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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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