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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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DA-8159, a new phosphodiesterase 5 inhibitor, was assessed for its erectogenic potential by a penile erection test in rats, the relaxation of isolated rabbit corpus cavernosum , and estimation of the intracavernous pressure in the anesthetized dog. Oral administration of DA-8159 (0.3 to 10 mg/kg) increased the number of erections in rats with increasing dosage, with the highest penile erection index at 10 mg/kg. DA-8159 induced the relaxation of phenylephrine-induced contractions in the rabbit corpus cavernosal smooth muscle and decreased the IC50 of the nitric oxide donor sodium nitroprusside in a dose-dependent fashion. In pentobarbital- anesthetized dogs, the intravenous administration of DA-8159 (1 ~ 300 μg/kg) potentiated the increase in intracavernosal pressure induced by the intracavernosal sodium nitroprusside in a dose-related manner. These findings suggest that DA-8159 has significant therapeutic potential in the treatment of erectile dysfunction.

[PA1-13] [10/18/2001 (Thr) 14:00 - 17:00 / Hall D]

Antifibrogenic effect of butein in carbon tetrachloride-induced rat liver fibrosis

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Butein (3, 4, 2', 4'-tetrahydroxychalcone) is a chalcone compound belonging to the flavonoid subclass. The aim of this work was to investigate the effect of butein on liver fibrosis by induced carbon tetrachloride (CCl_4) in rats and to explore its antifibrotic mechanism.

Liver hydroxyproline content, malondialdehyde level, hisoto- and immunohistopathology and collagen type I and tissue inhibitor of metalloproteinase-1 (TIMP-1) mRNA expression were assessed. Butein (10 mg/kg/day or 25 mg/kg/day)-treated fibrotic rats showed a significant reduction in hydroxyproline content and malondialdehyde level. Smooth muscle α-actin expression was also decreased in rats treated with butein, which indicates inhibition of hepatic stellate cell (HSC) activation. The expression of α_1(I) collagen and TIMP-1 mRNA in liver was clearly decreased in rats given butein compared with control CCl_4 rats, dose-dependently. In summary, treatment with butein reduced all of the studied parameters of fibrogenesis.
In conclusion, butein prevent liver fibrosis by suppressing the expression of TIMP-1 mRNA of HSC in fibrogenesis, resulting in reduce expression of collagen mRNA.

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

Benzylamide derivative compound attenuates ultraviolet-induced hyperpigmentation of the skin

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This study was conducted to evaluate the effects of benzylamide derivative, SY 010 compound on ultraviolet B (UVB)-induced hyperpigmentation of the skin. UVB-induced hyperpigmentation was elicited on the skin of brownish guinea pigs according to the method of Hideya et al. with modifications. A lightening effect was observed following topical application of the compound on UV-stimulated hyperpigmented dorsal skin of brownish guinea pigs. A visible decrease in hyperpigmentation was observed at the sites treated with the compound for 2 weeks, as compared with control. After 8 weeks of treatment with the compound, the skin recovered to its original color. The production of melanin in the pigmented area and the number of melanocytes were significantly decreased in the compound treated animals, as assessed by using Fontana-masson and S-100 stain. In vitro experiments using cultured melanoma cells showed that 30% inhibition of melanin production by compound at 100 ppm. But, the compound had no effect on the mushroom tyrosinase activity.