relations for E-4031 of hERG channel block were obtained in the concentrations between 1, 10 and 100 nM. At 26°C(room temperature), 1, 10 and 100 nM E-4031 decreased hERG currents by 17, 36 and 99% respectively. IC_{50} was 14.18 nM. At 30°C(middle temperature), 1, 10 and 100 nM E-4031 decreased hERG currents by 13, 28 and 67% respectively. IC_{50} was, 6.55 nM. At 35°C(physiological temperature), 1, 10 and 100 nM E-4031 decreased hERG currents by 21, 43 and 99% respectively. IC_{50} was 9.98 nM. It may be concluded that the effect of E-4031 on hERG currents was temperature-independent.

[PA1-41] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

Studies of the functional roles of DRY motif in dopamine D2 and D3 receptors

Beom SunRyeo°, Yang JeeHyeo, Kim KyeongMan
College of Pharmacy, Chonnam National University

Asparate-arginine-tyrosine (DRY) motif is highly conserved among GPCRs, and the alternation of this motif has been reported to exist naturally and involved with various diseases that involves constitutive activation or desensitization of receptor. To understand the interaction between G protein and β-arrestin more systemically, we produced the DHY mutants for the D2R and D3R. The introduction of R to H mutation in DRY motif caused differential effects on the characteristics of D2R and D3R: for both receptors receptor-effector coupling and agonist-induced translocation of b arrestins were disrupted; for D2R agonist-induced receptor phosphorylation and receptor sequestration were blocked; the subcellular localization was not changed for D2R but more receptors were observed intracellularly for D3R; the ligand binding properties of D2R were not changed but the affinity for the antagonists was slightly increased for D3R.

[PA1-42] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

Induction of cell cycle arrest and apoptosis by an indirubin analog, a CDK inhibitor, in human lung cancer cells

Lee Jong-Won°, Moon Myung-Ju, Kim Yong-Chul, Lee Sang Kook
College of Pharmacy Ewha Womans University, Kwangju Institute of Science & Technology

Cyclin-dependent kinases (CDKs) regulate the cell division cycle, apoptosis, transcription and differentiation. Inhibition of CDK is a promising target in development of anti-cancer agents. An indirubin analog (AGM011), a CDK inhibitor, is a synthetic compound that inhibits human cancer cell growth in vitro. AGM011 showed a potent cytotoxicity in cultured human cancer cell lines (IC_{50}= 5.43 μM for A549, human lung cancer cell; IC_{50}= 1.21 μM for SNU-638, human stomach cancer cell; IC_{50}= 25.49 μM for Col2, human colon cancer cell; IC_{50}= 5.87 μM for HT1080, human fibrosarcoma cell; IC_{50}= 9.23 μM for HL-60, human leukemia cell). Prompted by the potent cytotoxicity, additional action mechanism studies were performed with cultured A549 human lung cancer cells. Using flow cytometric analysis, AGM011 showed G2/M phase cell cycle arrest and induction of apoptosis in a concentration- and time-dependent manner with characterizing apoptotic features under microscopic observation and DNA fragmentation by agarose gel electrophoresis. These results indicate that AGM011 induces the cell cycle arrest and apoptosis against human cancer cells. Therefore, it might be developed as an effective anti-cancer agent.

[PA1-43] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

Chronic administration of quercetin in rats causes the suppression of glutathione metabolism

Choi Eun Jeong°, Chee Kew-Mahn, Lee Byung Ho
Korea University, Department of Biotechnology, Korea Research Institute Chemical Technology, Medicinal Science Division

The present study was performed to investigate the effects of chronic administration of quercetin on lipid

peroxidation and glutathione concentrations in rat liver. Male Sprague-Dawley rats were divided into two groups, one of which was fed a normal diet and the other a vitamin E-free diet. Each of these groups was divided further into three subgroups and treated with quercetin administered orally at either 2 or 20 mg/day or with vehicle for four weeks. The concentrations of α-tocopherol in serum and liver increased following quercetin treatment, and these increases were significantly greater in rats maintained on a vitamin E-free diet. Quercetin significantly decreased the concentration of malondialdehyde (an indicator of lipid peroxidation) in the liver and this decrease was more pronounced in vitamin E-deprived rats than in those maintained on a normal diet (55-60% and 25-35% decrease in malondialdehyde concentrations, respectively). Quercetin treatment decreased the glutathione concentrations and glutathione reductase activity (40 and 34%, respectively) in the liver significantly and to a similar extent in vitamin E-deprived and undeprived rats. Collectively, these results suggest that quercetin may act not only as an anti-oxidant, but also as a pro-oxidant in rats.

[PA1-44] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

Suppression of RelA/p65 Transactivation Activity by a Lignoid Manassantin isolated from Saururus chinensis

Kim Kyung-Sook°, Lee Jeong-Hyung, Hwang Bang Yeon, Nam Jeong Beom, Lee Jung Joon
KRIBB and College of Pharmacy, Chungbuk National University

In our search for NF-kB inhibitors from natural resources, we have previously identified two structurally related dilignans, manassantin A and B as specific inhibitors of NF-kB activation from Saururus chinensis. However, their molecular mechanism of action remains unclear. We here demonstrate that manassantin A and B are potent inhibitors of NF-kB activation by the suppression of transciptional activity of RelA/p65 subunit of NF-kB. These compounds significantly inhibited the induced expression of NF-kB reporter gene by LPS or TNF-a in a dose-dependent manner. However, these compounds did not prevent the DNA-binding activity of NF-kB assessed by electrophoretic mobility shift assay as well as the induced-degradation of IkB-a protein by LPS or TNF-a. Further analysis revealed that manassantin A and B dose-dependently suppressed not only the induced NF-kB activation by overexpression of RelA/p65, but also transactivation activity of RelA/p65. Furthermore, treatment of cells with these compounds prevented the TNF-a-induced expression of anti-apoptotic NF-kB target genes Bfl-1/A1, a prosurvival Bcl-2 homologue, and resulted in sensitizing HT-1080 cells to TNF-a-induced cell death. Similarly, these compounds also suppressed the LPS-induced inducible nitric oxide synthase expression and nitric oxide production. Taken together, manassantin A and B could be valuable candidate for the intervention of NF-kB-dependent pathological condition such as inflammation and cancer.

[PA1-45] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

Oxyresveratrol Derivative Compound DMPB Act as Potent Dipigment agent in Brown Guinea Pig Skin

Choi Sang Yoon°, Kim Sanghee, Hwang Jae Sung, Kim Hocheol, Kim Sun Yeou
Gradurate School of East-West Medical Science, Kyunghee University, Seoul 130-701, Korea, Natural Products Reserch Institute, Seoul Natioal University, Seoul 110-460, Korea, Skin Reserch Institute, Amore-Pacific Corp, Yongin 449-900. Korea

This study with the object of reported to depigment agent, oxyresveratrol derivative, compound DMPB . Compound DMPB with a two methoxy groups and modified connection chain. It was synthesized in accordance with a simple combination process. Compound DMPB exhibits depigmentaion ability on ultraviolet B-induced hyperpigmention of the brown guinea pig skin. In addition, this Compound exhibited 30% inhibitory effect of melanin generation without cell toxicity as a result of the treatment with 100 ppm in melan-a cells. Furthermore, we are conducted to evaluate the effects of compound DMPB on tyrosinase and dopachrome tautomerase activity and revelation for investigative the pathway of inhibit melanin production. The compound DMPB had no effect on the tyrosinase. But, it showed catalyzing effect of dopachrome transformation into 5,6-dihydroxyindole-2-carboxylic acid. Our result suggested that the pigment-lightening effects of the compound may