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4-hydroxy Hexenal Induced Tubular Cell Apoptosis is Mediated by Activation of NF-kB Through ERK and JNK

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Background: Lipid peroxidation and its products such as 4-hydroxy-2-hexenal (HHE) are known to affect redox balance during aging and other degenerative processes. HHE-modified protein might be responsible for the pathogenesis of kidney injury. The present study was aimed to investigate the effects of HHE on tubular epithelial cells and to explore the possible signalling mechanisms involved.

Methods: Human proximal tubular epithelial (HK-2) cells were treated with 10 μM of HHE. Cell viability was assessed using MTT assay in HK-2 cells. The fluorescent probe 2',7'-dichlorofluorescein diacetate (DCF-DA) was used to measure intracellular levels of reactive oxygen species. The protein expression of NF-kB, mitogen activated protein kinase (MAPK), pro-apoptoic Bax, and anti-apoptotic protein Bcl-2 was determined by semiquantitative immunoblotting. Apoptosis was determined by flowcytometry analysis after the cells were stained by annexin V-FITC and propidium iodide.

Results: Incubation with various doses of HHE (5-30 μM) for 24 hr caused dose-dependent decreases of cell viability. HHE caused an enhanced generation of reactive oxygen species. HHE increased the expression of p38 MAPK, extracellular signal regulated kinase (ERK), and c-jun NH2-terminal kinase (JNK). HHE induced NF-κB activation and translocation via IκB-α degradation. Increased nuclear NF-κB activation was blocked by an inhibitor of signaling by the ERK (PD98059) and JNK (SP600125), but was not affected by those of signaling by the MAPKs p38 (SB203580). HHE decreased the expression of Bcl-2, while it increased that of Bax. Annexin V-FITC and propidium iodide staining revealed that HHE induced early and late apoptosis in HK-2 cells.

Conclusion: HHE-induced tubular cell apoptosis is mediated by the modulation of Bax and Bcl-2 via ROS generation. In HK cell, HHE-mediated accumulation of ROS may induce redox sensitive transcription factor, NF-κB, through the activation of ERK and JNK.

Key Words: 4-hydroxyhexanal, 지질과산화물, NF-kB
4-hydroxyhexanal, Lipid peroxidation, HK-2 cells, NF-kB