

Chronic exposure of nicotine modulate the expressions of cerebellar glial glutamate transporters in rats

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To study the expressions of glutamate transporter subtypes in cerebellar astrocytes following the chronic exposure of nicotine from mating, rats were treated with nicotine (25 ppm) from the beginning of mating through drinking water. After delivery, each group was divided into two groups. Groups were exposed to either distilled water or nicotine. From 7 day-old pups at each group, cerebellar astrocytes were prepared. Ten days after culture, the expressions of glutamate transporter subtypes (GLAST and GLT-1) were determined using immunohistochemistry and immunoblot. In addition, the developmental expressions of glutamate transporter subtypes in cerebellum were also determined from 2, 4 and 8 weeks-old rats during the continuous treatments. The expressions of GLAST in cultured astrocytes from either pre- or post-natally exposed groups were higher, but those from continuously exposed group were lower than those from control. The expressions of GLT-1 were higher in all nicotine-treated group, especially in continuously treated group. The expressions of cerebellar GLAST and GLT-1 in all nicotine-treated groups were lower than in the control group at each age using immunohistochemistry. However the expressions of cerebellar GLT-1 in all nicotine-treated groups were higher than those in the control except 8 weeks of continuously treated group using immunoblot. These results indicate that the expressions of glial glutamate transporters are differently altered depending on the initial exposure time and periods of nicotine and nicotine exposure during gestation have persistent effects on glial cells.

[PA4-7] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

Safety pharmacology study of AS2-006A, a new wound healing drug

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The safety pharmacological core battery studies of AS2-006A, a newly developed wound healing drug, were investigated according to the ICH S7A guidelines in compliance with Good Laboratory Practice (GLP) Regulations. The doses given were 0, 100, 300 and 1000 mg/kg and drugs were administered subcutaneously. The animals used for this study were mice, rats and guinea pigs. AS2-006A showed no effects on the central nervous system such as motor activity, behavioral changes, coordination, sensory/motor reflex responses and body temperature, no effects on blood pressure (BP), heart rate (HR), and ECG profiles and respiratory system. It was concluded that AS2-006A possess no general pharmacological effects at all doses tested.

[PA4-8] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

The toxicity of Aceporol 460 as a novel high loading capacity solubilizer of paclitaxel

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Previously, we reported a novel polymeric micellar solubilizer, Aceporol 330, that showed relatively low toxic effects when it was compared with that of Cremophor EL which is currently being used for paclitaxel. In this study, we have developed a new micellar solubilizer, Aceporol 460, that has 3-4 times higher loading capacity for paclitaxel than Aceporol 330. The single-dose and the repeated-dose toxicity of Aceporol 460 were evaluated in ICR mice. For single dose toxicity test, male and female mice were randomly assigned to one of five study groups to receive, and injected intravenously with dosages of 0, 3, 4mL Cremophor EL/kg body weight, and 3, 4mL Aceporol 460/kg body weight, respectively. In both male and female mice, LD50 for Aceporol 460 can not be

determined even at the maximal administrable dosage, 4mL/kg, due to the high viscosity of chemical and there was no significant change in body weight, hematological and serum biochemical analysis, organ weight, and histopathological examination compared with that of Cremophor EL. For the repeated dose toxicity test, male and female mice were given the dosage of 0, 1.6mL Cremophor EL/kg body weight/day, and 1.6mL Aceporol 460/kg body weight/day for 2 weeks. Results of repeated dose toxicity tests for 2 weeks suggested that Aceporol 460 treated group show no significant toxicological findings with body weight, hematological and serum biochemical analysis, organ weight, urinalysis, and ophthalmoscopic and histopathological examination compared with that of Cremophor EL. These results indicate that Aceporol 460 have higher paclitaxel-loading capacity than Aceporol 330 and less toxic effects than Cremophor EL in male and female mice.

[PA4-9] [10/18/2002 (Fri) 09:30 – 12:30 / Hall C]

Effects of aqueous extract isolated from *Platycodon grandiflorum* against oxidative stress in rat primary hepatocytes

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Herbal medicines are increasingly being utilized to treat a wide variety of disease processes. The aim of this study was to evaluate the ability of aqueous extract from the roots of *Platycodon grandiflorum* A. DC (Campanulaceae), Changkil (CK), to affect cellular response in primary cultures of rat hepatocytes to t-butyl hydroperoxide (t-BHP) induced oxidative stress and hepatotoxicity. CK-treated cells showed an increased resistance to oxidative challenge, as revealed by a higher percent of survival capacity in respect to control cells. CK added prior or simultaneously with t-BHP reduced enhanced lipid peroxidation measured as production of malondialdehyde and enhanced intracellular reduced glutathione depletion by t-BHP. Furthermore, CK protected from the t-BHP-induced intracellular generation of reactive oxygen species assessed by monitoring dichlorodihydrofluorescein fluorescence. It can be concluded that CK exerts an antioxidant action inside the cell, responsible for the observed modulation of the cellular response to oxidative challenge, and CK have a marked antioxidative and hepatoprotective potency.

[PA4-10] [10/18/2002 (Fri) 09:30 – 12:30 / Hall C]

Effects of *Platycodi Radix* on dimethylnitrosamine-induced hepatic fibrosis in rats

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Herbal medicines are increasingly being utilized to treat a wide variety of disease processes. We previously reported that aqueous extract from the roots of *Platycodon grandiflorum* A. DC (Campanulaceae), Changkil (CK), had hepatoprotective effects against acetaminophen induced liver injury. In the present study, we assayed the preventive and therapeutic effects of CK on experimental hepatic fibrosis induced by dimethylnitrosamine (DMN) in rats. Rats were given a single intraperitoneal injection of 20 mg/kg DMN twice weekly for 4 weeks. CK was given orally at 10–200 mg/kg daily for 4 weeks after the first injection of DMN. CK reduced the hepatic levels of malondialdehyde, a production of lipid peroxidation and partially prevented the marked decrease in body weight and reduced the mortality rate. The degree of fibrosis was evaluated by image analysis and also by measurements of collagen and hydroxyproline content in the liver. The expression of α -smooth muscle actin (α -SMA) in the liver was also evaluated. CK treatment significantly decreased the occurrence of DMN-induced hepatic fibrosis and reduced the collagen and hydroxyproline content and α -SMA expression in the liver. These findings indicate that CK suppress the induction of hepatic fibrosis and suggest that CK might be useful therapeutically in hepatic fibrosis/cirrhosis.

[PA4-11] [10/18/2002 (Fri) 09:30 – 12:30 / Hall C]

Protective effect of *Platycodon grandiflorum* against t-butyl hydroperoxide-induced hepatic toxicity in rats