

Activated Local Renin–angiotensin System Plays a Role in Albumin Permeability in Glomerular Endothelial Cells Under High Glucose Conditions

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Backgrounds: Local renin–angiotensin system (RAS) is present in mesangial cells and podocytes, and their activation has been demonstrated to play an important role in the pathogenesis of diabetic nephropathy. However, it has never been explored whether local RAS is also present in glomerular endothelial cells (GECs), whether it is activated under diabetic conditions, and whether its activation is involved in the pathogenesis of diabetic nephropathy.

Purpose: This study was undertaken to investigate the existence of RAS components in GECs, their changes under high glucose conditions, and the role of local RAS in morphological and functional changes in high glucose–stimulated GECs.

Methods: GECs were exposed to 5.6 mM glucose (NG), NG+24.4 mM mannitol (NG+M), or 30 mM glucose (HG) with or without 10^{-7} M losartan for 24 hours. Real–time PCR and Western blot analysis were performed for angiotensinogen (AGT), angiotensin–converting enzyme (ACE), and angiotensin II (AII) type 1 (AT1R) and 2 receptor (AT2R). AI and AII concentrations in conditioned media were measured by ELISA. Renin activities were defined as the formation of AI in the presence of porcine AGT. Morphological changes were examined by scanning electron microscopy (SEM) and a Transwell assay was performed to determine FITC–tagged albumin permeability.

Results: AGT mRNA and protein expression were significantly increased in HG–stimulated GECs compared to NG and NG+M cells ($p<0.05$). AI and AII concentrations were also significantly higher in HG–conditioned media compared to NG media ($p<0.05$). In contrast, there were no differences in ACE, AT1R, and AT2R mRNA and protein expression, and renin activities among the groups. On SEM examination, the diameters of endothelial fenestrae in HG–stimulated GECs were significantly greater compared to NG cells (108 ± 12 nm vs. 76 ± 6 nm, $p<0.05$). The number of fenestrae tended to be increased in GECs exposed to HG, but did not reach statistical significance. A Transwell assay revealed that FITC uptake in filtered media through HG–stimulated GECs were 3.3–fold higher compared to NG cells ($p<0.05$). The increase in fenestrae diameter and enhanced albumin permeability through GECs under HG conditions were significantly abrogated by losartan pretreatment ($p<0.05$).

Conclusion: These findings suggest that local RAS is activated in GECs under high glucose conditions and this activated RAS may play an important role in the development of albuminuria in diabetic nephropathy.

High glucose

Key Words: Glomerular endothelial cell, Renin–angiotensin system