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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

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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

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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

damage in the cerebral hemisphere was reduced by 36.3% ($p < 0.01$). Neurological scores were also significantly improved at 24 h after the surgery ($p < 0.01$). These results demonstrate the neuroprotective effect of wogonin in a rat model of permanent occlusion of MCA and provide strong pharmacological basis for the use of Scutellaria baicalensis or wogonin in the treatment of stroke.

[PB3-5] [10/17/2002 (Thr) 13:30 - 16:30 / Hall C]

Neuroprotective Effects of Treatment with Aloesin in Rat Model of Permanent Focal Cerebral Ischemia

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Brain injury resulting from cerebral ischemia remains a major public health problem. Aloesin, main component of aloe possesses various biological activities such as wound healing, anti-gastric ulcer, and chemopreventive activity. In this study we investigated whether treatment with aloesin could protect brain injury induced by permanent focal cerebral ischemia in rats. We also compared aloesin with other neuroprotective drugs such as MK801 and ebselen. Permanent focal cerebral ischemia was induced by occlusion of middle cerebral artery for 24 hr without reperfusion in male Sprague-Dawley rat. Neurological deficit scores were measured at 24 hr after onset of ischemia immediately before sacrifice. Coronal slices of the brain were stained 2,3,5-triphenyltetrazolium chloride at 24 hr after onset of ischemia and infarct volumes was measured. Administration of aloesin (10 ㎎/㎏, i.v.) and MK801 (1 ㎎/㎏, i.p.) significantly reduced total infarct volume by 63% and 41%, respectively compared with control group. Ebselen (10 or 30 ㎎/㎏, i.p.) reduced infarct volume but not significantly. Immunohistochemical analysis was done using anti-caspase-3 antibody. DNA fragmentation was confirmed in agarose gel. Activated caspase-3 expression and DNA fragmentation was inhibited by administration of aloesin. The result suggest that aloesin can serve as a lead chemical for the development of neuroprotective agents by providing neuroprotection against permanent focal ischemic brain injury.

[PB3-6] [10/17/2002 (Thr) 13:30 - 16:30 / Hall C]

Erk activation mediates lipopolysaccharide-induced induction of matrix metalloprotease-9 from rat primary astrocytes

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In central nervous system, matrix metalloproteinases (MMPs) are produced by neuron as well as glia and implicated in physiological events such as neurite outgrowth and myelination etc. In addition, MMPs also contribute to the pathogenesis of several CNS diseases such as multiple sclerosis, Alzheimer's disease and malignant glioma. In spite of their functional importance, little is known about the signal transduction pathways leading to the induction of MMPs in CNS. Here, we investigated whether the activation of Erk(1/2) is involved in the induction of MMP-9 in LPS-stimulated primary astrocytes. The activity, protein and mRNA level of MMP-9 but not those of MMP-2 were increased by LPS treatment, which were assessed by gelatin zymography, immunoblotting and RT-PCR, respectively. LPS treatment induced activation of Erk(1/2) within 30min, which was dose-dependently inhibited by PD98059, a specific inhibitor of the Erk(1/2) kinase (MEK). In this condition, PD98059 blocked the increase in MMP-9 protein and mRNA level as well as gelatin-digesting activity. The treatment of phorbol mirystoyl acetate (PMA) activated Erk(1/2) with concomitant increase in MMP-9 production in a dose-dependent manner. The results from the present study suggest that induction of MMP-9 in rat primary astrocytes by LPS is mediated at least in part by the activation of Erk(1/2). The Erk(1/2)-mediated MMP-9 induction may provide insights into the regulation of MMP-9 production in CNS, which may occur in vivo in pathological situations such as CNS inflammation.

[PB3-7] [10/17/2002 (Thr) 13:30 - 16:30 / Hall C]

Cholinergic involvement of spatial memory impairment in μ-opioid receptor knockout mice