The diabetic proximal tubule: part of the problem, and part of the solution

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Physiological interest in renal glucose handling dates to the era of whole organ experiments, with the description of a renal glucose threshold (Tm) and osmotic diuresis (22). Micropuncture identified the proximal tubule as the locus of glucose reabsorption (3), and brush border vesicle preparations (1, 8) and cellular electrophysiology (4, 18) established the Na⁺ dependence of that luminal glucose flux. Careful analysis of vesicle kinetics suggested two glucose transporters, one high-capacity, low-affinity site and a second with high affinity and smaller fluxes (17). The low-affinity carrier localized to the outer cortical region, and the high-affinity carrier localized to outer medullary vesicles. Corresponding to the affinity difference was the determination of a 1:1 (glucose:Na⁺) stoichiometry of the cortical cotransporter (6) and a 1:2 stoichiometry of the high-affinity carrier (16). Perfusion of isolated tubule segments confirmed the high-capacity carrier in the proximal convoluted tubule and the high-affinity transporter in the proximal straight tubule, whose maximum flux was ~10–15% of that of the convoluted segment (2). An important advance in renal glucose transport came with the cloning of the gene for the intestinal cotransporter SGLT1 (SLC5A1) (5). In situ hybridization localized SGLT1 to the S3 segment of the proximal tubule, precisely the site suggested by the kinetic data (9). Oocyte expression of SGLT1 enabled extensive electrophysiological investigation and formulation of a mathematical model of the transporter. This work revealed that solute binding affinity is asymmetric, comparing inside and outside of the carrier, and translocation of the empty carrier is the important rate-limiting step and sensitive to the transmembrane potential difference (14). In pursuit of the high-capacity Na⁺-glucose cotransporter, homology screening revealed the gene for SGLT2 (SLC5A2), expressed in the kidney, for which the stoichiometry is 1:1 and which in situ hybridization localized to the S1 segment of the proximal tubule (7). Kinetic studies confirmed that SGLT2 is the low-affinity, high-capacity system identified in brush border vesicles (23).

Subsequent study of Na⁺-glucose cotransport became more biophysically oriented, until the recent development of specific and specific inhibitors of SGLT2 thrust the topic back into view of the larger biomedical community. These substances are related to phlorizin, the classic nonspecific Na⁺-glucose cotransport inhibitor, and comprise a growing list, which includes dapagliflozin, canagliflozin, empagliflozin, ipragliflozin, and tofogliflozin. When given to humans, especially at times of hyperglycemia, these drugs produce glycosuria; when given to diabetic patients, the glycosuria enhances glycemic control and in a manner that promotes caloric loss, rather than weight gain. With the advent of these medications, a new contingent of scientists and physicians has taken an interest in renal glucose metabolism. One point of concern in the adoption of these drugs was the specter of osmotic diuresis, in which glycosuria would produce natriuresis and hypovolemic, but this has not happened. Indeed, the observation is that the drugs inhibit <50% of the reabsorption of filtered glucose, and there has been little hypoglycemia with their use. This finding has been posed as a paradox, in view of the fact that SGLT2 is normally responsible for >90% of renal glucose transport (10). In that regard, it must be remembered that the amount of glycosuria depends upon local reabsorption rates of both Na⁺ and glucose, tubule fluid flow rate, and the fact that SGLT2 and SGLT1 are situated in series, so that the overall inhibitor impact is difficult to intuit without the aide of a model.

This is the context for the work of Nagata et al. (13), whose paper reports innovations across several levels of function, and in so doing, is truly systems oriented. At the most basic level, this group has cloned SGLT1 and SGLT2 from the cynomolgus monkey and expressed the transporter in COS-7 cells. In these cells, they determine inhibitor affinities and demonstrate the 1,000-fold specificity of tofogliflozin for SGLT2 relative to SGLT1. They then perform classic whole animal studies in the monkeys, in which glucose excretion is plotted as a function of the filtered glucose load. One difficulty in these experiments is to implement a method of data analysis, which can capture the inhibitor’s impact. Because tofogliflozin is a competitive inhibitor, its effect diminishes at the highest luminal glucose concentrations, so that the Tm glucose is little changed; thus, representing the titration curve as two line segments won’t do. What these workers do is fit their glucose titration curve to an exponential, with three unknown parameters: the threshold for the filtered load at which excretion begins (x₀), the classic Tm, and an exponential coefficient for the transition to complete glucose excretion. With this formulation, they capture the drug’s effect as the “splay” or difference of the integrated glucose excretion over the range of filtered loads. Within this analytic framework, both the threshold and splay are demonstrated to be functions of the inhibitor dose. What is (understandably) missing from this analysis is a model of the proximal tubule bridging the gap from the COS-7 cell data, i.e., using inhibitor Kᵢ and luminal solute concentrations, to predict the three model coefficients. Nevertheless, the data for anchoring such a model, at the transporter level and the whole kidney, have been supplied.

What makes this work worth broadcasting in an editorial focus is the prospect that this line of investigation stands at the threshold of treatments that may protect the diabetic kidney. Vallon and coworkers (19, 20) have advanced the hypothesis that glomerular hyperfiltration in the diabetic kidney is the result of a primary increase in proximal Na⁺ reabsorption, producing a decrease in distal fluid delivery, and thus a secondary activation of tubuloglomerular feedback. The pathophysiology underlying the primary increase in Na⁺ transport is

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http://www.ajprenal.org 1931-857X/14 Copyright © 2014 the American Physiological Society
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uncertain, but Vallon has pointed to oxidative cell stress with episodic high cytosolic glucose. Deficiency of the natriuretic action of dopamine has been implicated in the diabetic kidney, due to both decreased generation of dopamine (15), and decreased dopamine receptor (D1) activity (11, 12). Finally, even in the absence of cell damage, the model proximal tubule shows enhanced net Na\(^+\) reabsorption and decreased distal delivery, when increases in ambient glucose are still insufficient to provoke osmotic diuresis (21). The causal chain from glomerular hyperfiltration to the appearance of proteinuria, to glomerular fibrosis, to renal failure has become established teaching, and is supported by the observation that interventions which mitigate the hyperfiltration (angiotensin-converting enzyme inhibition or angiotensin receptor block) can, in some circumstances, delay the progression of renal damage. In this regard, the SGLT2 inhibitors appear to come with the potential for blunting episodic increases in cellular glucose uptake, and thus mitigating glomerular hyperfiltration at a point upstream in the pathophysiological chain of events.

GRANTS

This investigation was supported by Public Health Service Grant R01-DK-29857 from the National Institute of Arthritis, Diabetes, and Digestive, and Kidney Diseases.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

Author contributions: A.M.W. drafted manuscript; A.M.W. edited and revised manuscript; A.M.W. approved final version of manuscript.

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