【P-30】

Protective Effect of Celecoxib, a Selective Cyclooxygenase-2 Inhibitor, Against Beta-Amyloid-Induced Apoptosis: Possible Involvement of Proinflammatory Signals in Beta-Amyloid-Mediated Cell Death

Jung-Hee Jang and Young-Joon Surh
College of Pharmacy, Seoul National University 151-742, South Korea

Inflammatory as well as oxidative tissue damage has been implicated in pathophysiology of Alzheimer's disease (AD), and non-steroidal anti-inflammatory drugs have been reported to have beneficial effects in the treatment or prevention of AD. In the present study, we investigated the effect of celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, on 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 underwent apoptotic death as determined by positive in situ terminal end-labelling (TUNEL staining), decreased mitochondrial membrane potential, an increased ratio of proapoptotic Bax to antiapoptotic Bcl-XL, elevated caspase-3 activity and the cleavage of poly(ADP-ribose)polymerase. Exposure of PC12 cells to beta-amyloid resulted in time-dependent induction of COX-2 mRNA and protein expression and production of prostaglandin E_2 (PGE_2). Celecoxib attenuated beta-amyloid-induced cytotoxicity and apoptotic cell death through inhibition of COX-2 expression and PGE_2 production. beta-Amyloid caused activation of NF-κB through degradation of the inhibitory protein IκBα and also of subsequent translocation of the p65 subunit to nucleus. Furthermore, addition of NF-κB inhibitors, pyrolidine dithiocarbamate or L-tosylamido-2-penetyl chloromethylketone to the media decreased the expression of COX-2. beta-Amyloid treatment resulted in transient activation of mitogen-activated protein kinases (MAPKs), such as extracellular signal-regulated kinase 1/2 (ERK1/2) and p38 MAPK, which appeared to be upstream of NF-κB. The MEK1/2 inhibitor U0126 and p38 inhibitor SB203580 strongly inhibited NF-κB activation and subsequent COX-2 expression. These results suggest that celecoxib could modulate cell death caused by beta-amyloid and may have preventive or therapeutic potential in the

management of AD. The elucidation of intracellular signaling cascades in response to beta-amyloid-induced inflammatory cell death and their regulation by celecoxib may provide additional insights into the molecular basis of neuroprotection in AD.

Keyword : Apoptosis, beta-Amyloid, Celecoxib, Cyclooxygenase-2, proinflammatory signals