrane. In contrast, SGLTs mediate the transport of glucose against a concentration gradient by cotransport with sodium. The energy for this process, which is known as secondary active transport, is provided by the sodium gradient across the cell membrane, which is maintained by activity of the sodium-potassium adenosine triphosphatase pump.

Table 1 lists distributions and kinetic properties of the major GLUT and SGLT transporters expressed in renal tissue. With 1 notable exception (SGLT2, encoded by the SLC5A2 gene), the majority of these transporters also are expressed in other tissues. It should be noted that most cells express more than 1 glucose transporter, and the metabolic requirements of each tissue are reflected by its pattern of transporter expression.

Of the 4 SGLT proteins expressed in the kidney shown to transport glucose (SGLT1, SGLT2, SGLT4, and SGLT6), SGLT2 is the most important. This SGLT, which is expressed predominantly on the luminal surface of cells of the first part of the proximal tubule (S1 and S2 segments), is a low-affinity high-capacity SGLT with a 1:1 sodium ion to glucose molecule co-
transport ratio (Fig 2). 17,22 Animal studies suggest that SGLT2 is responsible for reabsorbing 90% of the glucose filtered at the glomerulus. 24 The remaining 10% is reabsorbed by SGLT1, a high-affinity low-capacity SGLT with a 2:1 sodium ion to glucose molecule cotransport ratio that is expressed on the luminal (brush border) surface of cells of the S3 segment of the proximal tubule. 17,22

GLUT2 is the major facilitated glucose transporter expressed in the kidney. This protein, which is present on the basolateral membrane of epithelial cells of the S1 and S2 segments of the proximal tubules, has a lower affinity for glucose (Michaelis constant \(K_m\), 40 mmol/L) than the other glucose-transporting GLUT proteins (\(K_m\) values for GLUT1, GLUT3, and GLUT4 are 20 mmol/L, 10 mmol/L, and 3 mmol/L, respectively). 22,24 The role of GLUT2 is to release into the circulation the glucose reabsorbed into the proximal tubular cells by the SGLTs. 22 In the S3 segment of the proximal tubule, this role is performed by GLUT1. 24,25

It is evident from this discussion that SGLT2 is the predominant effector of glucose reabsorption in the kidney. Moreover, this transporter is expressed almost exclusively in the kidney. Tazawa et al. 26 used real-time quantitative polymerase chain reaction to determine levels of SGLT1, SGLT2, and SGLT4 expression in 12 human tissues. These investigators found 11,200 copies of SGLT2 messenger RNA per 1 ng of complementary DNA in renal tissue, 28 copies per 1 ng of complementary DNA in small intestinal tissue, and none in brain, colon, heart, liver, lung, skeletal muscle, placenta, spleen, stomach, or trachea. In contrast, SGLT4 was expressed in all 12 tissues, and SGLT1 was expressed in all except placenta. 26 Chen et al. 27 found SGLT2 in renal tissue only. The predominant role of SGLT2 in the renal reabsorption of glucose raises the prospect that targeted blockade of this protein may be beneficial in patients with diabetes. 28

**DISORDERS WITH ABNORMAL RENAL GLUCOSE TRANSPORT**

Renal glucose handling is abnormal in patients with a number of inherited and acquired diseases. Understanding these conditions is important because symptoms shown by affected patients may inform us about some of the potential consequences of pharmacological manipulation of glucose transporter activity.

The 2 main causes of naturally occurring renal glucosuria are familial (primary) renal glucosuria (FRG) and glucose-galactose malabsorption (GGM). FRG is characterized by persistent glucosuria in the absence of hyperglycemia and without signs of general renal tubular dysfunc-
This condition occurs secondary to a number of different SGLT2 mutations and may be inherited in an autosomal recessive or autosomal dominant fashion. In 2003, Santer et al characterized the SGLT2 genes of 23 families with index cases. A total of 21 different mutations were detected, most confined to a single family. Glucosuria was more severe in homozygous and compound heterozygous patients than in heterozygotes. However, not all heterozygous individuals were affected, suggesting that other genetic or nongenetic factors can modify the expression of SGLT2 mutations (i.e., the condition shows variable penetrance). Variants of FRG have been termed types A, B, and O, according to the severity of glucosuria. The most severe form is type O, defined as the complete absence of renal tubular glucose reabsorption resulting from nonfunctioning mutations within the SGLT2 gene. The large majority of patients with FRG have no clinical manifestations, and thus FRG is described as a "nondisease" and is synonymous with the condition known as benign glucosuria. Even extreme glucose loss characteristic for the type O variant has a favorable prognosis. Because FRG generally is asymptomatic, affected individuals generally are identified through routine urinalysis.

GGM is an autosomal recessive disease caused by mutation of the SGLT1 transporter. The condition is dominated by intestinal symptoms that manifest within the first few days of life and result from failure to absorb glucose and galactose from the intestinal tract. This leads to severe diarrhea and dehydration that may be fatal if a glucose- and galactose-free diet is not instituted. Glucosuria is present in some patients with GGM, but typically is mild. Moreover, in accordance with the minor role of SGLT1 in renal reabsorption of glucose, some patients show no evidence of abnormal urinary glucose excretion.

GLUT2 is a widely distributed facilitative glucose transporter that has a key role in glucose homeostasis through its involvement in intestinal glucose uptake, renal reabsorption of glucose, glucosensing in the pancreas, and hepatic uptake and release of glucose (Table 1). Homozygous or compound heterozygous mutations of the gene encoding this protein result in Fanconi-Bickel syndrome, a rare autosomal recessive glycogen storage disease (type XI) that results in glucose and galactose intolerance, postprandial hyperglycemia, fasting hypoglycemia, a characteristic tubular nephropathy, hepatomegaly and renomegaly (secondary to glycogen accumulation), rickets, and stunted growth. Because GLUT2 is involved in the tubular reabsorption of glucose, glucosuria is a feature of the nephropathy.

The ubiquitous involvement of GLUT2 in glucose metabolism means that dysfunction of this protein has wide-ranging clinical consequences. Mutations of SGLT1 may also cause symptoms in more than 1 organ system (gastrointestinal tract and renal system). In contrast, SGLT2 is present almost exclusively in renal proximal tubular cells, and changes in renal function thus are the only consequence of dysfunction of this transporter.

FRG, GGM, and Fanconi-Bickel syndrome all involve mutations of the genes encoding glucose transporters. However, there is evidence that changes in glucose handling also may be acquired. Increased GLUT2 expression and the abnormal presence of this transporter at the brush-border surface of renal proximal tubular cells have been reported in diabetic rats. Moreover, increased glucose uptake and SGLT2 and GLUT2 expression have been identified in exfoliated proximal tubular epithelial cells from patients with type 2 diabetes. It should be noted that the converse relationship (i.e., a possible effect of glucose transporter function on diabetes risk) is evident in the recent observation that particular GLUT2 polymorphisms are associated with an increased incidence of type 2 diabetes. These observations may help explain the altered renal glucose handling seen in patients with diabetes (e.g., increases in TmG and occasional absence of glucosuria in patients with hyperglycemia).

**TARGETING RENAL GLUCOSE REABSORPTION WITH INHIBITORS OF SGLT2**

In the last 2 decades, inhibition of renal glucose reabsorption has been pursued as a strategy for the control of diabetes through the development of SGLT inhibitors. Investigations gener-
ally have focused on selective SGLT2 inhibition. This approach avoids development of the diarrhea and secondary dehydration characteristic of individuals with SGLT1 dysfunction (GGM) when fed a normal diet.

Unlike most glucose transporters, SGLT2 is expressed almost exclusively in 1 tissue (the renal proximal tubules), and selective inhibition of this protein thus is unlikely to affect other metabolic processes. Moreover, the observation that FRG is not associated with upregulation of other sodium-dependent glucose transporters suggests that SGLT2 inhibition is likely to remain effective in the long term. SGLT2 inhibitors developed to date include phlorizin, T-1095, sergliflozin, and dapagliflozin (Fig 3). These compounds can be differentiated on the basis of their selectivity, chemical structure, and stability.

Phlorizin was the first SGLT inhibitor to be discovered. This naturally occurring O-glucoside, which can be isolated from the root bark of the apple tree, is a potent glucosuric agent. Phlorizin has proved useful as a physiological research tool and has been used in this capacity for more than 150 years. However, several major limitations make phlorizin unsuitable for therapeutic use. First, this agent is nonselective, inhibiting both SGLT2 and SGLT1. Because naturally occurring SGLT1 dysfunction (GGM) requires careful dietary management to avoid the severe diarrhea that normally accompanies this condition, administration of a potent SGLT1 inhibitor is not a viable therapeutic strategy. Additional limitations of phlorizin include poor bioavailability after oral administration and susceptibility of the O-linkage to cleavage within the gastrointestinal tract by β-glucosidase. This leads to production of the aglycon phloretin, a compound that blocks GLUT transport. To be effective, phlorizin therefore must be administered parenterally. An “ideal” SGLT2 inhibitor would have high potency and selectivity for SGLT2, metabolic stability, oral bioavailability, a pharmacokinetic profile that enables convenient dosing, suitability for use in combination with other antidiabetic drugs, and good tolerability.

Early attempts to improve on phlorizin led to the development of T-1095A, a derivative of phlorizin that can be administered orally as the prodrug T-1095. This O-glucoside has better metabolic stability than phlorizin. However, it is a nonselective SGLT inhibitor. Development of T-1095 was discontinued without progressing further than phase 2 clinical trials.

Additional work on this class of compounds led to the development of more selective SGLT2 inhibitors, such as sergliflozin (recently described in phase 2 clinical trials, but now believed to have been discontinued) and dapagliflozin (currently in phase 3 clinical trials). Like phlorizin and T-1095, sergliflozin is an O-glucoside SGLT2 inhibitor. As a result, it must be administered as a prodrug (the ethyl carbonate) to avoid degradation by glucosidase within the gastrointestinal tract. Sergliflozin has a 50% inhibitory concentration of 9.2 nmol/L and greater than 90-fold specificity for SGLT2 over SGLT1. In an animal model, sergliflozin, 30 mg, caused 24-hour urinary glucose excretion of approximately 300 mg (Fig 4). Dapagliflozin is a C-aryl glucoside, a structure not susceptible to degradation by glucosidase, and dapagliflozin therefore can be administered orally without the need for development of a prodrug. This chemical structure also is resistant to degra-
by the hepatic and renal glucosidases to which the $O$-glucosides are susceptible. Dapagliflozin has a 50% inhibitory concentration of 1.1 nmol/L and approximately 1,200-fold specificity for SGLT2 over SGLT1. In an animal model, dapagliflozin, 10 mg, caused 24-hour urinary glucose excretion of approximately 1,700 mg (Fig 4). The clinical significance of any differences between different drugs noted in preclinical testing is unclear and would need to be tested in clinical trials.

It is unclear whether this degree of glucosuria would be expected to result in osmotic diuresis. However, preliminary 14-day phase 2a dose-ranging data for dapagliflozin in 47 patients with type 2 diabetes showed that dosages of 5, 25, and 100 mg/d caused substantial glucosuria (loss of 45.2, 75.3, and 81.3 g of glucose in urine in the 24 hours after the first dose, respectively) that was not associated with an increase in urine volume. Daily glucose excretion was consistent during the 14-day study.

A number of other compounds are already in clinical development (Table 2), and the safety and efficacy of this novel approach to the management of type 2 diabetes will become more apparent as clinical development continues. SGLT2 inhibition is unusual in having a naturally occurring model in humans. The observation that most individuals with SGLT2 dysfunction (FRG) generally are healthy suggests that chronic inhibition of renal glucose reabsorption and the associated chronic glucosuria may not be associated with adverse consequences per se.

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Data from Wolters Kluwer Health Research & Development Insight database.

**SUMMARY**

The concept of tackling hyperglycemia in patients with type 2 diabetes by inhibiting renal glucose reabsorption is a strategy that investigators have been pursuing for almost 2 decades. New drugs targeting this mechanism are now approaching the final stages of clinical development. Glucose reabsorption within the kidney is driven by GLUT and SGLT transporters, both expressed in cells of the proximal renal tubule. The majority of active glucose reabsorption within the kidney is performed by SGLT2. Preclinical data suggest that targeted blockade of this protein may be beneficial in patients with type 2 diabetes. Because SGLT2 is expressed almost exclusively in renal proximal tubules, selective inhibition of this protein is unlikely to affect other metabolic processes. Moreover, long-term data from individuals with glucosuria secondary to naturally occurring SGLT2 dysfunction (FRG), most of whom are asymptomatic, suggest that chronic glucosuria in itself may not be associated with adverse consequences. Phase 3 clinical trials will determine whether SGLT2 inhibitors fulfill their theoretical promise as an approach to the management of type 2 diabetes.

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**Figure 4.** The glucosuric response after oral administration of phlorizin, T-1095, sergliflozin, and dapagliflozin to normal rats. Data are expressed per 200 g of body weight and represent urinary glucose excretion during a 24-hour period. Adapted with permission from Meng et al, © 2008 American Chemical Society.
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