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Angiotensin II induces oxidative podocyte injury via the upregulation of Nox4

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Objectives: Angiotensin II (Ang II) induces glomerular and podocyte injury via systemic and local vasoconstrictive or non-hemodynamic effects including oxidative stress. The release of free radicals from podocytes may participate in the development of glomerular injury and proteinuria. We studied the pathophysiologic roles of oxidative stress in Ang II-induced podocyte apoptosis.

Methods:

Mouse podocytes were incubated in media containing various concentrations of Ang II and at different incubation times and transfected by Nox4 or AT1R siRNAs or negative control scrambled siRNA for 24 h. The changes of podocyte oxidative stress and apoptosis were observed by confocal imaging, western blotting, realtime PCR, FACS and TUNEL assay according to the presence of Ang II.

Results: Ang II increased the generation of superoxide anions and intracellular reactive oxygen species levels but suppressed superoxide dismutase activity that was reversed by an antioxidant, probucol. Ang II also increased Nox4 protein and expression in podocytes, measured using western blotting and real-time PCR analysis that was also reversed by probucol. Nox4 suppression by small interference RNA (siRNA) reduced the oxidative stress induced by Ang II. These results suggest that Ang II induced oxidative stress via the upregulation of Nox4 protein in a transcriptional mechanism. Ang II promoted podocyte apoptosis that was reduced significantly by probucol and Nox4 siRNA. Ang II-induced podocyte apoptosis were also recovered by Ang II type 1 receptor (AT1R) siRNA.

Conclusions: Our findings suggest that Ang II induced podocyte oxidative stress and apoptosis through AT1R and Nox4. These findings suggest that Ang II promoted podocyte oxidative stress and apoptosis through AT1R and via the upregulation of Nox4, which could be preventive by Nox4 inhibition and/or antagonizing AT1R as well as antioxidants.