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Background: Aldehyde products of lipid peroxidation such as 4-hydroxy-2-hexenal (HHE) may in part be responsible for the pathogenesis of various kidney injuries. The present study was aimed at investigating the effects of HHE on cellular apoptosis in renal tubular epithelial cells.

Methods: Human proximal tubular epithelial (HK-2) cells were treated with HHE. Cell viability was examined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The fluorescent probe 2',7'-dichlorofluorescein diacetate was used to measure intracellular levels of reactive oxygen species (ROS). The expression of NF- κ B, mitogen activated protein kinase (MAPK), pro-apoptotic Bax, and anti-apoptotic Bcl-2 proteins was determined by semiquantitative immunoblotting. Apoptosis was assessed by flow-cytometry after the cells were stained by fluorescein isothiocyanate-conjugated annexin V protein and propidium iodine.

Results: HHE caused dose-dependent decreases of cell viability along with increases of ROS. Flow-cytometry confirmed HHE-induced apoptosis. HHE increased the expression of p38 MAPK, extracellular signal regulated kinase (ERK), and c-Jun N-terminal kinase (JNK). HHE also induced an activation of NF- κ B and degradation of I κ B- α . The NF- κ B activation was prevented by inhibitors of ERK (PD98059) or JNK (SP600125), but was not affected by inhibitors of p38 MAPK (SB203580). HHE decreased the expression of Bcl-2, while it increased that of Bax; of which magnitudes were attenuated by NF- κ B inhibitors (Bay 117082). The inhibition of NF- κ B also prevented HHE-induced apoptosis.

Conclusion: HHE-induced tubular cell apoptosis is mediated by ROS generation and modulation of Bax and Bcl-2 in HK-2 cells; in which ROS may play a role inducing redox-sensitive transcription factors, NF- κ B, through activation of ERK and JNK.

Key Words: 4-Hydroxy-2-hexenal, Lipid peroxidation, Apoptosis, HK-2 cells, NF- κ B