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지방산 함유 알부민에 의한 세뇨관 세포에서의 VCAM-1 발현 및 신호 전달 경로 : L-carnitine의 효과

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Signaling Pathways Involved in Tubular Cell VCAM-1 Expression in Response to Fatty Acid-bearing Albumin: Effect of L-carnitine

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Background : Fatty acid- bearing albumin [FA(+) albumin] exerts more deleterious effects in proximal tubular cells than albumin alone. However, precise mechanisms by which FA (+) albumin induces tubulointerstitial injury are not completely understood. We investigated the effect of FA (+) albumin on the VCAM-1 expression and verified the underlying signaling pathways including c-Src kinase, MAP kinase, IκB kinase, activation of AP-1 and NF-κB in cultured human proximal tubular cell. We further examined the effect of L-carnitine on the FA (+) albumin- induced signaling pathway, since L-carnitine was known to modulate intracellular fatty acid concentration.

Methods : Activation of AP-1 and NF-κB were assessed by electrophoretic mobility shift assay. Phosphorylation of protein kinases was examined by Western blot analysis. VCAM-1 mRNA and protein expression was measured by Northern blot analysis and cell ELISA.

Results : FA (+) albumin induced AP-1 and NF-κB activation. FA (+) albumin was a more potent inducer of NF-κB activation than fatty acid- depleted albumin. FA (+) albumin- induced AP-1 and NF-κB activation was mediated through activation of c-Src kinase, followed by MAP kinase (P38, ERK 1/2, JNK) and IκB kinase-IκB-α, respectively. FA (+) albumin also increased the VCAM-1 mRNA and protein expression via activation of AP-1 and NF-κB. Protein kinase C inhibitors (staurosporine, calphostin), tyrosine kinase inhibitors (genistein, herbimycin A), anti-oxidants (NAC, tiron) and intracellular calcium chelator (BAPTA-AM) suppressed the FA(+) albumin-induced c-Src kinase activation. L-carnitine dose dependently suppressed the FA (+) albumin-induced VCAM-1 expression via inhibition of c-Src kinase activation.

Conclusion : c-Src kinase played a central role in the signaling pathway that linked FA (+) albumin to the activation of AP-1 and NF-κB, leading to VCAM-1 expression. Protein kinase C, tyrosine kinase, oxidative stress and intracellular calcium were involved in the FA (+) albumin- induced c-Src kinase activation. L-carnitine suppressed the VCAM-1 expression via inhibition of c-Src kinase activation.