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BETA-AMYLOID INDUCES OXIDATIVE AND/OR NITRATIVE PC12 CELL DEATH VIA PRO-INFLAMMATORY MECHANISMS

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Oxidative stress induced by reactive oxygen and/or nitrogen species has been considered as a major cause of cellular injuries in a variety of neurodegenerative disorders including Alzheimers disease (AD). Inflammatory as well as oxidative tissue damage has been associated with pathophysiology of AD, and non-steroidal anti-inflammatory drugs have been reported to have beneficial effects in the treatment or prevention of AD. In this study, we have investigated the molecular mechanisms underlying oxidative and inflammatory cell death induced by beta-amyloid, a neurotoxic peptide associated with senile plaques formed in the brains of patients with AD. Rat pheochromocytoma (PC12) cells treated with beta-amyloid exhibited increased intracellular accumulation of reactive oxygen species and underwent apoptotic death as determined by characteristic morphological features, internucleosomal DNA fragmentation and positive *in situ* terminal end-labeling (TUNEL staining). beta-Amyloid treatment also led to the cleavage of poly(ADP-ribose)polymerase and an increase in the Bax/Bcl-X_L ratio in PC12 cells. Furthermore, transfection of PC12 cells with *bcl-2* rescued these cells from apoptotic death inducd by beta-amyloid. beta-Amyloid caused activation of NF-κB, which appeared to be preceded by activation of mitogen-activated protein kinases (MAPKs), such as extracellular signal-regulated kinase 1/2 (ERK1/2), p38 MAPK and c-Jun N-terminal kinase/stress-activated protein kinase. Exposure of PC12 cells to beta-amyloid resulted in time-dependent induction of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase. Pretreatment with the selective COX-2 inhibitor celecoxib or the peroxynitrite scavenger ergothioneine attenuated beta-amyloid-induced cell death. These results suggest that prooxidative and proinflammatory pathways play a role in the oxidative and/or nitrative cell death in mediating the neurodegeneration associated with AD.