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Roles of Reactive Oxygen Species and Ca^{2+} in Ciglitazone-Induced Apoptosis in Opossum Kidney Cells

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Roles of Reactive Oxygen Species and Ca^{2+} in Ciglitazone-Induced Apoptosis in Opossum Kidney Cells

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We have previously demonstrated that the synthetic peroxisome proliferators- activated receptor (PPAR) agonist ciglitazone induces caspase- independent apoptosis through the p38 mitogen- activated protein kinase (MAPK)-dependent mechanism and causes nuclear translocation of apoptosis inducing factor (AIF) in opossum kidney (OK) renal epithelial cells. However, the precise mechanism by which ciglitazone induces activation of p38 MAPK and the role of AIF in the induction of the apoptosis are not defined. This study was therefore undertaken to determine roles of reactive oxygen species (ROS) generation, intracellular Ca^{2+} and AIF in the ciglitazone- induced apoptosis in OK renal epithelial cells. Ciglitazone- induced cell death was not inhibited by PPAR antagonist GW9662, indicating that ciglitazone induces apoptosis through a PPAR- independent mechanism. Ciglitazone induced an increase in generation of ROS and intracellular Ca^{2+}. Ciglitazone- induced cell death was reduced by the antioxidant Trolox, the Ca^{2+} chelator EGTA, and the store- operated Ca^{2+} channels (SOCC) blocker lanthanum chloride (La^{3+}), indicating the involvement of ROS and Ca^{2+} in ciglitazone- induced cell death. Ciglitazone- induced ROS production was not decreased by EGTA and La^{3+} but Trolox inhibited the ciglitazone- induced Ca^{2+} increase, suggesting that the increase in intracellular Ca^{2+} is mediated by ROS generation. Transfections of small interfering RNA (siRNA) of p38 MAPK or AIF prevented ciglitazone- induced cell death. Activation of p38 MAPK, mitochondrial membrane depolarization and AIF nuclear translocation induced by ciglitazone were inhibited by Trolox, EGTA, and La^{3+}. Taken together, these results suggest that ROS- dependent intracellular Ca^{2+} increase plays a pivotal role in the ciglitazone- induced apoptosis by mediating activation of p38 MAPK and nuclear translocation of AIF.

Key Words : PPARγ , Ca^{2+}, ROS