[PA1-7] [10/19/2000 (Thr) 10:00 - 11:00 / [Hall B]]

The inhibition of NO production by 5-Fluorouracil is linked to the inactivation of NF-kB in stomach cancer cells

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The antimetabolite 5-fluorouracil (5-FU) is one of the more prominent clinical antitumor agents for stomach and colorectal cancers. In the present study, we characterized the effects of 5-FU on nitric oxide (NO) production by stomach cancer cells, NCI-N87. IFN-γincreased the production of NO and pretreatment of 5-FU inhibited the production of NO in response to IFN-γin a dose dependent manner. The increased expressions of iNOS mRNA and protein by IFN-γwere completely blocked by 5-FU through the inactivation of NF-kB and the stabilization of IkBαin stomach cancer cells. These data suggest that the efficacy of 5-FU may, at least, include the inactivation of NF-kB and the inhibition of NO production.

[PA1-8] [10/19/2000 (Thr) 10:00 - 11:00 / [Hall B]]

OST-3033, A Potent Cathepsin K Inhibitor, Inhibit Bone Resorption In Vitro

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Cathepsin K (CK), a cysteine protease that degrades type I collagen, is highly and selectively expressed in osteoclasts. CK was emerged as a potential target for antiresorptive therapy. In a search for potent CK inhibitors for the treatment of osteoporosis, we found several compounds with subnanomolar level of IC50 on CK. Among these, OST-3033 showed the superior CK inhibitory activity with an IC50 value of 0.7 nM as well as the high selectivity.
In the present studies, the effects of OST-3033 on bone resorption and bone formation were determined in osteoclastic and bone marrow stromal cell culture systems in vitro, respectively. In the bone resorption assay, osteoclast-rich cell suspensions isolated from fetal rabbit long bones were cultured on the ivory slices for 48h. The level of bone resorption was assessed by microscopy and the levels of C-terminal telopeptides of type I collagen, CTx, released from resorption pits. The bone formation was determined by measurement of the markers of enrichness of osteoblasts such as alkaline phosphatase, osteocalcin levels and bone-like nodule formation in rat bone marrow stromal cell cultures.
OST-3033 was found to inhibit osteoclastic bone resorption with an IC50 value of about 100 nM in CTx release and the treatment with OST-3033 also resulted in decrease of pit formation. The effect of OST-3033 on bone formation showed that none of alkaline phosphatase, osteocalcin levels and bone-like mineralized nodule formation was affected by up to 1 uM of OST-3033. These results indicate that OST-3033, a very potent and selective CK inhibitor, efficiently suppresses the bone resorption in vitro, and may have therapeutic potential in diseases caused by the excessive bone resorption such as osteoporosis.
[This study was supported by a grant of the Korea Health 21 R&D Project, Republic of Korea (HMP-98-D-4-0028)]

[PA1-9] [10/19/2000 (Thr) 10:00 - 11:00 / [Hall B]]

In vitro inhibition of DDB toward CYP3A4 : inhibitory patterns are substrate -

dependent

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Dimethyl-4, 4'-dimethoxy-5, 6,5', 6'-dimethylenedioxybiphenyl-2, 2'-dicarboxylate (DDB), an anti-viral hepatitis agent, has been identified as a selective CYP3A4 inhibitor through the formation of stable MI-P450 complex.
In this study, the inhibitory effects of DDB on CYP3A4 activity were investigated using a series of CYP3A4-specific substrate to clarify potential drug-drug interactions. The inhibitory potency of DDB was depending on the type of substrates in human liver microsomes.Testosterone hydroxylation and nifedipine oxidation were highly inhibited with IC_{50} value of 0.35μM and 4.04μM, respectively. However metabolism of midazolam, erythromycin, and terfenadine in human liver microsomes were less inhibited by DDB with 10-100 times higher IC_{50} values compared to testosterone 6β-hydroxylation. These results indicated that interaction between drugs metabolized by CYP3A4 are substrate-dependent and these phenomena can be explained by the existence multiple substrate-binding site in CYP3A4.

[PA1-10] [10/19/2000 (Thr) 10:00 - 11:00 / [Hall B]]

Mechanism of Hypoglycemic Effect of (R)-JG-381 in Rat

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The present study was undertaken to investigate hypoglycemic mechanism of (R)-JG-381, a new oxirane-2-carboxylate derivative. Diabetes mellitus was produced for intravenous injection of streptozotocin (45 mg/kg b.wt.). After 1 week of administration of streptozotocin, the rats then received vehicle (0.5% CMC) or (R)-JG-381(10, 40 mg/kg b.wt./day) orally for 4 weeks. We have determined blood glucose, the lipid metabolites such as b-hydroxybutyrate, triglyceride and cholesterol concentrations in blood and carnitine palmitoyl transferase activity, triglyceride and cholesterol content in liver. In streptozotocin-treated rat, blood glucose levels were significantly increased and the level of lipid metabolites, b-hydroxybutyrate, triglyceride and cholesterol in blood were also increased. (R)-JG-381 decreased the elevated glucose level. The increase in b-hydroxybutyrate, triglyceride and cholesterol concentrations in blood was suppressed by (R)-JG-381 treatment. Our findings suggest that (R)-JG-381 decreases lipid oxidation in diabetic rats.

[PA1-11] [10/19/2000 (Thr) 10:00 - 11:00 / [Hall B]]

The influences of ELF magnetic fields on hyperalgesia and convulsion in rat

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The effect of extremely low frequency (ELF, 60Hz) magnetic fields (MFs) on hyperalgesia and convulsion was studied using hot plate tests and convulsion tests in rats. In addition, we measured GABA concentration using HPLC-ECD in rat brain. In hot plate tests, MFs or diazepam (0.5 μg, i.c.v.) had hyperalgesic effects. These effects were blocked by flumazenil (1.5 mg/kg, i.p. ; benzodiazepine receptor antagonist). Flumazenil also inhibited hyperalgesia induced by MFs and diazepam. This indicate that MFs-induced hyperalgesia may be mediated through activation of benzodiazepine receptor. MFs-induced hyperalgesia was not changed by bicuculline (0.1 μg,