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## 15-Deoxy- $\Delta$ 12,14-Prostaglandin J<sub>2</sub> Protects Against Nitrosative PC12 Cell Death Through Up-Regulation of Intracellular Glutathione Level

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Recent studies suggest that inflammatory events are implicated in a variety of human diseases including cancer and neurodegenerative diseases. It has been reported that expression of inducible cyclooxygenase (COX) and nitric oxide (NO) synthase and subsequent production of prostaglandins (PG)s and NO, respectively are elevated in many inflammatory disorders. NO can rapidly react with superoxide anion, producing more reactive peroxynitrite. In the present study, we have investigated the pro-apoptotic potential of peroxynitrite in PC12 cells. Treatment of PC12 cells with the peroxynitrite donor 3-morpholinosydnonimine hydrochloride (SIN-1) induced cell death as revealed by depletion of intracellular glutathione (GSH), JNK activation, mitochondrial membrane depolarization, DNA fragmentation and the cleavage of poly(ADP-ribose)polymerase (PARP). During SIN-1-induced apoptotic cell death, expression of COX-2 and peroxysome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ) was elevated. Both COX-2 inhibitor Celecoxib and PPAR- $\gamma$  antagonist GW9662 aggravated SIN-1-induced cytotoxicity, suggesting induction of COX-2 and PPAR- $\gamma$  in peroxynitrite-exposed PC12 cells is associated with the cellular protective response against nitrosative stress. 15-Deoxy- $\Delta$ 12,14-PGJ<sub>2</sub> (15d-PGJ<sub>2</sub>) is one of COX-2 products and also an endogenous ligand of PPAR- $\gamma$ . 15d-PGJ<sub>2</sub>-pretreated PC12 cells were resistant to nitrosative stress. To elucidate the protective mechanism by 15d-PGJ<sub>2</sub>, level of intracellular GSH, an endogenous peroxynitrite scavenger, was determined. 15d-PGJ<sub>2</sub> pretreatment recovered SIN-1-induced GSH depletion by upregulating intracellular GSH pool. 15d-PGJ<sub>2</sub> induced  $\gamma$ -glutamyl cysteinyl ligase gene transcription as well as its promoter activity. The above findings suggest that 15d-PGJ<sub>2</sub> may act as a survival mediator by up-regulating the intracellular GSH level in nitrosative stress-induced PC12 cell death process.

**Keyword** : peroxynitrite, prostaglandin J, glutathione, PC12 cell