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.