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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 (Abeta), a neurotoxic peptide associated with senile plaques formed in the brains of patients with AD, in cultured PC12 cells. PC12 cells treated with Abeta exhibited increased intracellular accumulation of reactive oxygen species and underwent apoptotic death. Abeta caused activation of redox sensitive transcription factors NF-kB 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 Abeta resulted in time-dependent activation of COX-2 and production of prostaglandin E2. In another experiment, treatment of Abeta 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 Abeta- induced oxidative cell death. Both SB203580, a widely used p38 MAPK inhibitor and U0126, an inhibitor of MEK1/2 suppressed Abeta-induced cell death through downregulation of COX-2 expression. The above findings suggest that MAPKs and redox sensitive trnascriptional factors play an important role in Abeta-stimulated proinflammatory pathways.

Keyword : beta-amyloid, oxidative stress, MAPK, NF-kappaB