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.

Suggesting that the pigment-lightening effects of the compound may be due to the suppression of melanin production by active melanocytes.

[PA1-15] [10/18/2001 (Thr) 14:00 - 17:00 / Hall D]

Discovery of isoxazol(in)ylalkylpiperazines as novel dopaminergic D3/D4 receptor antagonists

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Selective D3 and/or D4 antagonism may represent a novel and potent antipsychotic mechanism and may have application as an atypical antipsychotic drug which does not induce extrapyramidal side effects. Recently, a series of isoxazol(in)yl alkylpiperazines were synthesized, and their binding affinities for cloned dopamine receptors and in vivo anti-dopaminergic activities were evaluated. Radioligand-binding experiments showed that they have high-affinities (< 10 nM, IC50) for the D3 and/or D4 receptors with greater than 100-fold D3/D4 selectivity over D2 receptor. Some selected compounds strongly blocked apomorphine-induced climbing behavior without any rotarod deficit in mice. In addition, hypothermia-induced by a selective D3 agonist, (+)-7-OH-DPAT, was also partially attenuated by those compounds in mice. It is likely, therefore, that they appear to be the potent and selective dopamine D3 and/or D4 antagonists.

[PA1-16] [10/18/2001 (Thr) 14:00 - 17:00 / Hall D]

Oltipraz inhibits dimethylnitrosamine-induced liver fibrosis through suppression of transforming growth factor-beta1 and tumor necrosis factor-alpha expression

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Oltipraz is a cancer chemopreventive agent active against a wide variety of chemical carcinogens. In spite of the intense chemoprevention and toxicology studies on oltipraz, no information is available on its antifibrotic efficacy. In the present study, the effects of oltipraz on dimethylnitrosamine-induced liver fibrogenesis were assessed in rats. As part of mechanistic studies, the expression of transforming growth factor-β1 (TGF-β1) and tumor necrosis factor-α (TNF-α) was monitored. Treatment of rats with DMN (10 ml/kg body weight, i.p., three times per week for 4 weeks) resulted in marked increases in plasma alanine aminotransferase (ALT), aspartate aminotransferase (AST) and γ-glutamyl transpeptidase (γ-GT) activities. DMN also caused an increase in the plasma bilirubin content, whereas total plasma protein and albumin levels were rather decreased. Oltipraz (50 mg/kg body weight, po, three times per week for 4 weeks) inhibited the increases in plasma ALT, AST, γ-GT and bilirubin by DMN. DMN increased liver fibrosis as histopathologically assessed by Van Gieson's staining and Masson's trichrome staining (fibrosis score, 3.7, Knodell score, 16), which was reduced by oltipraz treatment (fibrosis score, 2.5, Knodell score, 8.0). Reverse transcription-polymerase chain reaction analysis revealed that oltipraz inhibited an increase in the TGF-β1 mRNA by DMN. Oltipraz was also active in reducing the production of plasma TNF-α by DMN or lipopolysaccharide, which would contribute to its cytoprotective effect. These results demonstrated that oltipraz inhibited hepatocyte injury and impairment of liver function induced by DMN, and reduces DMN-induced liver fibrosis possibly through suppression of TGF-β1 and TNF-α production.