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The Farnesoid X Receptor Ligand Prevents Cisplatin-induced Renal Injury by Enhancing the Orphan Nuclear Receptor SHP

Eun Hui Bae[1], Hong Sang Choi[1], Soo Yeon Joo[2], In Jin Kim[2], Chang Seong Kim[1]
Joon Seok Choi[1], Seong Kwon Ma[1], Jong Un Lee[2], Soo Wan Kim[1]

Department of Internal Medicine[1] Chonnam National University Medical School
Department of Physiology[2] Chonnam National University Medical School

The farnesoid X receptor (FXR) has been shown to be largely expressed in liver, intestine, and kidney. In the present study, we investigated whether 6-ethyl chenodeoxycholic acid (6-ECDCA or INT-747), a semisynthetic derivative of chenodeoxycholic aicd (CDCA) which is FXR ligand, protects renal injury and modulate small heterodimer partner (SHP) in human proximal tubular (HK2) cell lines and cisplatin-induced renal injury mice model. Cisplatin decreased the protein expression of SHP on HK2 cell and cisplatin-treated mice, which is improved by FXR ligand treatment. Furthermore, FXR ligand attenuated renal injury in H&E stain compared with cisplatin-treated mice. FXR ligand also attenuated the protein expression of transforming growth factor β1 (TGF-β1), Smad signaling, and the subsequent epithelial-to-mesenchymal process, inflammatory markers and cytokines, and apoptotic markers in cisplatin-treated mice. The cisplatin induce NF-κB expression in HK2 cell which is attenuated by FXR ligand pretreatment. In SHP deletion state by siRNA, the protein expression TGF-β1, p-JNK and Bax which is proapoptotic protein was not attenuated, while overexpression of SHP induce decreasing of those protein expression by FXR ligand treatment in cisplatin pretreated HK2 cells. In conclusion, FXR ligand, 6-ECDCA prevents cisplatin-inudced renal injury and its potential mechanism might be the effect of 6-ECDCA in decreasing the antifibrosis, anti-inflammation, and anti-apoptosis effects by SHP induction.

Key Words: Farnesoid X receptor, Small heterodimer partner, Cisplatin