Learning From Glycosuria

Ele Ferrannini

Plasma glucose is filtered freely through the glomerular barrier. In a 70-kg adult with a glomerular filtration rate of 120 mL · min^{-1} per 1.73 m^2 and an average, around-the-clock plasma glucose concentration of 120 mg/dL (6.7 mmol/L), ~200 g of glucose are transferred daily from the bloodstream into the preurine. If nothing else happened, the whole-body mass of free glucose (some 20 g in a distribution volume of 250 mL/kg) would be emptied out in less than 3 h. What prevents this catastrophe is, on the one hand, virtually complete glucose reabsorption at the level of the kidney and on the other hand, a precisely matched modulation of endogenous glucose release (chiefly by the liver and possibly also by the kidney itself).

The kidney is well engineered to perform coupled glucose and sodium reabsorption. In the S1/S2 segment of the proximal tubule, a member of the sodium glucose transporter (SGLT) family of transmembrane proteins, SGLT-2—encoded in the *SLC5* gene—is expressed at high levels and cotransports filtered glucose and sodium into the tubular cell cytoplasm. Downstream to the S1/S2 segment along the S3 segment of the proximal tubule, another SGLT isoform—SGLT-1, abundantly expressed in the enterocyte—also performs coupled sodium-glucose cotransport. At the basolateral membrane of the tubular cell, a glucose transporter of a different family, GLUT-2, affects the transfer of intracellular glucose to the interstitium by a facilitated transport process (via Na$^+$-K$^+$-ATPase).

Recent detailed physiological studies (1) in human embryonic kidney (HEK293T) cells coexpressing human SGLT-2 and SGLT-1 have established that, contrary to a long held belief (2,3), the two isoforms have similar affinity for glucose (in the 2–5 mmol/L range), high affinity for sodium but different sodium:glucose stoichiometry (1:1 for SGLT-2 and 2:1 with SGLT-1), and similar electrogenicity. The proportion of in vivo renal glucose reabsorption due to the activity of each of the two transporters is a complex function on their in-series anatomical arrangement, their differential sodium coupling ratio, copy number, and protein turnover rate.

The in vivo kinetics of renal glucose handling are schematically depicted in Fig. 1. As plasma glucose concentrations and glucose filtration rates increase, reabsorption rises linearly to its maximum (Tm$_G$) at a splayed plasma glucose threshold (traditionally, 180 mg/dL), after which excretion linearly begins to increase. The simulation in Fig. 1

shows the effect of lowering Tm$_G$ by 30%: the leftward shift in the excretion curve predicts significant glycosuria—up to 30 g daily—within a glucose concentration interval of 150–130 mg/dL. With a 50% reduction in Tm$_G$, glycosuria would appear at a plasma glucose level of 90 mg/dL and rise to 80 g per day at a plasma glucose of 150 mg/dL, i.e., within the normoglycemic range.

Early clinical studies in patients with type 2 diabetes showed that the Tm$_G$ is increased by 20–40% in comparison with nondiabetic subjects (4). The same finding has been reported in patients with type 1 diabetes (5). More recent studies in cultured human renal tubular cells harvested from the urine of diabetic patients have shown that the expression of SGLT-2, its protein concentration, and its α-methyl-glucose transport capacity are all increased markedly in comparison with nondiabetic subjects (6). Thus, whether it is an intrinsic defect of diabetes or a result of chronic hyperglycemia, renal glucose reabsorption appears to be abnormally high in subjects with diabetes. At the other end of the spectrum is familial renal glycosuria, a rare disorder caused by private missense or nonsense mutations and deletions in the *SLC5A2* gene. Affected patients excrete between 1–170 g per day of glucose in the urine according to whether they are homozygous, heterozygous, or compound heterozygous (7). The condition is benign, as these patients do not develop renal disease even in the long term and are not reported to be prone to, and in fact may be protected against, diabetes and obesity. Finally, in an experimental model of diabetes, the 90% pancreatectomized rat (8), the peripheral and hepatic insulin resistance, and the β-cell defect that these animals develop have been shown to be fully reversed by a 4-week treatment with phlorizin, a nonspecific inhibitor of SGLT-2 and SGLT-1. The effects of the drug were abolished upon its withdrawal.

The article by Jurczak et al. (9) in this issue of *Diabetes* closes the loop on the SGLT-2 story by carefully describing the phenotype resulting from the deletion of SGLT-2 in mice bred onto a *db/db* strain background. SGLT-2-null mice develop massive glycosuria with normal serum electrolytes, no histopathologic changes in the tubular nephron, drink and eat more, and expend more energy. Metabolically, they are protected from hyperglycemia and high-fat–induced weight gain and show modestly enhanced insulin sensitivity in the liver. β-Cell function is improved in vivo but not ex vivo in isolated/perifused islets; islets and β-cell mass are increased because of slower β-cell death rates.

Collectively, these findings prove that reduced SGLT-2 activity—whether genetically or experimentally induced—is efficacious and relatively safe in lowering hyperglycemia and its toxicity with the added benefits of a degree of weight control and some natriuresis. The development of SGLT-2 inhibition as a therapeutic target in type 2 diabetes is therefore logical and attractive (10–14).

As the story unfolds, interesting questions emerge. Firstly, hypoglycemia typically does not occur with SGLT-2 inhibition, a key therapeutic value. Clearly, the liver must
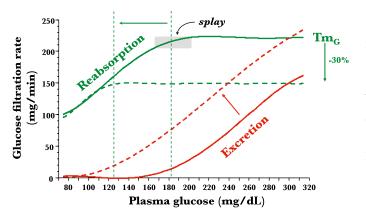
FIG. 1. Renal glucose handling. Flux rates (filtration, reabsorption, and excretion) were calculated using a glomerular filtration rate of 120 mL · min^{-1} per 1.73 m^2 and a renal threshold of 180 mg/dL (10 mmol/L). To visualize the splay, data were fitted with polynomials. The dotted lines simulate the effect of a 30% reduction in Tm_G on reabsorption and excretion.

react to the glycosuria by increasing glucose release, but how does it know that the kidney is leaking glucose? The findings by Jurczak et al. (9) in SGLT-2$^{-/-}$ mice suggest that liver glycogen depletion and/or slight decrements in plasma glucose may signal the liver to open up. Also, the increased reliance on fatty acids for energy production may imply further substrate or neural mechanisms. If preventing hypoglycemia is one good job the liver does, glucose output usually is not reduced enough to attain normoglycemia in the diabetic patient treated with SGLT-2 inhibitors (10–14). How does the liver know when to stop?

The second issue is that complete blockade of renal glucose reabsorption is never achieved with selective SGLT-2 inhibition. Even SGLT-2-null mice reabsorb one-third of the filtered glucose (15), and dapaglifozin—a selective SGLT-2 inhibitor in phase III clinical development—causes at most ~50% inhibition at the highest doses (16), whereas the nonselective inhibitor, phlorizin, completely blocks reabsorption. Perhaps SGLT-1 plays a greater role in the kidney than previously thought (1). Regulation of SGLT-2 expression by glycemia, binding kinetics of glucose and inhibitor concentrations in the lumen of the proximal tubule, and the impact of declining glomerular filtration are additional levels of complexity that need to be explored.

Finally, the increased calorie intake that follows SGLT-2 inhibition in transgenic mice (9) and, very likely, in diabetic patients (12–14) is intriguing. The resemblance to the hyperphagia of acute diabetic patients points toward energy-sensing pathways triggered by glycosuria, relaying at specific brain areas, and feeding forward to the liver to modulate glucose production (17). In this connection, it is of further interest that functional expression of SGLTs has recently been mapped to several brain regions, including the hypothalamus (18).

Clearly, glycosuria has gone a long way from a mere symptom of decompensated diabetes to a tool to learn more physiology and, in all likelihood, to help to treat glucose toxicity in man.

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