

오메가-3 지방산은 잔여 신장에서 세뇨관간질 손상을 개선한다: TGF- β 와 ERK-Smad 신호전달 과정의 관련

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Omega-3 Fatty Acid Ameliorates Tubulo-interstitial Injury in the Remnant Kidney : Involvement of TGF- β and ERK-Smad Signaling Pathways

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Introduction : Tubulo-interstitial injury and fibrosis is largely mediated by interstitial myofibroblasts which are derived from epithelial-to-mesenchymal transition (EMT) of tubular epithelial cells. This process is primarily driven by transforming growth factor- β (TGF- β) and extracellular signal-regulated kinase (ERK)-Smad signaling pathways and production of connective tissue growth factor (CTGF). The present study was undertaken to determine the effect omega-3 fatty acid (O-3FA) on expression of key molecules involved in the pathogenesis of inflammation, oxidative stress and fibrosis in an animal model of chronic renal disease induced by renal mass reduction.

Methods : The rats were randomly assigned to the six chronic renal failure (CRF) group, six CRF O-3FA group and six control group. The CRF group underwent 5/6 nephrectomy by surgical resection of the upper and lower thirds of left kidney, followed by right nephrectomy. Six CRF rats were supplied with O-3FA at a daily dose of 0.3 g/kg/day for 12 weeks with microsyringe. Protein abundance of markers were measured by Western blot technique. Immunohistology for TGF- β and α -smooth muscle (α -SMA) was done. Glomerulosclerosis and tubulointerstitial damage was scored using computer-assisted image analysis.

Results : The untreated CRF rats exhibited marked upregulations of COX-2 ($p=0.008$), NOX-4 ($p=0.014$), gp91 phox ($p=0.004$), p22 phox ($p<0.001$), p47 phox ($p=0.015$), p65 NFkB nuclear translocation ($p=0.002$), MCP-1 ($p=0.039$), PAI-1 ($p=0.007$), TGF- β ($p=0.007$), α -SMA ($p<0.001$), fibronectin ($p<0.001$), smad2 ($p<0.001$), phosphorylated-ERK1/2 ($p=0.008$) as well as tubulo-interstitial fibrosis ($p<0.001$) and glomerulosclerosis ($p<0.001$) in comparison with sham-operation control group. Smad 7 ($p=0.01$) was downregulated in the untreated 5/6 Nx rats. O-3FA supplementation resulted in significant attenuation of COX-2 ($p=0.033$), NOX-4 ($p=0.011$), gp91 phox ($p=0.001$), p22 phox ($p=0.001$), p47 phox($p=0.004$), p65 NFkB nuclear translocation ($p<0.001$), MCP-1 ($p=0.002$), PAI-1 ($p=0.043$), TGF- β ($p=0.006$), α -SMA ($p<0.001$), CTGF ($p=0.025$), fibronectin ($p=0.036$), smad2 ($p=0.006$), phosphorylated-ERK1/2 ($p=0.004$) as well as tubulo-interstitial fibrosis ($p=0.004$). TGF- β and α -SMA staining is markedly reduced in the tubulointerstitial areas of a remnant kidney treated with O-3FA.

Conclusion : Long-term O-3FA supplementation attenuates tubulo-interstitial injury in animals with chronic renal disease by mitigating oxidative stress, inflammation, fibrosis and epithelial-to-mesenchymal transition.

Key Words : 오메가-3 지방산, 세뇨관간질 손상, TGF- β
omega-3 fatty acid, Tubulointerstitial injury, TGF- β