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Advances in characterization of glucose transporter roles in glomerular disease

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Abstract

Glomerular glucose transporters play a significant role in regulating mesangial cell (MC) glucose uptake and extracellular matrix (ECM) production. The facilitative glucose transporter GLUT1 has been shown to be rate-limiting for glucose uptake into MC's, and is responsive to diabetes mellitus, where glomerular GLUT1 increases. These diabetes-induced increases in GLUT1 are relatively unique responses. In the kidney, neither glomeruli nor tubules protect themselves from diabetes and glucotoxicity .Increased GLUT1 in diabetic glomeruli, in high glucose – exposed MC's, and in nondiabetic GLUT1-overexpressing glomeruli leads to excessive glucose uptake, metabolism and signaling to ECM production, which in vivo leads to glomerulosclerosis (GS). Multiple studies have identified GLUT1 – susceptibility alleles associated with increased risk for kidney disease in diabetic subjects. PKC, VEGF, TGFß1, and more recently mechano-growth factor (MGF)& mTOR are upregulated in MC's or glomeruli with high GLUT1, promoting excessive FN, ColI-IV, Col-I and LN production. Glomerular hypertension, associated with MC stretch, also induces glomerular and MC GLUT1 and ECM production. Nondiabetic glomerular diseases with glomerular hypertension exhibit increased expression of the same growth factors and GLUT1 as seen with diabetes mellitus. Therefore, a similar enhancement ofglomerular glucose transport in these nondiabetic conditions promotesdevelopment of GS. Preliminary data in human kidney transplant rejection also revealed increased GLUT1 in glomeruli and renal tubules, with greater GLUT1 associated with greater sclerosis. Finally, experiments in which MC GLUT1 was suppressedin diabetic mice revealed protection against kidney scarring.Therefore, inhibition of MC GLUT1 expression in renal disease has potential therapeutic value.

Biography

Dr. Heilig completed his M.D. at the University of Minnesota, Minneapolis, MN. His Residency in Internal Medicine was completed at the Mayo Graduate School of Medicine in Rochester, MN. and his Nephrology Fellowship at Harvard Medical School, Brigham & Women's Hospital, Boston, MA. Dr. Heilig is currently Professor of Medicine, Chief of Nephrology & Hypertension, and Program Director for the Nephrology Fellowship at the University of Florida College of Medicine in Jacksonville, FL. His research focus is on glucose transporters in disease, particularly renal disease.