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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.

Keywords: *Familial glycosuria; SGLT-2; Kidney; Glucose*

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

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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.

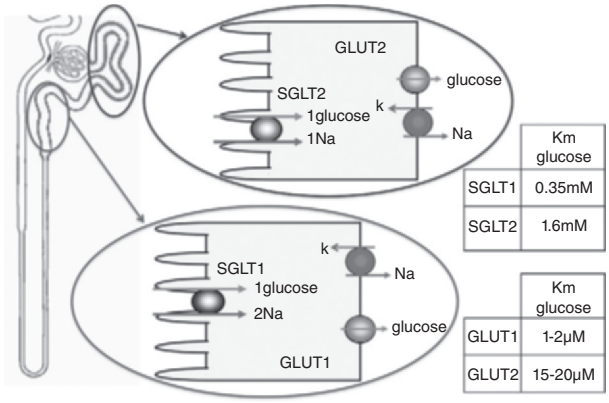

Fig. 1. Renal glucose reabsorption. Glucose is filtered by the glomerulus and completely reabsorbed in the proximal tubule under physiological conditions. SGLT-2 (apical side) and GLUT2 (basolateral side) convey glucose in the convoluted part of the proximal tubule. In the straight part, SGLT1 and GLUT1 transport is responsible for glucose uptake. The affinity of each transporter for glucose (in Km) is indicated.

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 reabsorbs 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,