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15-DEOXY-$\Delta^{12,14}$ PROSTAGLANDIN J_2 RESCUES PC12 CELLS FROM HYDROGEN PEROXIDE-INDUCED APOPTOSIS THROUGH POTENTIATION OF CELLULAR ANTIOXIDATIVE DEFENSE CAPACITY

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Purpose of Study: Oxidative stress induced by reactive oxygen intermediates (ROIs) has been implicated in a variety of human diseases including cancer, diabetes, rheumatoid arthritis and neurodegenerative disorders. Hydrogen peroxide (H_2O_2), a representative ROI which is produced during the cellular redox process, can cause cell death via apoptosis and/or necrosis depending on its concentrations. 15-D prostaglandin J_2 (15d-PGJ_2), a dehydration product of prostaglandin D_2, has been reported to possess a number of biological activities such as anti-inflammatory, anticarcinogenic, and antioxidative properties. In this study, we have investigated the protective effect of 15d-PGJ_2 on H_2O_2-induced oxidative stress in rat pheochromocytoma (PC12) cells.

Methods: H_2O_2-induced oxidative cell damage was initially assessed by measuring cytotoxicity. The induction of programmed cell death was determined by characteristic morphological features, internucleosomal DNA fragmentation, disruption of mitochondrial membrane potential, in situ terminal end-labeling and the expression of apoptosis-related marker proteins. To examine the levels of anti-apoptotic and/or antioxidative proteins, Western blot analysis was conducted using specific antibodies.

Results: H_2O_2 treatment caused intracellular accumulation of ROIs and cytotoxicity in a concentration dependent manner. PC12 cells treated with H_2O_2

exhibited apoptotic cell death as determined by morphological features, inter-nucleosomal DNA fragmentation, cleavage of poly (ADP-ribose)polymerase, an increased Bax/Bcl-X_L ratio and decreased mitochondrial membrane potential, which was protectied by relatively low cocentrations of 15d-PGJ_2 (< 3μM) pretreatment. In another experiment, H_2O_2 treatment led to transient activation of protein kinase B (Akt), extracellular signal-regulated kinase 1/2 and heme oxigenase-1 as an adaptive response of cells to oxidative insult, which was augmented by 15-dPGJ_2 pretreatment.

Conclusions: H_2O_2 caused apoptosis in PC12 cells by inducing oxidative stress, which was effectively protected by 15-dPGJ_2 through augmentation of the cellular antioxidant defence.