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**BETA-AMYLOID INDUCES OXIDATIVE AND/OR NITRATIVE
PC12 CELL DEATH: POSSIBLE INVOLVEMENT OF
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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 Alzheimer's disease (AD). Inflammatory as well as oxidative tissue damage has been implicated in 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, the increased Bax/Bcl-XL ratio and the decreased mitochondrial membrane potential in PC12 cells. Furthermore, transfection of PC12 cells with bcl-2 rescued these cells from apoptotic death induced by beta-amyloid. beta-Amyloid caused activation of NF- κ B and AP-1, 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. beta-Amyloid-induced cell death was attenuated by pretreatment with the selective COX-2 inhibitor celecoxib or the peroxynitrite scavenger ergothioneine. These results suggest that prooxidative and proinflammatory mechanisms are involved in the oxidative and/or nitrative cell death in mediating the neurodegeneration associated with AD.

keyword : oxidative stress, beta-amyloid, apoptosis, inflammation