acid. There are two isoforms of COX, designated as COX-1 and COX-2. While COX-1 is constitutively expressed in most tissues, COX-2 can be induced transiently by proinflammatory cytokines, endotoxins, growth factors, oncogenes, UV and mitogens. Elevated levels of COX-2 have been observed in cancers of breast, colon, and lung as compared with the surrounding normal tissues. Based on these findings, it is conceivable that targeted inhibition of inappropriate or abnormal up-regulation of COX-2 is one of the most broadly effective and promising approaches to cancer chemoprevention. Celecoxib, a selective COX-2 inhibitor, has been reported to prevent experimentally induced colon, breast and skin carcinogenesis. Moreover, daily intake of celecoxib resulted in significant reduction of polyps in patients with familial adenomatous polyposis. In the present study, we examined the effect of celecoxib on COX-2 induction in 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-treated mouse skin. Topical application of 0.1, 1.0, or 10 μ mole celecoxib onto shaven backs of female ICR mice (6 to 7 wk of age) 30 min prior to 10 nmole TPA inhibited expression of COX-2 protein and subsequent production of prostaglandin E_2 in a dose-related manner. Celecoxib inhibited activation of AP-1 and C/EBP transcription factors in a dose dependent manner. Furthermore, celecoxib inhibited both catalytic activity and phosphorylation of ERK1/2. These results suggest that celecoxib suppresses TPA-induced COX-2 expression in mouse skin by blocking activation of ERK, which appears to be mediated by transcription factors such as AP-1 and C/EBP.

[OC-2] [04/19/2002 (Fri) 14:50 - 15:00 / Hall A]

BETA-AMYLOID INDUCES OXIDATIVE DNA DAMAGE AND CELL DEATH: POSSIBLE INVOLVEMENT OF INFLAMMATORY CASCADES

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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-κB 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.

[OD-1] [04/19/2002 (Fri) 15:00 - 15:10 / Hall A]

Cytotoxic Terpenoids from the Sponge Sarcotragus Species

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Twenty-one new and two known terpenoids were isolated from the marine sponge Sarcotragus sp., including twelve furanosesterpene and their derivatives, seven new pyrrolosesterterpenes two trinorsesterterpenes, and two diterpenes were isolated from the same sponge by bioactivity-guided