

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

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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- κ B (NF- κ B), which was associated with the interaction between PPAR- α and NF- κ B p65 subunit as revealed in immunoprecipitation assays. Therefore, PPAR- α is capable of inhibiting doxorubicin-induced ROS and NF- κ B activity and protecting NRK-52E cells from

doxorubicin-induced apoptosis