[OA1-1] [2004-10-22 13:30 - 13:45 / Room 205]

Hesperetin inhibits rabbit platelet aggregation by inhibition of PLCγ2 phosphorylation and cyclooxygenase activity

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The objective of present study was to investigate antiplatelet activity of hesperetin in vitro and ex vivo. In addition, possible antiplatelet mechanism was also investigated. Hesperetin concentration-dependently inhibited washed rabbit platelet aggregation induced by collagen and arachidonic acid, with IC_{50} of 20.5 ± 3.5 and 69.2 ± 5.1 μM, respectively, while has little effect on thromboxane A_2 mimic, U46619- or thrombin-mediated platelet aggregation, suggesting that hesperetin may selectively inhibited collagen-mediated signal transduction. In accordance with these findings, hesperetin revealed blocking of the collagen-mediated phospholipase C gamma2 phosphorylation, and caused a concentration-dependent decrease of arachidonic acid liberation, cytosolic calcium mobilization and serotonin release. It was also supported by the ex vivo platelet aggregation study that administration of hesperetin (100 mg/kg) potently inhibited collagen-induced platelet aggregation in rats. Furthermore, hesperetin inhibited arachidonic acid-mediated platelet aggregation by interfering with cyclooxygenase activity as established by measuring the productions of thromboxane A_2 and prostaglandin D_2 when arachidonic acid was added. Taken together, the present results provide a molecular basis for the antiplatelet activity of hesperetin, through inhibition of phospholipase C gamma2 phosphorylation and cyclooxygenase activity.

[OB3-1] [2004-10-22 13:45 - 14:00 / Room 205]

Transcriptional regulation of glial cell-specific JC virus early promoter by phorbol ester and Interlukin-1β

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JC virus causes the fatal demyelinating disease, progressive multifocalleukoencephalopathy under immunosuppressive states such as AIDS. During thepathogenesis of AIDS, HIV-infected microglia secret cytokines including interleukin-1 andtumor necrosis factor-α (TNF-α), which affect neuronal cells resulting in dysfunction of theCNS. We hypothesized that extracellular stimuli released from HIV-infected microglia mayreactivate JC virus by affecting neighboring oligodendrocytes. In the present study, wefound that PMA and interlukin-1β (IL-1β) dramatically increased JC virus transcription inglial cells. Site-directed mutagenesis and gel shift analyses revealed that PMA and IL-1βstrongly induced nuclear factor-1 (NF-1) binding to the JC virus enhancer region,increasing transcriptional activity of the viral early promoter. Additionally, wedemonstrated that protein kinase C (PKC) pathways were involved in the PMA/IL-1β-mediated up-regulation of the JC virus early promoter. These findings may represent one ofthe possible mechanisms for higher incidence of PML among AIDS patients.

[OC1-1] [2004-10-22 14:00 - 14:15 / Room 205]

Redox-sensitive Transcription Factors in Cellular Defence against Oxidative and Inflammatory Cell Death Induced by beta-Amyloid

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Oxidative stress induced by reactive oxygen species (ROS) has been considered as a major cause of cellular injuries in a variety of neurodegenerative disorders including Alzheimer's disease (AD). Rat pheochromocytoma (PC12) cells treated with beta-amyloid (Aβ), a neurotoxic peptide associated with senile plaques formed in the brains of patients with AD, exhibited increased intracellular accumulation of ROS and underwent apoptotic death. Resveratrol, an antioxidant present in grapes, attenuated Aβ-induced apoptosis and intracellular ROS accumulation. PC12 cells transfected with bcl-2 exhibited relatively high constitutive DNA binding and transcriptional activity of NF-κB, which were accompanied by the activation of ERK1/2 and Akt/protein kinase B. The ectopic expression of bcl-2 augmented cellular antioxidant capacity via upregulation of glutamylcysteine ligase (GCL) and catalase which was suppressed by NF-κB inhibitors. NF-E2-related factor 2 (Nrf2) plays a key role in regulating expression of antioxidant or phase II detoxifying genes. Transfection of PC12 cells with nrf2 rescued these cells from Aβ-induced apoptosis and intracellular ROS accumulation through upregulation of GCL. During Aβ-induced apoptosis in PC12 cells, expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) was elevated. Pretreatment with celecoxib, a selective COX-2 inhibitor or ergothioneine, a