Lee SangHo°, Kim JooYoung, Kim SungHo, Eum HyunAe, Lee SunMee

College of Pharmacy, Sungkyunkwan University, Suwon 440-746, Korea

Sepsis remains the leading cause of morbidity and mortality following trauma. Although hepatocellular dysfunction occurs during trauma and sepsis, the mechanism responsible for this remains unclear. We investigated the role of Kupffer cells in the alterations in microsomal drug metabolizing function during trauma and sepsis. Rats were subjected to trauma by femur fracture (FFx). After 72 h, polymicrobial sepsis was induced by cecal ligation and puncture (CLP). To inactivate Kupffer cells, the gadolinium chloride ($GdCl_3$, 7.5 mg/kg) was injected intravenously at 1 and 2 days prior to surgery. Liver samples were taken 2 h and 6 h (early sepsis) and 24 h (late sepsis). After CLP alone, serum AST activity and lipid peroxidation level were elevated 24 h after CLP and started to increase 2 h and remained constant upto 24 h after CLP in FFx + CLP, which were suppressed by $GdCl_3$. Total cytochrome P-450 (CYP 450) content was decreased in CLP alone. This decrease was potentiated after FFx + CLP. NADPH-CYP 450 reductase activity was reduced 6 h and again after 24 h of CLP in both CLP and FFx + CLP, which were prevented by $GdCl_3$ treatment. CYP 2B1 activity was decreased 2 h in FFx + CLP and $GdCl_3$ restored this decrease. CYP 1A1 activity was decresed 24 h in CLP alone and 6 h and 24 h after CLP in FFx + CLP. CYP 2E1 activity was decreased 24 h in CLP alone and remained depressed throughout the experiment in FFx + CLP, which were prevented by $GdCl_3$. CYP 1A2 activity was decreased 24 h in CLP alone and 6 h after CLP in FFx + CLP. We concluded that sepsis alone decreases the activity of CYP 450 isozymes during late stage of sepsis, while sequential injury potentiates this decrease during early and late sepsis. Activation of Kupffer cells may contribute to hepatocellular dysfunction.

## Poster Presentations - Field B3. Neuroscience

[PB3-1] [ 10/17/2002 (Thr) 13:30 - 16:30 / Hall C ]

### Adenosine inhibits the death in immunostimulated murine astrocytes deprived of glucose

Choi Min Sik°, Chang Eun-Sook Choi Ji Woong Yoo Byung Kwon Park Gyu Hwan Lee Woo Jong Yoon Suh Young Ko Kwang Ho

Department of Pharmacology, College of Pharmacy, Seoul National University, Seoul, Korea

Adenosine has been associated with protection of neurons from noxious stimuli both by receptor- and non receptor-mediated mechanisms. Previously we have reported that immunostimulated astrocytes were highly vulnerable to glucose deprivation. In the present study we investigated the effect of adenosine and related nucleotides on the susceptibility of immunostimulated astrocytes to glucose deprivation. While neither 12-h glucose deprivation nor 2-day treatment with IFN-γ and LPS altered the viability of astrocytes, significant death of IFN-γ/LPS-treated astrocytes was observed after 4-h glucose deprivation. The augmented astrocyte death was blocked by adenosine with an apparent EC50 value of 20 mM. However, adenosine receptor agonist R-PIA or CHA did not inhibit the augmented cell death. Moreover, adenosine receptor antagonists DPCPX, XAC or DMPX did not alter the augmented death, ruling out the involvement of adenosine receptor in this process. Other purine nucleotides including guanosine, inosine, AMP, ADP and ATP, but not pyrimidine nucleotides such as cytosine, showed similar protective effects. Intracellular ATP level rapidly decreased prior to the release of LDH in immunostimulated astrocytes deprived of glucose. Adenosine and other purine nucleotides inhibited the loss of intracellular ATP. Since high micromolar concentrations of ATP and adenosine nucleotides were released in cerebral hypoxic/ischemic regions, ATP, adenosine and their metabolites may protect the astrocyte death by restoring intracellular ATP level, at least in our experimental systems.

[PB3-2] [ 10/17/2002 (Thr) 13:30 - 16:30 / Hall C ]

### Neuroprotective effects of baicalein, baicalin, and wogonin in primary cultured rat cortical cells

Cho Jungsook[O], DokGo Hyang, Lee KwangHeun, Lee HyungKyu

College of Medicine, Dongguk University, Kyongju, Korea; Korea Research Institute of Bioscience and Biotechnology, Taejon, Korea

Oxidative stress has been implicated in the pathophysiology of many neurodegenerative disorders including Alzheimer's and Parkinson's diseases. Baicalein, baicalin and wogonin, the major constituents of Scutellaria baicalensis, have been reported to exhibit antioxidant properties in many different bioassay systems. The present study evaluated neuroprotective effects of these flavonoids on various neuronal injuries induced in primary cultured rat cortical cells by oxidative stress, NMDA, oxygen-glucose deprivation, and Aβ(25-35). Baicalein dramatically inhibited the oxidative neuronal cell injuries induced by xanthine/xanthine oxidase, and hydrogen peroxide. Wogonin and baicalin moderately inhibited the oxidative injuries. Baicalein and baicalin considerably attenuated the neuronal damage induced by a GSH depleting agent DL-buthionine-(S,R)-sulfoximine, whereas wogonin had no effect at the concentrations of 1 and 3 μg/ml. The NMDA-induced excitotoxicity was also inhibited by baicalein, and to a less extent, by wogonin or baicalin. In addition, baicalein was capable of protecting neurons from injuries generated by oxygen-glucose deprivation or Aβ(25-35). Taken together, baicalein was the most potent and efficacious neuroprotectant among the three antioxidative flavonoids originating from Scutellaria baicalensis against the neuronal injuries induced by various oxidative insults.

[PB3-3] [ 10/17/2002 (Thr) 13:30 - 16:30 / Hall C ]

## Neuroprotective Mechanisms of Aloesin against Focal Ischemic Brain Injury

Lee moon jung[O], Cho EunYoung, Lee YongHa, Jung KyungJa, Song YunSeon, Jin ChangBae

Bioanalysis & Biotransformation Research Center, Korea institute of Science & Technology, PO Box 131, Chungryang, Seoul, 136-791, Korea

Recent studies have suggested that the cerebral ischemia induced the neuronal cell death by mediating multiple mechanisms with necrosis and/or apoptosis. The present study examined neuroprotective mechanism of aloesin against transient focal cerebral ischemia. Aloesin, main component of aloe possesses various biological activates such as wound healing, anti-gastric ulcer, and chemopreventive activity. Transient focal cerebral ischemia was induced by 120 min MCAO. Aloesin (10 mg/kg, i.v.) was administered 3 times at 0.5, 2 and 4 hr after onset of ischemia. Mutiple treatments with the doses of 10 mg/kg significantly reduced infarct compared with the vehicle-treated control group, producing remarkable behavioral recovery effect. Caspase-3 mediated the cleavage of proteins that are essential for cell stability, DNA repair and activation of DNase. Neuroprotective mechanisms by aloesin in 120 min MCAO was studied using fragmentation of DNA, western blot and immunohistochemistry. DNA laddering and activated caspase-3 were decreased in infarct region by aloesin. The results suggest that aloesin can serve as neuroprotective agents by providing neuroprotection through inhibiting activation of caspase-3 in transient focal ischemic brain injury.

[PB3-4] [ 10/17/2002 (Thr) 13:30 - 16:30 / Hall C ]

## Neuroprotective effect of wogonin in a rodent model of permanent focal cerebral ischemia

Cho Jungsook[O], Lee HyungKyu

Department of Pharmacology, College of Medicine, Dongguk University;Korea Research Institute of Bioscience and Biotechnology

Wogonin, a flavonoid originated from the root of Scutellaria baicalensis Georgi, is known to exhibit potent anti-inflammatory effects and variable degrees of antioxidant and free radical scavenging effects depending on the experimental systems. In addition, wogonin has been reported to protect neurons from excitotoxic and oxidative injuries in primary cultured rat cortical cells. In the present study, we evaluated the effect of wogonin in a rat model of permanent focal cerebral ischemia induced in male Sprague-Dawley rats by insertion of a nylon monofilament to the origin of middle cerebral artery (MCA). Twenty-four hours after surgery, areas of the cerebral infarction were measured by image analyses of the seven coronal slices stained with 2,3,5-triphenyltetrazolium chloride. Wogonin (20 mg/kg), intraperitoneally administered at 30 min before and 4 h after the surgery, was found to reduce the volume of infarction in the cerebral cortex as well as in the striatum. The volume of ischemic