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DIFFERENTIAL ROLES OF PROSTAGLANDIN E_2 AND 15-DEOXY-Δ12,14-PGJ_2 IN THE NITROSATIVE PC12 CELL DEATH

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Recent studies suggest that inflammatory events are implicated in a variety of human diseases including cancer and neurodegenerative diseases, and non-steroidal anti-inflammatory drugs have beneficial effects in treatment or prevention of these disorders. It has been reported that expression of inducible cyclooxygenase (COX) and nitric oxide synthase and subsequent production of prostaglandin (PG) and nitric oxide (NO), respecively are elevated in many inflammatory disorders. NO can rapidly react with superoxide anion and produce more potent peroxynitrite. In the present study, we have investigated the pro-apoptotic potential of peroxynitrite in PC12 cells and the role of PGE_2 and 15-deoxy-Δ12,14-PGJ_2(15d-PGJ_2) in the nitrosative PC12 cell death. Treatment of PC12 cells with 3-morpholinosydnonimine hydrochloride (SIN-1), a peroxynitrite donor, induced cell death as revealed by depletion of intracellular glutathione, JNK activation, DNA fragmentation and the cleavage of poly(ADP-ribose) polymerase (PARP). Bcl-2 overexpression led to protection against SIN-1-induced cytotoxicity. Mn(III)tetrakis (4-benzoic acid) porphyrin (MnTBAP), a superoxide dismutase mimetic, attenuated SIN-1-mediated JNK activation and the cleavage of PARP. During SIN-1-induced apoptotic cell death, expression of COX-2 and production of PGE_2 were elevated. To investigate the role of COX-2 in regulating the apoptotic process, we treated PC12 cells with PGE_2, a major COX-2 product, and 15d-PGJ_2, a natural ligand of peroxysome proliferator-activated receptor-γ (PPAR-γ). While PGE_2 enhanced the SIN-1-mediated cell death, pretreatment of 15d-PGJ_2 rescued PC12 cells from SIN-1-induced cytotoxicity. GW9662, a PPAR-γ antagonist, reduced the protective effect of 15d-PGJ_2. During the nitrosative PC12 cell death, expression of PPAR-γ was upregulated, and GW9662 rendered PC12 cells sensitized to SIN-1. The above findings indicate possible involvement of COX-2 induction and subsequent PG synthesis in regulating peroxynitrite-induced PC12 cell death. PGE_2 may sensitize PC12 cells to SIN-1-induced apoptosis. On the other hand, 15d-PGJ_2 may act as a survival mediator through PPAR-γ activation. Supported by the NOTRec-KOSEF.

Keyword PGJ, COX, peroxynitrite, nitric oxide, PPAR