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In the present study, the effects of THI 52 on NO production, and tumor necrosis factor (TNF)-α, and iNOS mRNA expression were investigated in RAW 264.7 cells exposed to LPS plus IFN-γ. In addition, the effects of THI 52 on vascular reactivity in vitro and ex vivo, and iNOS protein expression (rat lung) were investigated in LPS-treated rats. Treatment of THI 52 concentration-dependently reduced not only NO production (IC_{50} value, 12.5 μM) but also the expression of TNF-α, and iNOS mRNA in RAW 264.7 cells. Incubation of rat endothelium-removed thoracic aorta with LPS (300 ng/ml) for 8 h in vitro resulted in suppression of vasoconstrictor effects to phenylephrine (PE), which was restored by co-incubation with THI 52. Treatment THI 52 (15 and 20 mg/kg, i.p) 30 min before injection of LPS (10 mg/kg, i.p) resulted in significant reduction of the expression of iNOS protein in rat lung tissue, and restoration of vascular contractility to PE. Plasma NOx level was significantly ($p < 0.01$) reduced by THI 52 (15 and 20 mg/kg, i.p) in LPS-treated (10 mg/kg, i.p) rats. THI 52 concentration-dependently diminished the NF-κB-DNA complex, which is essential for expression of inflammatory genes. Using CCL1 cells, a TNF-α sensitive L929 fibroblast cell line, effect of THI 52 on TNF-α toxicity was measured. Inclusion of THI 52 significantly increased the cell viability, indicating THI 52 reduces TNF-α secretion to the media. These results strongly suggest that THI 52 can suppress both TNF-α and iNOS gene expression induced by LPS + IFN-γ in RAW 264.7 cells at the transcriptional level, and restore the vascular contractility to PE. Thus, THI 52, a new synthetic isoquinoline alkaloid, may be beneficial in inflammatory disorders where production of NO is excessed by iNOS expression (This work was supported by HMP98-D-4-0045)

[PA1-11] [10/18/2001 (Thr) 14:00 - 17:00 / Hall D]

Inhibition of TNF-a and IL-6 production by aucubin through blockade of NF-kB activation in RBL-2H3 mast cells

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IgE-stimulated mast cells induce synthesis and production of cytokines including tumor necrosis factor (TNF)-a and interleukin (IL)-6 with proinflammatory and immune regulatory properties. Expression of TNF-a and IL-6 proteins is dependent on the activation of a transcription factor, nuclear factor (NF)-kB. The iridoid glycoside, aucubin, has been found as a natural constituent of many traditional oriental medicinal plants. We studied the effect of aucubin on the TNF-a and IL-6 expression in IgE-stimulated rat basophilic leukemia (RBL)-2H3 mast cells. We show that aucubin inhibited IgE-induced TNF-a and IL-6 production and expression in RBL-2H3 cells. Aucubin also inhibited IgE- induced nuclear translocation of p65 subunit of NF-kB and degradation of IkBa. Inhibition of NF-kB activation by aucubin might be specific since activator protein-1 binding activity was not affected. In conclusion, these results suggest that aucubin is a specific inhibitor of NF-kB activation in mast cells, which might explain its beneficial effect in the treatment of chronic allergic inflammatory diseases.

[PA1-12] [10/18/2001 (Thr) 14:00 - 17:00 / Hall D]

DA-8159, a New Phosphodiesterase 5 Inhibitor, Induces Erection in the Anesthetized Dogs

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