GLUT2-mediated uptake provides a low-affinity, high-capacity route for glucose to enter proximal tubule cells during hyperglycemia and might therefore initiate the changes in cellular carbohydrate metabolism that have been linked to diabetic nephropathy. It is noteworthy that the Fanconi-Bickel syndrome, which is associated with glycogen accumulation in proximal tubule cells and a diabetic-like nephropathy, has been linked to mutations of the GLUT2 gene.

The emerging importance of GLUT2 in proximal tubule physiology suggests that expression of the transporter should be a major focus when considering the implications of chronic hyperglycemia for tubular damage.


Response to ‘Glucose transport across the proximal tubule brush border membrane: Response to diabetes mellitus’

Kidney International (2008) 73, 362; doi:10.1038/sj.ki.5002671

To the Editor: We agree with Dr Debnam that high glucose condition has a variety of effects on glucose transporters [Na+/glucose cotransporters (SGLTs) and facilitated diffusion glucose transporters (GLUTs)]. However, some studies have yielded conflicting results on the effects of diabetes conditions on SGLT-mediated glucose transport. Studies have reported both increased and decreased glucose transport mediated by SGLT in diabetes. In our previous studies, when primary proximal tubule cells (PTCs) were cultured in high glucose, the SGLTs were inhibited through reactive oxygen species, Ca2+/PKC, cPLA2/AA, as well as NF-kB pathways.

Primary cultured PTCs are a convenient means to evaluate the activity of glucose transporters because the kidney cell lines may have been changed and reduced activities of the transporter or enzyme after few passages. Instead of the serum-supplemented media (cause of fibroblast overgrowth), hormonally defined and serum-free conditions, supplemented with insulin, transferrin, and hydrocortisone, could maintain primary cultured PTCs to have a polarized morphology and distinctive proximal tubule functions. Therefore, PTCs in hormonally defined, serum-free culture conditions would be a powerful tool for studying the alteration of glucose cotransporters activity. In our opinion, the discrepancies among results may be due to the difference of experimental model (in vivo vs in vitro), species (rat vs rabbit), cell culture condition (serum-supplemented media vs hormonally defined and serum-free media), and/or cell specificity (primary cultured cells vs cell lines). Therefore, our studies suggest that high glucose-mediated abnormal glucose handling in the proximal tubule may play an important part in the development of diabetic nephropathy, although renal PTCs do not seem to be primary targets for diabetic injury.

ACKNOWLEDGMENTS

This research was supported by Grant SC2210 from the Stem Cell Research Center of 21st Century Frontier Research Program funded by the Ministry of Science and Technology and authors acknowledge a graduate fellowship provided by the Ministry of Education and Human Resources Development through the Brain Korea 21 project, Republic of Korea.


Diagnosis of aldosterone producing adenomas


To the Editor: In a recent publication, Chung et al.1 showed the images of bilateral adrenal nodular lesions as bilateral aldosterone producing adenomas. Although the surgical resection of the both lesions corrected the clinical symptoms of primary aldosteronism, we think that the only one lesion might have been an aldosterone producing adenoma.

Because the radiolabeled cholesterol analogs concentrate in steroid hormone-synthesizing tissues, the scintigraphy with them is used for determining the site of excess hormone secretion. However, it is reported that the uptake primarily depends on the adenoma volume, and that the diagnostic accuracy of the scintigraphy for aldosterone producing adenomas, which are generally small, is not high even after
The CT image Chung et al. presented showed different contrast enhancement effect in the adrenal lesions, which indicates that the lesions would have different nature. Considering that the existence of adrenal nodular lesions in the patients with hypertension is reported to be not rare, it is possible that the only one lesion had aldosterone hypersecretion. Because the small size and the NP-59 accumulation in the case presented by Chung et al. indicate the benign nature of the lesions, the resection of the only one lesion with aldosterone hypersecretion might have been sufficient.

Adrenal vein sampling is now considered to be the most reliable diagnostic test to detect the site of aldosterone hypersecretion. Therefore, we would like to recommend adrenal vein sampling in the cases under the suspicion of primary aldosteronism, such as the case presented by Chung et al. The lesions should better be resected after the confirmation of their functional activity.

References

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Response to ‘Diagnosis of aldosterone producing adenomas’

We certainly appreciated the comments by Dr Tanemoto et al. regarding our report of Diagnosis of bilateral aldosterone-producing adenomas.

The preoperative diagnosis of bilateral aldosterone-producing adenomas remains elusive and can only be definitely made postoperatively by pathological existence of typical adenomas in the excised specimen, and strong expression of the aldosterone synthase by real-time PCR of the excised tumor.

Although computed tomography (CT) scanning might not reliably discriminate bilateral adrenal hyperplasia (BAH) from aldosterone-producing adenoma (APA), previous reports showed that the finding of a single-focal macroadenoma on CT scan had a high positive predictive value when the tumor size was >1.0 cm; and it will be more diagnostic of APA when combined with a positive NP-59 adrenocortical scintigraphy as a valid evaluation tool for primary aldosteronism. Even adrenal vein sampling (AVS), the gold standard of differential diagnosis of the subtypes of primary aldosteronism, has its limitation because of bilateral functional adenomas that may be present at the same time or metachronously. In our institute, there were four cases of simultaneous bilateral aldosterone-producing adenomas among 164 APA patients surgically treated and which were pathologically documented as APAs. These four bilateral aldosterone-producing adenoma patients presented with evidence of bilateral localized uptakes of NP-59 at dexamethasone-suppressed adrenocortical scintigraphy, with CT scan demonstrating tumors larger than 1.0 cm in diameter (1.2–2.0 cm, mean 1.5 cm) and negative postural test before operation. There were another three cases of metachronous bilateral aldosterone-producing adenomas, with the second contralateral tumor clinically detectable 18–48 months after the first adrenalectomy.

For this specific patient presented in our report, we also performed real-time PCR of the aldosterone synthase. The mRNA level of aldosterone synthase (CYP11B2) were corrected with the mRNA level of glyceraldehyde 3-phosphate dehydrogenase (GAPDH), and were quantified using real-time PCR as previously reported, and it is expressed as $2^{-\Delta\Delta C_T}$, where $\Delta\Delta C_T = (\Delta C_T \text{CYP11B2} - \Delta C_T \text{GAPDH})$. The mRNA level of the bilateral tumorous portions and the nontumorous portions were $\Delta\Delta C_T 2.73 \pm 0.13$ versus $12.47 \pm 0.68$ in this patient, indicating much higher mRNA activity in bilateral tumors, and proved that they both are functional APAs. And a radiologist was asked to review the CT scans of that patient again which revealed that his bilateral tumors were larger than 1.0 cm, and both were enhanced with contrast medium.

In conclusion, we believed that it is reasonable to perform bilateral subtotal adrenalectomies in treating bilateral APAs, which present with aldosterone-renin ratio >100 ng per 100 ml per ng ml$^{-1}$ h$^{-1}$, plasma aldosterone >20 ng per 100 ml, and bilateral macronodular tumors (>1.0 cm) and positive uptake in the adrenal scan.