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# 시스플라틴 신독성에서 TGF-β/Smad3 신호전달 경로의 활성화

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# Renal Interstitial Fibrosis in Cisplatin-treated Rats is Associated with Activation of TGF-β/Smad3 Signaling

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**Purpose :** Although activation of complex signaling pathways that lead to tubular cell injury and death has been reported by many studies on the mechanisms of cisplatin nephrotoxicity, whether the transforming growth factor (TGF)-$\beta$/Smad3 signaling pathway is involved has not been elucidated. This study was undertaken to investigate whether the TGF-$\beta$'s pro-fibrotic effect is activated via Smad3 in cisplatin-treated rats and to see if the effect is modulated by dietary sodium restriction.

**Methods :** Cisplatin was intraperitoneally administered to male Sprague-Dawley rats at a weekly dose of 2 mg/kg (n=6) for 7 weeks, and a half of them was fed low sodium diet. Control rats (n=4) received a weekly intraperitoneal injection of the vehicle solution only. At the end of the animal experiment, kidneys were harvested for western blot analysis and histopathologic studies. From PAS staining, tubulointerstitial injury was scored on a scale of 0 to 4. From Masson trichrome staining, tubulointerstitial fibrosis was estimated by the percentage of the total area using an image analyzer.

**Results :** Cisplatin-treated rats had higher levels of BUN (75.1±24.1 vs. 7.8±0.8 mg/dL) and serum creatinine (1.72±0.55 vs. 0.58±0.05 mg/dL) compared with vehicle-treated controls ($p<0.05$). On light microscopy cisplatin-treated rats showed remarkable tubulointerstitial injury (3.84±0.06 vs. 0.38±0.09, $p<0.05$) and tubulointerstitial fibrosis (5.81±0.73 vs. 0.08±0.02%, $p<0.05$), but no differences were found in cisplatin-treated rats between normal sodium versus low sodium intake. Western blot analysis revealed that the protein abundances of fibronectin (827±104 vs. 100±31%) and TGF-$\beta$ (333±63 vs. 100±21%) were increased by cisplatin treatment ($p<0.05$). Whereas the abundance of total Smad3 protein was decreased in cisplatin-treated rats (40±6 vs. 100±11%, $p<0.05$), the expression of phosphorylated Smad3 protein was increased in cisplatin-treated rats (160±10 vs. 100±19%, $p<0.05$). However, the expression levels of fibronectin, TGF-$\beta$, and Smad3 proteins were not significantly different between normal sodium- versus low sodium-fed cisplatin-treated rats.

**Conclusion :** We demonstrate that in cisplatin nephrotoxicity the TGF-$\beta$'s pro-fibrotic effect is activated by upregulation of Smad3 protein. The activation of TGF-$\beta$/Smad3 signaling pathway does not seem to be affected by dietary sodium restriction in cisplatin treatment.

**Key Words :** 시스플라틴 신독성, 간질 섬유화, Smad3
Cisplatin nephrotoxicity, Interstitial fibrosis, Smad3