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Protective Effect of Celecoxib Against Nitric Oxide-Induced Inflammatory Cell Death in Rat Pheochromocytoma (PC12) Cells

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Purpose of study: Recent studies suggest that inflammatory events are implicated in a variaty of human diseases such as cancer and neuro-degenerative diseases, and non-steroidal anti-inflammatory drugs have beneficial effects for the treatment or prevention of these disorders. Cyclooxygenase-2 (COX-2), the rate-limiting enzyme in the prostaglandin (PG) synthesis, is induced by various pro-inflammatory stimuli including nitric oxide (NO) and has been reported to cause and/or aggravate neuronal cell death. In this study, we have investigated the possible protective effect of celecoxib, a selective COX-2 inhibitor against sodium nitroprusside (SNP)-induced nitrosative and inflammatory cell death in cultured PC12 cells.

Methods: SNP-induced nitrosative cell death was assessed by measuring cytotoxicity, lipid peroxidation and the level of reduced glutathione (GSH). The pattern of apoptosis was determined by characteristic morphological features, *in situ* terminal end-labeling (TUNEL staining), changes in the mitochondrial membrane potential ($\triangle\Psi m$), and expression of pro-/anti-apoptotic proteins. The COX-2 expression and PGE2 production were monitored by Westen blot analysis and ELISA, respectively. The level of NO in the media was measured using the Griess assay.

Results: PC12 cells treated with SNP exhibited considerable levels of NO

and underwent apoptotic cell death as revealed by cleavage of poly (ADP-ribose)polymerase, decreased $\Delta\Psi m$, an increased Bax/Bcl-XL ratio and internucleosomal DNA fragmentation. SNP treatment also led to the depletion of intracellular GSH and lipid peroxidation. In addition, SNP caused elevated COX-2 expression and PGE2 production, which was accompanied by AP-1 activation. Pretreatment of PC12 cells with celecoxib rescued PC12 cells from apoptotic death and nitrosative damage by suppressing COX-2 expression and subsequent PGE2 production. The protective effect of celecoxib against SNP-induced cell death was not due to direct scavenging of NO.

Conclusions: Celecoxib attenuated SNP-induced inflammatory PC12 cell death as well as COX-2 expression.