

and treated for 8 weeks as follows: control group received powdered standard chow, treated groups were fed with a diet of chow supplemented with KHU-1 either 2 g/kg or 5 g/kg body weight(b.w.), positive control group received rosiglitazone(RSG), 10  $\mu$ mol/kg b.w. also administered via the diet. KHU-1 lowered plasma glucose in dose dependent manner from a week after treatment and the hypoglycemic activity was continued for 8 weeks. Triglyceride and free fatty acid were reduced in KHU-1(5 g/kg)-treated group. While the control group had a declining insulin concentration, KHU-1 treatment maintained or increased insulin level at the end of treatment. KHU-1 and RSG-treated rats also exhibited lowered urinary albumin excretion as compared to the control, indicative of renal glomerular damage. In the mechanism study, PPAR $\gamma$  mRNA and protein expressions in epididymal fat were increased in KHU-1-treated group, which was comparable to RSG-treated group. GLUT4 mRNA expressions in quadriceps muscle was also increased in KHU-1 and RSG-treated group. We have detected the expression of fibronectin, one of the ECM proteins, in kidney by immunohistochemistry. KHU-1 suppressed protein expression of fibronectin in comparison with control. We have also investigated TGF- $\beta$  mRNA expression in kidney and PEPCK mRNA expression in liver. There were no significant differences between control and treatment group in these parameters. From these result we may conclude that KHU-1 showed the excellent hypoglycemic activity and its mechanism was partially due to overexpression PPAR $\gamma$  in adipose tissue.

[PA1-50] [ 10/18/2001 (Thr) 14:00 – 17:00 / Hall D ]

### Hypoglycemic activity of KHU-3 in Ob/Ob mice

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KHU-3 has been known to be used for middle jiao of xiao-ke based on the traditional Korean ancient writings (dongeuibogam) and composed of three crude herbs. In male Ob/Ob mouse which is characterized by severe obesity, hyperinsulinemia and insulin resistance, features of NIDDM, the hypoglycemic activities and mechanisms of KHU-3 were examined. Mice were grouped and treated for 9 weeks as follows : lean control (C57/BL6J black mice) and Ob/Ob control groups received standard chow , treated groups were fed with a diet of chow supplemented with KHU-3 either 5 % or 10 % of total chow. KHU-3 lowered body weight and plasma glucose in dose dependent manner from a week after treatment and the hypoglycemic activity was continued for 9 weeks. Total cholesterol, triglyceride, free fatty acid and LDL cholesterol were decreased and HDL cholesterol was increased in KHU-3 treated groups at the end of treatment. KHU-3 also lowered HbA1c level by 1 % compared as Ob/Ob control. While the Ob/Ob control group showed sever high insulin and C-peptide concentration, KHU-3 treated groups lowered insulin and C-peptide concentration in dose dependent manner. In the mechanism study, quantification of mRNA and protein expression for glucose transporter (GLUT-4) in muscle and peroxisome proliferator activated receptor  $\gamma$  (PPAR- $\gamma$ ) epididymal fat were performed by RT-PCR and western blot. We have also investigated Insulin contents and secretions of  $\beta$ -cell in pancreas by immunohistochemistry. We may suggest that KHU-3 showed the excellent hypoglycemic activity and antidiabetic activities due to reducing hyperinsulinemia and insulin resistance throught affecting gene and protein expressions of fat PPAR- $\gamma$ , muscular GLUT-4.

[PA1-51] [ 10/18/2001 (Thr) 14:00 – 17:00 / Hall D ]

### Higenamine reduces infarct size and myocardial ischemic injury by modulation of immune cytokines

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Recent studies have shown that cytokines are capable of modulating cardiovascular function and that

some drugs which are used in the treatment of heart failure variably modulate the production of cytokines. Higenamine, a positive inotropic isoquinoline alkaloid, is traditionally used as a cardiac stimulant, and has been reported to reduce nitric oxide (NO) and inducible nitric oxide synthase (iNOS) expression in LPS- and/or cytokine-activated cells *in vitro* and *in vivo*. Therefore, we investigated the issue of whether higenamine modulates the production of proinflammatory cytokines during myocardial infarction (MI). The effects of higenamine on antioxidant action and antioxidant enzyme expression (MnSOD) were also examined. MI was confirmed by the measuring left ventricular (LV) pressure 5 weeks after the occlusion of the left anterior descending coronary artery (LAD) in rats. Higenamine treatment (10 mg/kg/daily) reduced the size of the infarct by about 35 %. This treatment was accompanied by a reduction in TNF- $\alpha$  and IL-6 production, but not IFN- $\gamma$  and IL-1 $\beta$  in the myocardium. The expression of TNF- $\alpha$  mRNA in an infarcted myocardium was significantly reduced by treatment with higenamine. Although iNOS mRNA was not detected, nitrotyrosine staining was significantly increased in the myocardium of MI compared to the higenamine-treated group, indicating that peroxynitrite-induced damage occurs during MI. Cytochrome c oxidation by peroxynitrite was reduced by higenamine in a concentration-dependent manner, an effect which was similar to glutathione. Higenamine treatment increased the expression of MnSOD mRNA in both myocardial tissues and perimyocardial tissues during MI, but was reduced in tissues of contralateral regions. Moreover, it is likely that the regulation of MnSOD mRNA possibly via cytokines, in particular, IL-6, may be an important protective mechanism of higenamine. Collectively, the findings herein suggest that higenamine may be beneficial in conditions of oxidative stress, such as ischemic-reperfusion injury and MI due to antioxidant action as well as the modulation of cytokines. (This work was supported by HMP-98-D-4-0045)

[PA1-52] [ 10/18/2001 (Thr) 14:00 - 17:00 / Hall D ]

#### **SPP002-induced stimulation of spontaneous contraction of pregnant rat uterus**

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The SPP002 is a mixture of extracts from *Cervi parvum Cornu*, *Angelicae gigantis Radix* and *Cnidii Rhizoma*. The objective of this study was to characterize *in vivo* the effect of SPP002 on the contractile functions in the non-pregnant and pregnant rat uterus. Pregnancy was confirmed by presence of the deep vaginal plug at 12 hr after mating and uterine contractility was measured at 21 days. Non-pregnant rats were excited by pretreatment of 6-estradiol benzoate for 2 days. After anesthetization, the lower abdomen was incised and a stainless steel cannula with suspended balloon was inserted in the right upper angle of uterus after one fetus was removed. The contractile force and frequency of the uterine contraction were recorded with a pressure transducer and a polygraph. A single (300, 900 mg/kg) and repeated (300, 600 mg/kg) treatment with SPP002 selectively increased uterine contractile functions in pregnant rat while oxytocin (500 mU/ml) increased uterine contractile functions in both pregnant and non-pregnant rat. Our findings suggest that SPP002 may have a beneficial uterotonic effect for labor.

[PA1-53] [ 10/18/2001 (Thr) 14:00 - 17:00 / Hall D ]

#### **The Effects of Chondroitin Digestion Products on Type II Collagen-induced Arthritis in DBA/1J Mice**

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The effects of chondroitin digestion products and intact chondroitin sulfate on arthritis were evaluated. Inhibition on elastase activity of chondroitin digestion products, chondroitin disaccharide, chondroitin oligosaccharide and intact chondroitin sulfate was examined *in vitro*. Chondroitin disaccharide and oligosaccharide inhibited the elastase activity but intact chondroitin sulfate did not influence the elastase activity. And the effects of these digestion products and intact one were examined on type II collagen-