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Angiotensin II induces podocyte injury by mitochondrial oxidative stress

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Objectives: Oxidative stress induced by non-hemodynamic effects of angiotensin II in podocyte participates in the development of glomerular injury and proteinuria. We studied the pathophysiologic roles of oxidative stress in angiotensin II-induced podocyte apoptosis.

Methods: Mouse podocytes were incubated in media containing various concentrations of angiotensin II and at different incubation times and transfected by Nox4 or negative control scrambled siRNA for 24 h. The changes of the intracellular and mitochondrial ROS production were measured using respective assays and observed by confocal imaging and western blotting according to the presence of angiotensin II.

Results: Angiotensin II increased NADH/NADPH oxidase 4 protein and expression in a transcriptional mechanism that was also reversed by probucol. In addition, the suppression of NADH/NADPH oxidase 4 by siRNA reduced the oxidative stress induced by angiotensin II. Angiotensin II also significantly increased the generation of superoxide anions and suppressed the superoxide dismutase (SOD) activity that were significantly recovered with probucol. Furthermore, angiotensin II increased the intracellular ROS levels in dose- and time-dependent manners that were also recovered with probucol.

The quantitative data of MitoSOX index demonstrated that mitochondrial superoxide production was significantly higher in angiotensin II -treated condition compared with that in untreated conditions with or without probucol at 24 h. When angiotensin II increased mitochondrial superoxide production by more than 2-fold, it was significantly recovered with probucol. We also found that cytoplasmic 8-oxo-dG immunoreactivity was significantly increased in angiotensin II -treated condition by 2-fold compared with that in untreated conditions with or without probucol at 24 h that was significantly recovered with probucol.

Conclusions: Our findings suggest that angiotensin II increased the generation of mitochondrial superoxide anions and ROS levels via the downregulation of the SOD activity and via the upregulation of NADH/NADPH oxidase 4 that were reversed by an antioxidant, probucol.