Nrf2 Protects against Oxidative and Nitrosative PC12 Cell Death through Up-regulation of -Glutamylcysteine Ligase and Heme Oxygenase-1

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Oxidative and nitrosative stress induced by reactive oxygen/nitrogen species (ROS/RNS) has been considered as a major cause of cellular injuries in a variety of neurodegenerative disorders including Alzheimer's disease (AD). Recently, considerable attention has been focused on identifying redox-sensitive transcription factors and their target genes that are able to counteract excess ROS/RNS, thereby protecting against oxidative and nitrosative cell death. In the present work we have investigated the role of NF-E2-related factor 2 (Nrf2) in cellular defense against oxidative and nitrosative cell death caused by β-amyloid (Aβ), H_2O_2 or SIN-1 in cultured rat pheochromocytoma PC12 cells. Nrf2, which regulates transcription of genes encoding phase II detoxifying enzymes and antioxidant proteins, blocks cell death induced by a wide array of death signals. Ectopic expression of Nrf2 rescued PC12 cells from Aβ- or H_2O_2-induced apoptosis and intracellular ROS accumulation through up-regulation of γ-glutamylcysteine ligase (GCL), a rate-limiting enzyme in cellular GSH biosynthesis, and heme oxygenase-1 (HO-1), a rate-limiting enzyme in heme degradation process. In another experiment, preincubation with 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2), an endogenous ligand of peroxisome proliferator-activated receptor-γ, fortified an intracellular GSH pool and increased the expression of GCL and HO-1 thereby preventing cells from H_2O_2 or SIN-1-induced apoptotic cell death. Treatment of PC12 cells with 15d-PGJ_2 resulted in increased nuclear translocation, DNA-binding and transcriptional activity of Nrf2, leading to upregulation of GCL and HO-1 expression. Epigallocatechin-3-gallate (EGCG), a green tea polyphenol and resveratrol, a phytoalexin present in grapes elevated the expression of antioxidant enzymes such as GCL and HO-1 by activating the Nrf2 signaling pathway and protected PC12 cells from A β-induced apoptosis.

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