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15-Deoxy-Δ12,14-Prostaglandin J_2 Protects against Nitrosative PC12 Cell Death Through up-Regulation of Intracellular Glutathione Synthesis

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Nitrosative stress with subsequent inflammatory cell death has been associated with many neurodegenerative disorders. Expression of inducible nitric oxide synthase and production of nitric oxide (NO) have been frequently elevated in many inflammatory disorders. NO can rapidly react with superoxide anion, producing more reactive peroxynitrite. In the present study, exposure of rat pheochromocytoma (PC12) cells to the peroxynitrite donor 3-morpholinosydnonimine hydrochloride (SIN-1) induced apoptosis which accompanied depletion of intracellular glutathione (GSH), c-Jun N-terminal kinase activation, mitochondrial membrane depolarization, the cleavage of poly(ADP-ribose)polymerase and DNA fragmentation. During SIN-1-induced apoptotic cell death, expression of inducible cyclooxygenase (COX-2) and peroxisome proliferator-activated receptor-γ (PPARγ) was elevated. SIN-1 treatment resulted in elevated production of 15-deoxy-⊿12,14-prostaglandin J_2(15d-PGJ_2), an endogenous PPARγ activator. Preincubation with 15d-PGJ_2 rendered PC12 cells resistant to nitrosative stress induced by SIN-1. 15d-PGJ_2 fortified an intracellular GSH pool through up-regulation of glutamylcysteine ligase, thereby preventing cells from SIN-1-induced GSH depletion. The above findings suggest that 15d-PGJ_2 may act as a survival mediator capable of augmenting cellular thiol antioxidant capacity through up-regulation of the intracellular GSH synthesis in response to the nitrosative insult.

Keyword : apoptosis, 15-deoxy-Δ12,14-prostaglandin J_2, glutamylcysteine ligase, 3-morpholinosydnonimine