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**REGULATION OF BETA-AMYLOID-STIMULATED
PROINFLAMMATORY RESPONSES VIA MITOGEN
ACTIVATED PROTEIN KINASES AND REDOX SENSITIVE
TRANSCRIPTION FACTORS**

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Inflammatory as well as oxidative tissue damage has been associated with pathophysiology of Alzheimer's disease (AD), and nonsteroidal anti-inflammatory drugs have been shown to retard the progress of AD. In this study, we have investigated the molecular mechanisms underlying oxidative and inflammatory cell death induced by beta-amyloid (A β), a neurotoxic peptide associated with senile plaques formed in the brains of patients with AD, in cultured PC12 cells. PC12 cells treated with A β exhibited increased intracellular accumulation of reactive oxygen species and underwent apoptotic death. A β caused activation of redox sensitive transcription factors NF- κ B and AP-1, which appeared to be mediated via transient induction of MAPKs such as ERK 1/2 and p38. Exposure of PC12 cells to A β resulted in time-dependent activation of COX-2 and production of prostaglandin E₂. In another experiment, treatment of A β led to increased iNOS expression, nitric oxide generation and subsequent peroxynitrite production. Pretreatment with the COX-2 selective inhibitor celecoxib or the peroxynitrite scavenger ergothioneine ameliorated A β -induced oxidative cell death. Both SB203580, a widely used p38 MAPK inhibitor and U0126, an inhibitor of MEK1/2 suppressed A β -induced cell death through downregulation of COX-2 expression. The above findings suggest that MAPKs and redox sensitive transcriptional factors play an important role in A β -stimulated proinflammatory pathways.

Keyword : beta-amyloid, oxidative stress, MAPK, NF- κ B