Molecular determinants of renal glucose reabsorption. Focus on “Glucose transport by human renal Na\(^+\)/D-glucose cotransporters SGLT1 and SGLT2”

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About 180 g of glucose are filtered daily in the glomeruli of the kidneys in a healthy normoglycemic subject, which is equivalent to approximately one third of the total energy consumed by the human body in a day. Most of the glucose entering the tubular system is reabsorbed along the nephron segments, primarily in the proximal tubule, such that urine is almost free of glucose. This is different in diabetes, where the filtered glucose exceeds the transport capacity of the tubular system for glucose and glucosuria occurs. On the basis of transport studies in membrane vesicles and analyses of mRNA expression in isolated nephron segments of rat and rabbit kidneys, performed largely between 1981 and 1995, the concept has been established that the bulk of tubular glucose uptake across the apical membrane occurs in the early proximal tubule and is mediated by the low-affinity/high-capacity Na\(^+\)-glucose cotransporter SGLT2 (SLC5A2); in comparison, the high-affinity/low-capacity SGLT1 (SLC5A1) is thought to “clean up” most of the remaining luminal glucose in further distal parts of the proximal tubule (2, 4, 6, 7, 9, 11, 18–21)(see Fig. 1). With newly available specific antibodies, recent studies directly document specific expression of brush border membrane SGLT2 in early proximal tubule and SGLT1 in later sections of the proximal tubule (1, 14). Much of the evidence for the relative quantitative contribution of these proteins to renal glucose reabsorption in human derives from the phenotype of subjects carrying gene mutations. Whereas mutations in SGLT1 are associated with intestinal glucose malabsorption with little or no glucosuria, individuals with gene mutations in SGLT2 have persistent renal glucosuria (10).

Interest in SGLTs has recently been sparked by the development of a novel antidiabetic therapeutic approach, namely, the selective pharmacological inhibition of SGLT2, which inhibits renal reabsorption of glucose, thereby increasing its urinary excretion and reducing plasma glucose levels (17). During diabetes, excess glucose uptake via SGLTs may contribute to the glucose toxicity in the diabetic kidney. Moreover, an increase in SGLT-mediated sodium/glucose reabsorption has been implicated in the enhanced proximal tubular sodium reabsorption in the diabetic kidney which lowers luminal NaCl concentration at the macula densa and, because of the normal physiology of tubuloglomerular feedback, can contribute to glomerular hyperfiltration observed in early diabetes (15). Thus, SGLT2 inhibitors may also have the potential to reduce the glucose toxicity and hyperfiltration observed in the diabetic kidney. Despite this new clinical interest in renal glucose handling, surprisingly little information has been available on the specific characteristics of human SGLT2 and SGLT1.

The timely study by Hummel and colleagues (5) in this issue of American Journal of Physiology-Cell Physiology builds on the previous pioneering studies of Wright’s group in the field.

Fig. 1. Glucose transport in the kidney. Under normoglycemia, ~97% of filtered glucose is reabsorbed via the Na\(^+\)-glucose cotransporter SGLT2 primarily in the early segments of the proximal tubule. A significant capacity of SGLT1 to reabsorb glucose in later segments of the proximal tubule is unmasked by SGLT2 inhibition (~40% of filtered glucose under normoglycemia; see numbers in parentheses), on the basis of our previous work (14) and the assumption that apical tubular glucose uptake in the kidney is primarily mediated by SGLT2 and SGLT1. The glucose transporters GLUT2 and GLUT1 mediate glucose transport across the basolateral membrane. Na\(^+\)-glucose cotransport is electrogenic, and luminal K\(^+\) channels serve to stabilize the membrane potential (12, 13): KCNE1/unknown α-subunit and KCNE1/KCNQ1 in early and late proximal tubule, respectively.
of SGLTs, which included the cloning of SGLT1 (4), showing that defects in SGLT1 trafficking and function cause intestinal glucose-galactose malabsorption (8), and their contributions to cloning of SGLT2 (18) and delineating the crystal structure of a sodium galactose transporter to reveal mechanistic insights into Na+/glucose co-transport (3). The new studies aimed to provide relevant insights on the characteristics of hSGLT2 and hSGLT1 in an experimental setting close to physiological conditions. To this end hSGLT2 and hSGLT1 were expressed in mammalian epithelial cells (HEK293T) and studied using whole cell patch-clamp electrophysiology at 37°C. The studies show that, under these conditions, the Na+:glucose coupling ratio equals a value of 1 for hSGLT2 and 2 for hSGLT1 (see Fig. 1). Na+-glucose uptake is electrogenic, and previous studies indicated that the ensuing depolarization is partly offset by luminal K+ exit (12, 13). Hummel and colleagues further found that hSGT2 transports glucose with similar affinity (5 versus 2 mM) and has lower concentrative power than hSGLT1. The studies confirm that unlike in hSGLT1, D-galactose is a poor substrate for hSGLT2. The results provide further information about how inhibitors block Na+/D-glucose cotransport. This includes data showing that the 10-fold lower affinity of phlorizin for hSGLT1 versus hSGLT2 is mainly due to differences in the rate of inhibitor release. Notably, the phlorizin-sensitive maximal transport rate, which depends on both protein copy number and on turnover rates, was 20-fold greater for hSGLT1 over hSGLT2 in this experimental setup. Whereas the hSGLT1 turnover and copy number can be determined from the measured maximum rate of transport and the magnitude of pre-steady-state charge movements, this analysis could not be performed for hSGLT2 since no pre-steady-state currents were detectable. Therefore, the reason behind the observed difference in the maximal transport rate between hSGLT1 and hSGLT2 and whether this is unique to this expression system remain unclear. Since diabetes and SGLT2 inhibitors will enhance the delivery of glucose to the later sections of the proximal tubule, the capacity of SGLT1 to transport glucose is of clinical relevance.

The present results are consistent with a dominant role of SGLT2 in renal glucose reabsorption complemented by a significant capacity of SGLT1 to reabsorb filtered glucose in the late proximal tubule of the human kidney. Hummel and colleagues inferred, on the basis of the current and previous data, that SGLT2 works at only 50% capacity in fasted human subjects. Recent micropuncture studies in knockout mice provided direct evidence that SGLT2 is responsible for all glucose reabsorption in the early proximal tubule and, overall, is the major pathway of glucose reabsorption in the kidney, whereas mice heterozygous for SGLT2 showed no urinary glucose loss (14). Surprisingly, the lack of SGLT2 suppressed renal SGLT1 mRNA and protein expression by ~40%. This may reflect a mechanism to blunt the increase in glucose reabsorption in the late proximal segments under conditions of increased luminal glucose delivery and uptake. Despite lacking SGLT2 and having suppressed SGLT1 expression, the SGLT2 knockout mice have increased absolute glucose reabsorption along the late proximal tubule and maintain a mean fractional renal glucose reabsorption of ~36% (between 10 and 60%, varying inversely with the amount of glucose filtered) (14). Preliminary studies in mice lacking SGLT1 indicated normal renal SGLT2 protein expression and a significant but minor reduction in fractional renal glucose reabsorption from 99.8% to 96.9% (16). If SGLT1 is the major pathway for renal glucose uptake in mice lacking SGLT2, then its contribution to glucose uptake is significantly enhanced by inhibition of SGLT2 (see Fig. 1). The physiological relevance of shifting glucose reabsorption to later segments of the proximal tubule deserves further investigation. Owing to differences in the Na+:glucose coupling ratio, shifting glucose reabsorption from SGLT2 to SGLT1 is expected to attenuate the renal sodium loss in response to SGLT2 inhibition.

The in vivo capacity of SGLT1 may be reflected by the observed high maximal glucose transport rate in the current expression studies by Hummel and colleagues (5). Overall, their studies provide new insights into the molecular physiology of hSGLT2 and hSGLT1 and a novel method for evaluating hSGLT inhibitors in a mammalian cell system. This will help to further elucidate the molecular mechanisms involved in the regulation of these cotransporters and their relevance in the physiology and pathophysiology of renal glucose transport and the development of new therapeutic strategies.

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REFERENCES


