Familial renal glycosuria and modifications of glucose renal excretion

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Abstract

Under physiological conditions, the kidneys contribute to glucose homoeostasis by producing glucose by gluconeogenesis and preventing glucose loss in urine. The glucose filtered by the glomeruli is completely reabsorbed in the renal proximal tubule. Renal gluconeogenesis produces 25% of the circulating glucose in the postabsorptive state, while the amount of glucose reabsorbed by the kidneys largely exceeds the quantity synthesized by kidney gluconeogenesis. Sodium-glucose cotransporter type 2 (SGLT-2) and glucose transporter 2 (GLUT2) carry out more than 90% of renal glucose uptake. In diabetes, both gluconeogenesis and renal glucose reabsorption are increased. The augmentation of glucose uptake in diabetes is due to the overexpression of renal glucose transporters SGLT-2 and GLUT2 in response to the increase in expression of transcription activator hepatic nuclear factor 1-alpha (HNF1α). The rise in glucose uptake contributes to hyperglycaemia and induces glomerular hyperfiltration by increasing sodium and water reabsorption in the proximal tubule that, in turn, modifies urine flux at the macula densa. SGLT-2 inhibitors improve glycaemic control and prevent renal hyperfiltration in diabetes. Loss of SGLT-2 transporter function is a benign state characterized by glycosuria. In contrast, mutations of other glucose transporters expressed in the kidney are responsible for severe disorders.

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1. Introduction

The kidney plays an important role in glucose homoeostasis. It helps to maintain plasma glucose concentration in the normal range by at least two mechanisms: it produces glucose by gluconeogenesis; and prevents glucose wastage by reabsorbing 100% of the glucose filtered by the glomeruli. However, gluconeogenesis and renal glucose reabsorption are modified in diabetes and contribute to disordered glucose homoeostasis. On the other hand, modulation of renal gluconeogenesis or renal glucose reabsorption by drugs can help to control plasma glucose concentration. I briefly present here recent data regarding renal gluconeogenesis, and detail the mechanisms of glucose handling by the kidneys in physiological and pathological conditions. Knowledge of the mechanism of sodium uptake in the kidney has allowed the development of inhibitors targeting a specific glucose carrier, sodium-glucose cotransporter type 2 (SGLT-2). Expression of SGLT-2 is altered in various genetic disorders. Analysis of the patient phenotype may help us to understand the consequences of drug-induced inhibition of renal glucose transporters.

2. Role of the kidney in glucose homoeostasis

The kidneys, like many other organs, use glucose as a source of energy. However, glucose is the main source of energy only in the medulla, as the renal cortex is mainly fuelled by fatty acid oxidation. Furthermore, the proximal tubules that, along with glomeruli, are the main constituents of the renal cortex, produce glucose by gluconeogenesis and reabsorb the glucose filtered by glomeruli, thus preventing glucose loss in urine. The key enzymes of gluconeogenesis-phosphoenolpyruvate carboxykinase (PEPCK) and glucose 6-phosphatase (G6Pase) – are expressed in the renal proximal tubules, but are absent in the renal medulla. The amount of glucose produced by the kidneys is substantial, and different studies have assessed their contribution to plasma glucose concentration in the postabsorptive state. The kidneys were found to produce 2.0-2.5 μmol of glucose/kg.min, which means that 20-25% of circulating glucose is produced by the kidneys under physiological conditions [1-4].

Globally, glucose production by the kidneys exceeds renal glucose consumption. The importance of the kidney’s
contribution to the maintenance of normal glucose serum concentration is illustrated by the lack of hypoglycaemia after prolonged fasting in mice with hepatic deletion of the G6Pase gene, which abolishes hepatic gluconeogenesis [5].

Renal gluconeogenesis is important in the prevention of hypoglycaemia, and its inappropriate increase in diabetes contributes to the genesis of glucose concentration disturbance. PEPCK expression is markedly increased in the diabetic rat kidney, resulting in an increase of renal gluconeogenesis in the proximal tubule [6]. PEPCK overexpression in diabetes is due to the decrease in insulin receptor signalling in the kidneys [7]. The importance of renal insulin signalling is illustrated by the consequences of specific deletion of the insulin receptor in the renal proximal tubule of mice. In these animals, PEPCK and G6Pase expression and activity in the kidneys are increased, resulting in fasting plasma glucose concentrations higher than in controls [8]. However, the consequences on renal glucose transport of deletion of the insulin receptor in the kidneys have not been reported in these animals.

3. Renal glucose transport

The release of glucose into the circulation by the kidneys is not limited to gluconeogenesis. Indeed, the kidney prevents the loss of glucose in urine by reabsorbing 100% of the glucose filtered by the glomeruli. Under physiological conditions, the kidneys filter around 180 g (1 mole) of glucose per 24 h, and reabsorb the same amount. In comparison, the adult kidney produces around 40 g (≈0.22 moles) of glucose/24 h by gluconeogenesis, and consumes 30 g/day (0.17 moles). Thus, the quantity of glucose reabsorbed every day by the kidneys greatly exceeds the amount produced by gluconeogenesis.

Renal glucose reabsorption takes place exclusively in the proximal tubule. The mechanism of the process is the same all along the proximal tubule, although the transporters involved differ across the initial part, the convoluted segment and the straight section of the proximal tubule (Fig. 1). Also, more glucose than water is reabsorbed, which means that the glucose concentration in urine decreases all along the tubule. Consequently, the affinity of the transporters for glucose along the tubule needs to increase to achieve complete removal of glucose molecules from urine.

The first step of glucose reabsorption is the uptake of glucose at the luminal side of the proximal tubular cells. This step requires energy, which is provided by the sodium gradient between the intra- and extracellular compartments generated by sodium-potassium ATPase. Glucose enters the cell along with sodium, and sodium exits the cell at the basolateral domain through sodium-potassium ATPase. The release of glucose into the interstitial compartment and blood circulation at the basolateral side of the cell requires no energy, as it is a facilitative transport: glucose movement is driven by its concentration gradient.

Glucose transporters expressed in the proximal tubule belong to two different families: the apical transporters are SGLT1 (type 1) and SGLT-2; while the glucose carriers expressed at the basolateral domain are called glucose transporters 1 (GLUT1) and 2 (GLUT2), and do not require sodium or any other ions. In the initial part of the proximal tubule, only SGLT-2 and GLUT2 are expressed, while SGLT1 and GLUT1 are expressed in the distal part of the tubule. The affinity of SGLT-2 (≈1.6 mM) for glucose is lower than that of SGLT1 (≈0.35 mM). SGLT-2 transports one molecule of glucose with one ion of sodium, while SGLT1 carries two sodium ions with one molecule of glucose. As a consequence, glucose reabsorption in the distal part of the proximal tubule requires more energy than in the initial part. The SGLT-2/GLUT2 coupling reabsors the vast majority (>90%) of the glucose filtered at the glomeruli. Similarly, the affinity of GLUT2 for glucose (15-20 μM) is lower than that of GLUT1 (1-2 μM), and the expression of SGLT-2/GLUT2 units exceeds that of SGLT1/GLUT1. Thus, SGLT-2/GLUT2 is a low-affinity, high-capacity system in contrast to SGLT1/GLUT1, which is a high-affinity, low-capacity coupling.

Under physiological conditions, the expression of renal glucose transporters does not vary and is not significantly modified by hormones. This means that the capacity of the kidneys to reabsorb glucose is constant for any given subject in the absence of diabetes. The maximum amount of glucose reabsorbed by the kidneys can be measured when the amount of glucose filtered exceeds this capacity, and glucose appears in urine. This is usually referred to as TmGlu and as TmGlu/glomerular filtration rate (GFR) when normalized for GFR. If the TmGlu decreases or the quantity of glucose filtered increases, then glycosuria arises. On the other hand, a rise in TmGlu may result in glucose accumulation.

A defect of glucose reabsorption in the proximal tubule induces glycosuria, but also affects the reabsorption of water and ions. Indeed, 70 % of the water filtered at the glomeruli is reabsorbed in the proximal tubule, driven by the reabsorption of osmoles, especially glucose. A decrease in glucose reabsorption is associated with a loss of water,
with consequences that depend on the level of the deficiency. Calcium reabsorption in the proximal tubule follows water reabsorption. Consequently, glycosuria is generally associated with augmentation of calcium excretion.

4. Mutations of renal glucose transporters

So far, only loss-of-function mutations have been identified in renal glucose transporters.

4.1. Mutations of SGLT1

SGLT1 is a protein comprising 664 amino acids with a molecular weight of approximately 73 kDa and 13 transmembrane domains. It is expressed in the kidneys and intestines. SGLT1 carries glucose as well as galactose. Mutations of SGLT1 are responsible for the glucose/galactose malabsorption syndrome, an autosomal-recessive disorder that causes diarrhoea due to the inability of intestinal cells to reabsorb galactose [9]. Eliminating galactose from the diet can correct the problem. Patients present with discreet glycosuria due to a slight decrease in TmGluc [10]. Artificial sweeteners stimulate SGLT1 expression in the gut, although their effect on SGLT1 renal expression has not been reported [11].

4.2. Mutations of GLUT1

In addition to kidney expression, GLUT1 is present in erythrocytes and the brain. In the brain, GLUT1 carries glucose from blood to cerebrospinal fluid (CSF), and is essential for normal glucose concentrations in CSF. Heterozygous GLUT1 deficiency induces hypoglycorrhachia, a condition responsible for seizures and neurological disorders that begin within the first months of life [12]. Heterozygous disruption of the GLUT1 gene in mice reproduces the human disorder [13].

4.3. Mutations of GLUT2

Facilitative GLUT2 is expressed in the kidneys, liver, pancreas and intestines. In pancreatic beta cells, GLUT2 transports glucose to the cells and contributes to the coupling of insulin secretion with plasma glucose concentration. In the liver, GLUT2 is important for the release of glucose in the blood circulation. Biallelic mutations of GLUT2 cause the Fanconi-Bickel syndrome, characterized by hepatorenal accumulation of glycogen [14]. In addition to glycosuria, these patients present with a renal proximal tubulopathy with hypophosphataemia, renal phosphate loss, aminoaciduria, episodes of albuminuria and, less frequently, neonatal diabetes [15-17].

Homozygous GLUT2-deficient mice have abnormal glucose tolerance, high plasma glucose concentrations, elevated glucagon plasma levels and inappropriately low levels of insulin [18].

4.4. Mutations of SGLT-2

The SGLT-2 gene encodes a protein with 672 amino acids that share a 59% similarity with those of SGLT1. SGLT-2 has 14 putative transmembrane domains, and is exclusively expressed in the renal proximal tubule. Heterozygous, homozygous and compound heterozygous SGLT-2 mutations cause benign renal glycosuria, an autosomal-dominant condition. Heterozygous patients present with various degrees of glycosuria in the absence of hyperglycaemia. These mutations do not affect specific regions of the SGLT-2 protein and are considered private [19,20]. Studies of such mutations show various degrees of altered glucose transport. Some mutations retain an 80% capacity of glucose transport compared with the wild-type form, while others completely abolish protein expression [21]. Thus, the abundance of glycosuria varies from very low levels (0.1 g/day) to more than 100 g/day, depending on the mutation and whether the subject is heterozygous, compound heterozygous or homozygous.

These mutations are not associated with any problems other than glycosuria. In particular, no hypoglycaemic episodes have been reported and there is no evidence of higher rates of infections of the urinary tract in humans. Age at diagnosis ranges from childhood to adulthood. Low levels of glycosylated haemoglobin (HbA1c) and insulin have been reported [22], and polyuria associated with sodium wasting and/or aminoaciduria has been observed when daily urinary excretion of glucose is abundant [23,24]. Investigations of subjects with familial benign glycosuria show a decrease in TmGluc/GFR proportional to the importance of the functional defect. In general, subjects with SGLT-2 mutations are in good condition.

Two models of SGLT-2 gene disruption have been obtained in mouse models. The Sweet Pee model carries a nonsense mutation of the Slc5a2 gene, which encodes the SGLT-2 protein [25]. This mouse strain was obtained by nitrosourea-induced mutations followed by screening based on the presence of glycosuria in the absence of hyperglycaemia. The mutant strain was selected by backcrossing. In this model, the mice present a phenotype similar to that of humans with SGLT-2 mutations, including glycosuria, and water, sodium and calcium loss via urine. However, at variance with humans, the mutant mice exhibit growth retardation, a decrease in survival and a high frequency of severe pyelonephritis. It is not yet known whether these differences are due to the selection process or perhaps the use of nitrosourea, which could have caused mutations in other genes as well as Slc5a2. Targeted disruption of the Slc5a2/SGLT-2 gene induces glycosuria without modification of plasma glucose levels or increased water and food intakes [26]. GFR remains unchanged, and survival is unaffected. The absence or decrease in SGLT-2 expression improves glycaemic control in mice with streptozotocin-induced diabetes [25,27]. Interestingly, the absence of SGLT-2 prevented glomerular hyperfiltration, but not renal hypertrophy or lesions [27].
5. Decreased SGLT-2 expression in the absence of SGLT-2 mutation

Maturity-onset diabetes of the young type 3 (MODY3) is among the most frequent causes of genetic diabetes. This is an autosomal-dominant disorder due to loss-of-function mutations in the gene encoding transcription factor hepatic nuclear factor 1-alpha (HNF1α). HNF1α is expressed in the liver, kidneys and pancreas. Inactivation of the HNF1α gene in mice results in severe glycosuria due to a specific decrease in SGLT-2 expression in the proximal tubule [28]. HNF1α can bind to the SGLT-2 gene promoter and allow SGLT-2 gene expression. Patients with HNF1α mutations exhibit a decrease in TmGlu/GFR, which induces glycosuria even when plasma glucose levels are normal [28,29]. Also, levels of plasma glucose concentration differ widely among subjects, and some patients with the HNF1α mutation may never develop overt diabetes. No specific complications have been reported in MODY3 patients who do develop diabetes.

6. Modification of SGLT-2 expression in diabetes

Rises in plasma glucose concentration in diabetes are associated with the presence of glucose in urine. However, TmGlu/GFR is increased in humans and animals with diabetes. Thus, the amount of glucose reabsorbed by the kidneys is greater than in non-diabetic subjects and contributes to the disequilibrium of glycaemic control. SGLT-2 and GLUT2 mRNAs and proteins, and glucose uptakes in renal proximal cells, in diabetic animals and humans are increased [30,31]. These increases correlate with the elevated expression of HNF1α in the kidneys of diabetic rats [32,33].

A consequence of the increased glucose reabsorption in the proximal tubule is the augmentation of sodium, water and chloride reabsorption, resulting in a reduction of sodium and chloride flux at the macula densa at the extremity of Henle’s loop. Physiologically this induces a rise in GFR, which is the hyperfiltration observed in diabetes. This mechanism is supported by the lack of hyperfiltration in diabetic animals with no SGLT-2 expression or which are being treated with SGLT-2 inhibitors [27,34,35].

All these data show that the resistance of the kidneys to insulin is associated with an augmentation of HNF1α expression, which increases SGLT-2 and GLUT2 expression that, in turn, worsens glycaemic control disequilibrium and induces glomerular hyperfiltration. As a consequence, the increase in GFR observed at the beginning of diabetes may reflect the severity of kidney resistance to insulin. However, decreasing the initial hyperfiltration phase with the use of drugs that diminish glucose reabsorption will not necessarily result in kidney protection.

7. Conclusion

By producing and reabsorbing glucose, the kidneys play a central role in glucose homeostasis under physiological conditions and during diabetes. With diabetes, HNF1α expression is augmented, thereby stimulating SGLT-2 and GLUT2 expression in the kidneys. The resulting increase in glucose reabsorption triggers glomerular hyperfiltration, which can be prevented by the use of SGLT-2 inhibitors that, in both diabetic animals and humans, improved glycaemic control by reversing the ‘over-reabsorption’ of glucose by the kidneys. Nevertheless, the protective effect of SGLT-2 inhibition on kidney function remains to be assessed.

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References


