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Role of Reactive Oxygen Species in High Glucose-induced Tissue Injury

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Diabetes is the leading cause of end-stage renal disease worldwide. In Korea, diabetic kidney disease accounted for 39% of all new dialysis patients in 1998. Diabetic nephropathy is characterized by glomerular hyperfiltration, albuminuria, and expansion of glomerular mesangium. Since glomerular mesangial cells regulate glomerular filtration rates and are capable of producing extracellular matrix (ECM) proteins, the functional abnormalities of mesangial cells under diabetic milieu play an important role in the development and progression of diabetic nephropathy. Under hyperglycemia, excessive glucose enters into mesangial cells mainly through glucose transporter 1 and induces various intracellular responses. As in other membrane receptor signaling, reactive oxygen species (ROS) generated by glucose metabolism may act as integral signaling molecules under hyperglycemia leading to diabetic nephropathy. We have found that high D-glucose generates intracellular ROS in mesangial cells. Neither L-glucose nor 3-O-methyl-D-glucose increased intracellular ROS and cytochalasin B, an inhibitor of glucose transporter, effectively inhibited high glucose-induced ROS generation, suggesting that glucose uptake and subsequent metabolism are required in high glucose-induced ROS generation. The high glucose-induced generation of ROS, in turn, activate protein kinase C (PKC), mitogen activated protein kinases (MAPK), and transcription factors leading to upregulation of cytokines, growth factors, and ECM proteins. We have demonstrated that hydrogen peroxide induced PKC, nuclear factor-κB (NF-κB) and activator protein-1 (AP-1) activation and upregulated TGF-β1 and fibronectin mRNA and protein expression and that structurally different antioxidants effectively ameliorated high glucose-induced PKC, NF-κB, and AP-1 activation and TGF-β1 and fibronectin upregulations. Understanding of precise signal transduction pathways linking high glucose, ROS, PKC, MAPKs, transcription factors, and ECM protein synthesis in mesangial cells may provide novel therapeutic and preventive strategies for diabetic nephropathy. Antihypertensive therapy and glycemic control are current treatment for diabetic nephropathy but are not successful in all patients.