on secretion of catecholamines (CA) from the isolated perfused rat adrenal gland and to establish the mechanism of its adrenomedullary secretion.
The perfusion (0.31ml/min) into an adrenal vein of for 90 min resulted in great increases in CA secretions. Tachyphylaxis to releasing effect of CA evoked by CCCP was not observed by repeated perfusion of it. The net increase in adrenal CA secretion evoked by CCCP still remained unaffected in the presence of pirenzepine or chlorisondamine. However, the releasing effects of CA evoked by CCCP were depressed by *pretreament with pirenzepine, chlorisondamine, nicardipine*, TMB-8, and the perfusion of EGTA plus Ca2+-free medium. CA secretory responses induced by Ach, high K+, DMPP, and McN-A-343 were significantly enhanced in the presence of CCCP (3?0-5 M).
Taken together, these experimental results indicate that CCCP causes the rat adrenomedullary CA secretion in a calcium-dependent fashion, suggesting strongly that this facilitatory effects of CCCP may be mediated by both stimulation of the Ca2+ influx and Ca2+ release from cytoplasmic Ca2+ store.

[PA1-10] [04/18/2002 (Thr) 14:00 - 17:00 / Hall E]

High Throughput Fluorometric Assay for Cathepsin S inhibitors

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Lysosomal cysteine proteases are involved not only in protein metabolism but also in tissue remodeling, hormone activation and antigen presentation. Among the known cysteine proteases, cathepsin S exists exclusively as a single-chain proteinase. It is also characterized uniquely by its high stability at neutral pH and bell-shaped pH-activity profile. Cathepsin S has received attentions due to its role in the pathogenesis of asthma, Alzheimer's disease, rheumatoid arthritis and other diseases involving tissue destruction. Recently, several evidences demonstrate that selective inhibition of cathepsin S could be a potential strategy for modulating the immune response in autoimmune diseases such as asthma and rheumatoid arthritis.
We established a fluorometric assay with recombinant human enzyme to explore cathepsin S inhibitors from in-house chemical libraries. The assay in the format of 96-well plate is easily adapted for high throughput screening. Therefore, our HTS system can be robustly applicable to the discovery of cathepsin S inhibitor owing to its high sensitivity, precision, accuracy, and stability.

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[PA1-11] [04/18/2002 (Thr) 14:00 - 17:00 / Hall E]

Preclinical studies of CKD-732, an antiangiogenic and antitumor agent.

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We have developed a novel water-soluble fumagillin derivative, CKD-732, and performed preclinical studies as an antiangiogenic antitumor agent. In endothelial cell proliferation assay, CKD-732 was found to show a 72 fold more potent activity compared to fumagillin. In addition, in the Matrigel assay, the hemoglobin content of Matrigel in CKD-732 treatment mice was less than 20% of that in control. Therefore, CKD-732 was found to effectively inhibit a neovessel formation through an angiogenic process. In tumor xenograft models, s.c. injection of CKD-732 induced the growth inhibition of PC-3, CX-1, SKOV-3, LX-1, SNU-16, MDA-MB-231 and Hep3B tumors in a dose dependent manner as much as 64, 74, 69, 69, 68, 70 and 65%, respectively. In animals bearing A375-SM and PC-3 tumors, CKD-732 induced stasis of tumor growth and displayed ILS of >200%. To evaluate the pharmacokinetic property of CKD-732, ADME studies were performed in vitro and in vivo. CKD-732 and 14 metabolites were found from the in vitro samples, and a major metabolite(M11) was identified as a N-oxide form. CKD-732 and M11 exhibited similar plasma kinetic profiles with linear pharmacokinetics, which were detected at 6~8 hrs after an i.v. administration in rat and dog. Therefore, CKD-732 was shown to be relatively stable and to have a long half-life in plasma. These results suggest that the strong antiangiogenic antitumor activity and the improved metabolic

pharmacokinetic properties of CKD-732 warrant clinical trials.

[PA1-12] [04/18/2002 (Thr) 14:00 - 17:00 / Hall E]

Locomotor Stimulant Effects of Cocaine and Morphine in mu-Opioid Receptor Knockout Mice

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Administration of psychostimulants and opioids leads to an increased locomotor activity to the drugs. The locomotor stimulatory properties of cocaine and opioid may be related to their rewarding properties and these substances are primarily abused for their rewarding or euphoric qualities. The majority of evidence indicates that the neurochemical effects of cocaine and morphine underlying its ability to increase the motor activity related to the dopaminergic system. However, the roles of other neurotransmitter systems have received less attention and are poorly understood, although the role of dopamine in the behavioral effects of these drugs is well-established.
The present study was investigated the locomotor activity of wild-type(Wild) and mu-opioid receptor knockout (KO) mice following cocaine and morphine administration to examine the role of mu-opioid receptors. Furthermore we examined gender differences effects of locomotor activity. Locomotor activity was measured by video-tracking system after administration of cocaine(15mg/kg, i.p.) and morphine (10mg/kg, s.c.) for 30 min. Treatment with morphine enhanced by 46% in Wild (vs KO), by 42% in Wild-female (vs KO-female). Treatment with cocaine augmented the locomotor activity by 48% in Wild (vs KO), by 67% in Wild-male (vs Wild-female), and by 40% in Wild-male (vs KO-male).
These results suggest that morphine and cocaine stimulate locomotor activity through mu-opioid receptors. It was observed gender difference that male mouse is more vulnerable in cocaine-induced locomotor activity.[This work was supported by grant No 2000-1-21300-001-3 from Basic Research Program of the Korea Science & Engineering Foundation]

[PA1-13] [04/18/2002 (Thr) 14:00 - 17:00 / Hall E]

In vivo inhibitory activity of YJA203798 against Helicobacter pylori

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Helicobacter pylori(H. pylori) is a microaerophilic spiral bacterium and infection by the organism may cause gastritis in the human stomach. Futhermore, it is considered to be involved in the pathogenesis of peptic ulcers and the development of gastric carcinoma. In this study, we assessed the in vivo inhibitory activity of YJA203798, a novel antiulcer agent, against H. pylori. YJA203798 was administered to H. pylori infected Mongolian gerbils which is a useful small animal model to study the pathogenesis of H. pylori in gastric ulceration. The degree of inflammation was scored in a blind manner on a scale of 0~3 for body and antrum and that of density was checked in the same manner. All scores were mean values of 6 animals. The degrees of inflammation and density were dose dependently reduced. From these results, it is suggested that YJA203798 exhibited in vivo antiinflammatory and antimicrobial activity against H. pylori. Therefore, YJA203798 may be developed as a candidate for non-antibiotic therapeutic strategy against H. pylori.

[PA1-14] [04/18/2002 (Thr) 14:00 - 17:00 / Hall E]

Antithrombotic Activity of VK-708, a Newly Synthesized Vitamin K Derivative

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