The following is the abstract of the article discussed in the subsequent letter:

Linden, Kelly C., Carrie L. DeHaan, Yuan Zhang, Sylwia Glowacka, Alison J. Cox, Darren J. Kelly, and Suzanne Rogers. Renal expression and localization of the facilitative glucose transporters GLUT1 and GLUT12 in animal models of hypertension and diabetic nephropathy. Am J Physiol Renal Physiol 290, F205–F213, 2006.—Renal tubular glucose reabsorption is mediated by facilitative glucose transporter (GLUT) proteins and energy-dependent sodium glucose luminal transporters. Glucose transport in the diabetic kidney is upregulated and has been implicated in the pathogenesis of progressive diabetic nephropathy. Hyperglycemia, hypertension, and activation of the renin-angiotensin system are believed important in the development of the disease. The present study examines the renal expression of the facilitative glucose transporters GLUT1 and GLUT12 in rat models of diabetic nephropathy. Sprague-Dawley and transgenic (mRen-2)27 rats received either streptozotocin-induced diabetes or vehicle. GLUT12 expression and localization were determined by immunohistochemistry, immunoblotting, in situ hybridization, and confocal immunofluorescence. GLUT1 immunolabeling was detected on the basolateral membrane throughout the nephron. GLUT12 was localized to the distal tubules and collecting ducts. A significant increase in GLUT12 immunolabeling was measured in Ren-2 controls and Ren-2 diabetic animals compared with Sprague-Dawley controls. GLUT12 expression was higher in Ren-2 diabetic compared with Sprague-Dawley diabetic rats. Long-term diabetes resulted in significant increases in GLUT1 levels in the renal proximal tubules and expression was higher in Ren-2 diabetic than Sprague-Dawley diabetic rats. GLUT12 protein was localized to the cytoplasm and to the apical membrane of human and rat distal tubules and collecting ducts. The apical localization of GLUT12 in the distal tubules and collecting ducts suggests that it could contribute to additional glucose reabsorption in the late nephron. Levels of both GLUT1 and GLUT12 are elevated in animal models of hypertension and diabetic nephropathy.

Glucose Transporters in Animal Models of Diabetes and Hypertension

To the Editor: It is well-known that hyperglycemia and hypertension interact in the development of diabetic nephropathy (DN), as shown by clinical and experimental studies. The role of glucose transporters in this setting is now emerging and exciting. Linden et al. (6) described the renal expression and localization of GLUT1 and a novel glucose transporter, GLUT12, in an animal model of diabetes and hypertension, the STZ-Ren-2 rat. GLUT12 was characterized by them in the fetal rat kidney (7).

In the basolateral membranes of epithelial cells GLUT1 is present in the S3 segment of the proximal tubule (PT), Henle’s loop, and collecting duct, and in the glomeruli (3, 4, 11, 12). GLUT2 is present in the S1 segment of the convoluted PT (CPT) (3, 4, 11). As the authors discuss, appropriately, the bulk of renal glucose reabsorption occurs in the CPT (SGLT2 and GLUT2), with some residual reabsorption taking place in the straight PT (SGLT1 and GLUT1) (1, 2). In diabetes, SGLT2 and GLUT2 expression increases (2, 13), and GLUT2 protein in brush-border membrane (BBM) was reported (8), contributing to increasing glucose reabsorption in CPT. However, GLUT1 protein in PT is reduced in vivo (1, 2) and in vitro (9) by diabetes and high glucose exposure, respectively. Conversely, mesangial cells (outcortex) increased GLUT1 expression in vivo (1, 10), and in vitro (5) under the same conditions, respectively. The final result would be high interstitial glucose concentration in the perimesangial area, increased glucose uptake and extracellular matrix formation (4), key events in DN, as confirmed by rising levels of urinary albumin and TGF-β1 (1). Outcortex GLUT1 and 2 are overexpressed in hypertensive rats, working in an additive way with diabetes, further increasing intracellular glucose levels, urinary albumin and TGF-β1 (10).

We have a few major concerns about study by Linden et al.: 1. The authors describe that in glucose load and extracellular volume expansion, glucose is additionally reabsorbed in the later parts of the nephron. If there is additional reabsorption in the intermediate segment, between the late proximal tubule and distal tubule (14), what could be the role of GLUT12 in the distal tubules and collecting ducts? Which role could the GLUT12 at the distal tubule and collecting ducts have? Even if the glucose reabsorption could be increased in the collecting ducts, what role could a low-capacity glucose transporter system have in DN, compared with the well-described prominent increase of the very high capacity SGLT2 and GLUT2 transporters in the CPT? How would this contribute to an increase in the perimesangial cell glucose concentration?

2. The abstract states that GLUT12 is elevated in models of DN. However, their results did not show any change in GLUT12 expression in the diabetic rats, so we question how a role in DN could possibly be assigned to GLUT12.

3. Considering the localization of GLUT1, why was this transporter not identified by the authors in the glomeruli, and why was the GLUT1 expression identified (in the CPT) elevated in contrast to the opposite GLUT1 modulation already described in literature in this location?

The expression and localization of GLUT12 in the kidney of adult rats and its increased expression in hypertensive Ren-2 rats are important features of the study by Linden et al., but the functional meaning of GLUT12 and its regulation remain to be explained. Based on our comments, we do not agree with the speculation on a role of GLUT12 in DN.

REFERENCES

As discussed in our immunohistochemical study, GLUT1 protein levels were significantly elevated in the proximal tubules of diabetic animals (9). Following Western blot analyses, D’Agord Schaan et al. (3) reported that GLUT1 levels are increased in the rat renal cortex but not the medulla after 45 days of STZ-induced diabetes. Also, as discussed, other studies reported that untreated STZ-induced diabetes for 2–4 wk resulted in a reduction of GLUT1 protein levels in the proximal tubules (4). Our study was performed 30 wk post-STZ treatment, a time point that represents advanced, stage III nephropathy. At this stage, the kidney develops significant pathological changes such as glomerulosclerosis and tubulointerstitial fibrosis (8). We interpret our results as implicating the upregulation of GLUT1 in the pathogenesis of progressive diabetic nephropathy (9). Using a commercially available antibody, we have detected this isoform in glomeruli and in a characteristic basolateral location in the renal tubules. In our study, staining was weak in the glomeruli, but we did not increase the concentration of the antibody, as the focus was tubular glucose transporter expression. Other published studies show similar weak immunohistochemical detection of GLUT1 in the glomeruli of Wistar-Kyoto (WKY) and spontaneously hypertensive (SHR) rats, in the presence of very strong tubular staining and with detectable GLUT1 by Western blot analysis of isolated mesangial cells (6).

Although renal GLUT12 expression was not elevated in the diabetic state, this does not preclude a role for this transporter in diabetic nephropathy. Regulation of glucose transport and glucose transporter protein activity frequently occurs via mechanisms other than increased mRNA or protein expression (2). Our view is that increased tubular glucose transport could contribute to tubulointerstitial as opposed to perimesangial injury, a feature of diabetic nephropathy (5). Further investigations are required to ascertain the exact functional roles of GLUT1 and GLUT12 in progressive diabetic nephropathy.

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To the Editor: The authors appreciate the comments made by Schaan and Machado. However, it would appear from our work and that of others that the pattern of expression of glucose transporter proteins in the kidney is more complex than had been previously thought. In addition to the expression patterns of GLUT1, GLUT2, SGLT1, and SGLT2 described by Schaan and Machado, recent reports have described GLUT8 expression in podocytes, in the distal tubules, and in the collecting ducts of murine kidney (11). Also, GLUT9 expression has been localized to renal distal tubules (7). Some years ago, significant levels of GLUT4 were demonstrated in the distal tubules of the kidney (1). We have demonstrated GLUT12 expression in renal distal tubules and collecting ducts (9). The individual roles of each glucose transporter in renal glucose transport are still being elucidated, but, as is the case in other tissues, the expression of multiple glucose transporter isoforms is likely to have physiological significance. The kinetics of glucose transport mediated by these isoforms is still under study. In particular, GLUT12-mediated glucose transport has been demonstrated (10), but to our knowledge there are no published data on the kinetics of GLUT12-mediated glucose transport. Thus at this stage there is no evidence to suggest that GLUT12 is a low-capacity transporter.


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