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AMPK activation ameliorates angiotensin II-induced downregulation of podocyte ZO-1

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Objectives : Angiotensin II (Ang II) promotes the development and progression of proteinuria and renal diseases and induces podocyte apoptosis. ZO-1 (zonular occludens-1) protein as a component of the slit diaphragm plays a pivotal role in glomerular permeability by connecting slit diaphragm structure and actin cytoskeleton. AMP-activated protein kinase (AMPK), as a sensor of cellular energy status, has been known to play an important role in the pathophysiology of metabolic diseases, including diabetes, and its renal complications. We investigated the role of AMPK on the changes of ZO-1 of podocyte induced by Ang II.
Methods : Mouse podocytes were incubated in media containing various concentrations of Ang II and AMPK-related agents. The changes of ZO-1 and permeability were observed by confocal imaging, western blotting, and permeability assay in the presence of Ang II.
Results : Ang II induced the fusion of microvilli and the gap pores on podocytes, which were improved by AICAR, an AMPK activator. Ang II also reduced and disrupted the intercellular ZO-1 staining, resulting in increased podocyte intercellular permeability. The intensities of fluorescences and bands of ZO-1 protein were decreased by Ang II in a dose-dependent manner by confocal microscopy and western blot analysis, respectively. AICAR and metformin, AMPK activators, ameliorated the abnormal distributional changes and the protein of ZO-1. Losartan, Ang II type I receptor blocker, also ameliorated the decrease of ZO-1 protein.
Conclusions : Our findings suggest that Ang II induces the relocation and suppression of podocyte ZO-1 via Ang II type 1 receptor which is ameliorated by AMPK-activating agents.