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It has been reported that vitamin K analogues have various pharmacological effects such as antiviral, antifungal, anticancer, and antiplatelet activities. It has also been reported that some synthetic naphthoquinone compounds showed antiplatelet activities. In the present study, the antithrombotic activity of VK-708 (2-[N-2-bromo-4-fluoro-phenyl]amino-3-chloro-5-hydroxy-1,4-naphthoquinone), a newly synthesized vitamin K derivative, was investigated. Effects of VK-708 on the murine pulmonary thrombosis *in vivo*, human platelet aggregation *in vitro*, rat platelet aggregation *ex vivo*, and coagulation parameters were examined. VK-708 prevented the death due to pulmonary thrombosis in mice dose-dependently *in vivo*. It also inhibited ADP- and collagen-induced rat platelet aggregation *ex vivo* in a dose-dependent manner. Moreover, VK-708 potently inhibited collagen-, thrombin-, and A23187-induced aggregation in washed human platelet concentration dependently *in vitro*. VK-708, however, did not alter such coagulation parameters as activated partial thromboplastin time and prothrombin time in human plasma.
These results suggest that VK-708 may be a promising antithrombotic agent, and the antithrombotic activity of VK-708 may be due to the antiplatelet activity, but not to anticoagulation activity.

[PA1-15] [04/18/2002 (Thr) 14:00 - 17:00 / Hall E]

Effects of nalbuphine on the development of morphine-induced tolerance and dependence in rats

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Morphine is central to the treatment of many types of chronic pain. But the development of tolerance to morphine can become a problem, most notably in pain therapy in opioid addicts. The purpose of the present study was to investigate whether combined administration with nalbuphine affect development of tolerance and dependence to continuous exposure to morphine. Morphine (10 mg/kg) was injected intraperitoneally for 5 days. Nalbuphine (0.1, 1.0 and 5.0 mg/kg) was administered IP in combination with morphine injection. Morphine tolerance was assessed antinociceptive effect by the Randall-Selitto test. Morphine dependence was determined by precipitated withdrawal signs induced by naloxone (10 mg/kg, IP). Nalbuphine did not attenuate morphine-induced antinociceptive effect in rats. Combined administration of nalbuphine with morphine significantly inhibited the development of morphine tolerance and dependence We hypothesize that the use of compounds such as nalbuphine may prove to be useful adjunct therapy in the management of some forms of clinical pain by morphine.

[PA1-16] [04/18/2002 (Thr) 14:00 - 17:00 / Hall E]

Nonpeptide Angiotensin II Receptor Antagonist, Studies with BR-A-657

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BR-A-657(2-n-butyl-5-dimethylaminothiocarbonylmethyl-6-methyl-3- [[2'-(1H-tetrazol-5-yl)biphenyl-4-yl] methyl] pyrimidin-4(3H)-one, potassium salt·$3H_2O$) is shown to be a novel, nonpeptide, antihypertensive, specific angiotensin II (AII) receptor antagonist. In rabbit aorta, it noncompetitively inhibited the contractile response to AII with pD_2 9.05. In guinea pig ileum, it inhibited the responses to AI and AII (IC_{50} 0.89 and 0.5 nM, respectively). In conscious normotensive rats, BR-A-657 (0.01, 0.1, 1 mg/kg i.v.) inhibited AII-induced pressor responses in a dose-dependent manner (ID_{50} 0.02) and BR-A-657 (0.3, 1, 3 mg/kg p.o.) produced long lasting inhibition of AII pressor responses (ID_{50} 0.32). In renal

hypertensive rats, BR-A-657 at 3 mg/kg p.o. and 0.3 mg/kg i.v. decreased mean arterial blood pressure (MAP) by 42.8% and 30%, respectively. In spontaneously hypertensive rats, BR-A-657 at 10 mg/kg p.o. induced maximal decrease in MAP by 27%. Any agent did not affect the heart rate significantly at any dose used. These results suggest that BR-A-657 may be potentially useful for treatment of hypertension.

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

Effects of Capsicum annuum L. var. angulosum Mill on changing morphology, and apoptosis of Hepatoma and MCF-7 cell

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Capsicum annuum L. var. angulosum Mill. of edible plants relatively showed good anticancer effects. Morphological characterization, such as apoptic body, of MCF-7 and Hepatoma cell on plants was shown by electronic microscopy. The cells included in medium were investigated to be aggregated and destroyed by treatment with some edible plants. Especially, the case of Capsicum annuum L. var. angulosum Mill, it led sample-treated MCF-7 and Hepatoma cells to apoptosis faster than others. So now, We studied that the solvent, harvest time, and the part of Capsicum annuum L. var. angulosum Mill: Leaf, Fruit unripen, Fruit ripen, Seed ripen, Seed unripen, are how much has the anti-proliferating effect on MCF-7 and Hepatoma cells. Now We'll present the results.
The cells by treated Capsicum annuum L. var. angulosum Mill show the apoptic characterization. all part of *Capsicum annuum* L. var. angulosum Mill was changing faster the morphology of the cells. To continue our search for anticancer effects, we also observed changes through using a fluorescent microscope by PI staining. These results show that each sample exerted anticancer effects on MCF-7 and hepatoma cells. Especially Capsicum annuum L. var. angulosum Mill, Leaf exerted significant anticancer effects.

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

Attenuation of iNOS induction by SNUP through inhibition of I-κBα phosphorylation and of p65 nuclear translocation

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SNUP is a compound isolated from *Beta vulgaris* L. var. *cycla* L.(Chenopodiaceae). The effect of SNUP on the nuclear factor-κB (NF-κB)-mediated inducible nitric oxide synthase (iNOS) gene expression was studied in Raw264.7 cells. Inhibitory effect on NF-κB activation was determined by gel mobility shift assay, immunocytochemistry and immunoblot analysis of I-κBα. Expression of the iNOS gene was assessed by RT-PCR. NO production was monitored using Griess reagents. SNUP(10 μM) inhibited lipopolysaccharide (LPS)-inducible nuclear NF-κB activation and nuclear translocation of p65, which was accompanied by inhibition of I-κBα phosphorylation. LPS-inducible increase in the iNOS mRNA was suppressed by 10 μM SNUP. Immunoblot analysis revealed that SNUP significantly inhibited the induction of iNOS. Production of nitrite and nitrate by LPS in culture medium was also comparably suppressed by SNUP. These results showed that SNUP inhibits LPS-inducible iNOS expression in murine macrophages through suppression of I-κBα phosphorylation and nuclear translocation of p65. Inhibition of LPS-inducible NO production in macrophages may constitute anti-inflammatory effect of *Beta vulgaris* L.var. *cycla* L.

[PA1-19] [04/18/2002 (Thr) 14:00 - 17:00 / Hall E]

Anti-coagulant and/or Platelet Anti-aggregatory Activities of Opuntia vulgaris Mill.

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