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Nitric Oxide-Induces Apoptosis in Rat Pheochromocytoma (PC12) Cells Through AP-1 Mediated Induction of COX-2

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Cyclooxygenase-2 (COX-2), the rate-limiting enzyme in the prostaglandin (PG) synthesis, is induced by various pro-inflammatory stimuli including nitric oxide (NO). COX-2 has been implicated in pathophysiology of neuronal cell death. In this study, we have investigated the functional relationship between AP-1 and COX-2 signaling and the role of COX-2 in inflammatory cell death induced by the NO releasing compound sodium nitroprusside (SNP) in cultured rat pheochromocytoma (PC12) cells. PC12 cells treated with SNP underwent apoptotic cell death as revealed by cleavage of poly(ADP- ribose)polymerase, decreased mitochondrial membrane potential, an increased Bax/Bcl-XL ratio, activation of caspase-3, accumulated p53 and internucleosomal DNA fragmentation. Ectopic expression of anti-apoptotic Bcl-2 protected against SNP-induced cytotoxicity. SNP treatment also led to the depletion of intracellular GSH and lipid peroxidation. In addition, SNP induced elevated COX-2 expression and PGE2 production and significantly increased DNA binding and transcriptional activation of AP-1. To better assess the role of AP-1 activation in SNP-induced COX-2 expression, we pretreated PC12 cells with AP-1 antisense oligonucleotides. NO-induced expression of COX-2 was abolished by AP-1 antisense oligonucleotides. To clarify the function of COX-2 in NO-induced cell death, we have investigated the possible protective effect of a selective COX-2 inhibitor (SC58635) against PC12 cell death induced by NO. Pretreatment with SC58635 rescued PC12 cells from SNP-induced apoptotic death. Similar results were obtained when COX-2 expression was blocked by RNA interference. DNA binding and transcriptional activities of AP-1 induced by SNP were also blocked by SC58635. SC58635 fortified an intracellular GSH pool through up-regulation of glutamyl-cystein ligase, thereby preventing cells from SNP-indeced GSH depletion. These results suggest that NO induces nitrosative and oxidative PC12 cell death through AP-1 mediated COX-2 expression.

Keyword : COX-2, NO, AP-1, apoptosis, PC12 cells