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Peroxisome Proliferator-activated Receptor-gamma Agonist 15-Deoxy-△12,14-prostaglandin J2 Induces Renal Epithelial Cell Death through Production of Reactive Oxygen Species and Inhibition of NF-κB Activity

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The peroxisome proliferator-activated receptor-γ (PPARγ) ligand 15-Deoxy-△12,14-prostaglandin J2 (15d-PGJ2) induces cell death in renal proximal tubular cells. However, the underlying molecular mechanism (s) remains unidentified. The present study was undertaken to examine the roles of reactive oxygen species (ROS), mitogen-activated protein kinase, and NF-κB in opossum kidney (OK) cell death induced by 15d-PGJ2. Treatment of OK cells with 15d-PGJ2 resulted in a concentration- and time-dependent cell death, which was largely attributed to apoptosis. 15d-PGJ2 increased ROS production, and the effect was inhibited by catalase and N-acetylcysteine. The 15d-PGJ2-induced cell death was also prevented by these antioxidants, suggesting that the cell death was associated with ROS generation. The PPARγ antagonist GW9662 did not prevent the 15d-PGJ2-induced cell death. 15d-PGJ2 caused a transient activation of extracellular signal-regulated kinase (ERK). However, inhibitors (PD98059 and U0126) of MEK, an ERK upstream kinase, did not alter the 15d-PGJ2-induced cell death. Transfection with constitutively active MEK and dominant-negative MEK had no effect on the cell death. 15d-PGJ2 inhibited the NF-κB transcriptional activity, which was accompanied by an inhibition of nuclear translocation of the NF-κB subunit p65 and impairment in DNA binding. The 15d-PGJ2-induced cell death was attenuated by transfection with p65. Inhibition of NF-κB with a NF-κB specific inhibitor pyrrolidinecarbodithioate and transfection with IκB (S32A/36A) caused cell death. These results suggest that the 15d-PGJ2-induced OK cell death was associated with ROS production and NF-κB inhibition, and the process was independent of PPARγ.