

Inhibitory effects of isoquinoline alkaloids on proinflammatory cytokines of tumor necrosis factor(TNF- α), interleukine-1 β (IL-1 β), interleukine-5(IL-5) have been estimated. Among 11 kinds of isoquinoline alkaloids (tetrahydropapaverine, salsolinol, berberine, coralyne chloride, hydrastine, laudanosine, pamatine chloride, noscapine, papaverine, ethaverine, and tetrahydropapaveroline) tested, 9 samples exhibited inhibitory effects on the IL-5 bioactivity with an IC50 value of 7.5 μ M by tetrahydropapaverine, 3.5 μ M by salsoline, 0.9 μ M by berberine, 0.3 μ M by coralyne chloride, 24 μ M by laudanosine, 15.8 μ M by pamatine chloride, 1.4 μ M by papaverine, 1.4 μ M by ethaverine, and 1.6 μ M by tetrahydropapaveroline. However, the compounds have no inhibitory effects on TNF- α and IL-1 β bioactivities. Experiments to know effects on IL-3, IL-4 and IL-6 are in progress.

[PC1-11] [10/19/2001 (Fri) 09:00 – 12:00 / Hall D]

Celastrol, a quinone methide triterpenoid, suppresses NF- κ B Activation by inhibiting phosphorylation of I κ B α

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Celastrol, a quinone methide triterpenoid, was isolated as a NF- κ B inhibitor from *Celastrus orbiculatus* by activity-guided fractionation. This compound dose-dependently inhibited the induced NF- κ B reporter gene expression and DNA-binding activity of NF- κ B in different cell lines by various stimuli without affecting DNA-binding activity of AP-1 transcription factor. Preincubation of celastrol completely blocked the induced degradation and phosphorylation of I κ B α protein by LPS, TNF- α , or PMA. Moreover, celastrol suppressed the induced NF- κ B activation by overexpression of NEKK-1, NIK, or IKK- α , but not by p65, suggesting that celastrol suppressed the induced NF- κ B activation by preventing phosphorylation of I κ B, possibly through inhibiting kinase activity of I κ B kinase complex. To verify that celastrol is a NF- κ B inhibitor, we investigated its effect on some NF- κ B target genes expressions. Celastrol prevented not only LPS-induced mRNA expression of iNOS and TNF- α , but also TNF- α induced expression of Bfl-1/A1, a prosurvival bcl-2 homologue. Consistent with these results, this compound significantly suppressed the production of NO and TNF- α in LPS-stimulated RAW264.7 cells, and increased the cytotoxicity of TNF- α in HT-1080 cells. Taken together, this study extends our understanding on the molecular mechanisms underlying the antiinflammatory activities of celastrol and celastrol-containing extracts that are used in traditional oriental medicine. Furthermore, celastrol could be an interesting lead compound for the modulation of NF- κ B-dependent pathological conditions such as inflammatory diseases and cancer.

[PC1-12] [10/19/2001 (Fri) 09:00 – 12:00 / Hall D]

Mechanism of Cinnamaldehyde induced-apoptosis in human leukemia HL-60 cells

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In the previous report, we found that cinnamaldehyde, isolated from the stem bark of Cinnamomum cassia, induced cytotoxicity and apoptosis. These effects were completely prevented by pretreatment with antioxidant N-acetyl-L-cysteine (NAC). Cinnamaldehyde activated various caspases, such as caspase-3, caspase-8 and caspase-9 activities, and induced the release of cytochrome-c from mitochondria into the cytosol. Bid, a death agonist member of the Bcl-2 family, was processed following exposure of cells to cinnamaldehyde. These data suggest that cinnamaldehyde induced apoptosis of HL-