Peroxisomal proliferator-activated receptor-alpha protects renal tubular cells from doxorubicin-induced apoptosis. Molecular pharmacology.

蘇裕謀

Lin H;Hou CC;Cheng CF;Chiu TH;Hsu YH;Sue YM;Chen TH;Hou HH;Chao YC;Cheng TH;Chen CH

摘要

Abstract

Peroxisome proliferator-activated receptor-α (PPAR-α) is a transcription factor and has been reported to inhibit cisplatin-mediated proximal tubule cell death. In addition, doxorubicin (Adriamycin)-induced nephrosis in rats is a commonly used experimental model for pharmacological studies of human chronic renal diseases. In this study, we investigated the protective effect of PPAR-α on doxorubicin-induced apoptosis and its detailed mechanism in NRK-52E cells and animal models. The mRNA level of PPAR-α was found to be reduced by doxorubicin treatment in NRK-52E cells. PPAR-α overexpression in NRK-52E cells significantly inhibited doxorubicin-induced apoptosis and the quantity of cleaved caspase-3. Endogenous prostacyclin (PGI2) augmentation, which has been reported to protect NRK-52E cells from doxorubicin-induced apoptosis, induced the translocation and activation of PPAR-α. The transformation of PPAR-α short interfering RNA was applied to silence the PPAR-α gene, which abolished the protective effect of PGI2 augmentation in doxorubicin-treated cells. To confirm the protective role of PPAR-α in vivo, PPAR-α activator docosahexaenoic acid (DHA) was administered to doxorubicin-treated mice, and it has been shown to significantly reduce the doxorubicin-induced apoptotic cells in renal cortex. However, this protective effect of DHA did not exist in PPAR-α-deficient mice. In NRK-52E cells, the overexpression of PPAR-α elevated the activity of catalase and superoxide dismutase and inhibited doxorubicin-induced reactive oxygen species (ROS). PPAR-α overexpression also inhibited the doxorubicin-induced activity of nuclear factor-κB (NF-κB), which was associated with the interaction between PPAR-α and NF-κB p65 subunit as revealed in immunoprecipitation assays. Therefore, PPAR-α is capable of inhibiting doxorubicin-induced ROS and NF-κB activity and protecting NRK-52E cells from

doxorubicin-induced apoptosis.