Dimethylnitrosamine-induced Experimental Liver Cirrhosis in Rats

Cho H°, Oh TY, Ahn BO, Kim SH, Kim WB

Research Laboratories, Dong-A Pharm. Co., Ltd., Yongin, Korea

The effect of DA-9601, an Artemisia asiatica extract, on hepatic fibrogenesis or fibrosis was evaluated using experimental liver cirrhosis induced in rats by the administration of dimethylnitrosamine (DMN) intraperitoneally three times a week for 2 weeks. DA-9601 at a dose of 30 or 100 mg was orally administered to DMN treated rats daily for 3 weeks from 1 week before the DMN. Seven days after last DMN treatment, the animals were sacrificed in order to assess the degree of hepatic fibrogenesis and damage using serum biochemical, hepatic biochemical and histopathological examination. Treatment of DA-9601 significantly reduced the elevation of serum ALT, AST and total histological score on the damaged liver ($p<0.05$). The hepatic levels of collagen and malondialdehyde (MDA), an indicative of lipid peroxidation, in DA-9601 treated rats were decreased significantly when compared to DMN-treated control ($p<0.05$). In addition, immunohistochemical examination showed that DA-9601 reduced the disposition of type I collagen in the liver than DMN-treated control. These results suggest that DA-9601 may be useful to prevent the aggravation of liver cirrhosis through the inhibition of lipid peroxidation and disposition of collagen.

[OC-1] [04/21/2000 (Fri) 10:40 - 10:55 / Rm B113, Bldg 26]

Bacterial injection induced syntheses of N-b-alanyldopamine and DOPA decarboxylase in the hemolymph of coleopteran insect, Tenebrio molitor larvae

Chang Hun JOO*, Mi Hee KIM, Mi Young CHO, Tae Hyuk KWON, Kwang Moon LEE, Tae Ho LEE*, Bok Luel LEE

College of Pharmacy, *College of Natural Sciences, Pusan National University

Injection of *Escherichia coli* into larvae of the coleopteran *Tenebrio molitor* resulted in the appearance of a dopamine-like substance on the electrochemical detector. To characterize this dopamine-like substance, we purified it to homogeneity from the immunized hemolymph and determined its molecular structure to be N-b-alanyldopamine (NBAD) by the liquid chromatographic/tandem mass spectrometric (LC/MS) method. Chemically synthesized NBAD showed the same retention time on HPLC as the purified NBAD from immunized larvae. To elucidate the molecular mechanism of NBAD synthesis in vivo, we examined the enzyme activity of DOPA decarboxylase (DDC) against *E. coli* injected hemolymph of *T. molitor* larvae. The enzyme activity of DDC dramatically increased about 8 h after injection; DDC activity of injected larvae being 10-times higher than naive larvae after 24 h. To evaluate the extent of quantitative changes of DDC in *Tenebrio* response to bacterial challenge, *Tenebrio* DDC was purified to homogeneity from the whole larvae and a cDNA clone for *Tenebrio* DDC was isolated. RNA blot hybridization revealed that expression of the DDC gene was transiently activated from 3 to 8 h after *E. coli* challenge. Immunoprecipitation experiments showed that *Tenebrio* DDC was detected from 8 to 24 h in *E. coli*-injected larval extract. Thus, bacterial injection into *T. molitor* larvae might induce transcriptional activation of a DDC gene, and then synthesis of NBAD. The synthesized NBAD might be used as a substrate by phenoloxidase during melanin synthesis in the humoral defense response or the melanotic encapsulation reaction of the cellular defense response. (*Eur.J.Biochem.*in press, 2000)

[OC-2] [04/21/2000 (Fri) 10:55 - 11:10 / Rm B113, Bldg 26]

BCL-2 ATTENUATES HYDROGEN PEROXIDE- AND BETA-AMYLOID-INDUCED OXIDATIVE PC12 CELL DEATH VIA NF-KAPPA B ACTIVATION

Jang Jung-Hee° and Surh Young-Joon

College of Pharmacy, Seoul National University, Seoul 151-742

A substantial body of evidence indicates that reactive oxygen intermediates (ROIs) are implicated in pathogenesis of diverse human diseases, including cancer, diabetes, and neurodegenerative disorders. Recent studies have revealed that moderate amounts of intracellular ROIs can cause cell death via apoptosis while their excessive cellular accumulation leads to necrotic death. Cell death is regulated by plenty of functional genes and their protein products. Bcl-2 which is an integral inner mitochondrial membrane protein blocks cell death induced by a wide variety of toxicants. In the present work, we have investgated the possible protective role of *bcl-2* on oxidative death induced by hydrogen peroxide and beta-amyloid in cultured PC12 cells. Hydrogen peroxide is a typical ROI produced by xenobiotic redox molecules. It is also generated under normal physiological conditions and is recognized as an important messenger mediating the intracellular signaling in response to external stimuli. Beta-Amyloid is a peptide accumulated in the certain brain regions of patients with Alzheimer disease, and is known to exert its toxicity through ROI generation. When PC12 cells were treated with hydrogen peroxide or beta-amyloid, they underwent apoptotic death as determined by morphological features, internucleosomal DNA fragmentation and positive *in situ* terminal end-labeling (TUNEL staining). Transfection of PC12 cells with the anti-apoptotic *bcl-2* gene protected these cells from oxidative damage caused by either hydrogen peroxide or beta-amyloid. PC12 cells overexpressing *bcl-2* exhibited relatively high constitutive DNA binding and transcriptional activities of NF-kappa B, compared with the vector-transfected control cells. In addition, sustained NF-kappa B activation was observed in the *bcl-2*-overexpressing cells after treatment with hydrogen peroxide or beta-amyloid. Western blot analyses revealed that *bcl-2* transfected PC12 cells exhibited the higher level of p65, the functionally active subunit of NF-kappaB, in the nucleus than did the vector-transfected controls. In contrast, the cytoplasmic inhibitor IkappaB-alpha was present to a lower level in the cells overexpressing *bcl-2*. These results suggest that the ubiquitous eukaryotic transcription factor NF-kappa B plays a role in cell survial against oxidative stress.
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[OD-1] [04/21/2000 (Fri) 11:10 - 11:25 / Rm B113, Bldg 26]

Computer Graphics: Theoretical Study of DNA-Intercalation

Suh ME°, Park SY

Department of Medicinal Chemistry, College of Pharmacy, Ewha womans

Most DNA-intercalators bind to DNA bases, cytidines and guanidines, which are affected by hydrogen-bonding, electrostatic energy and Van der Waals energy in the DNA.
Generally, the study of DNA-intercalation has been carried out with NMR analysis, Gel-electrophoresis and so on. By the computer-aided molecular modeling, we inserted anticancers, 9 types of the Ellipticin derivatives which are already well-known as DNA-intercalators, into the DNA centers of a form (CGCG)2- DNA and b form (CGCG)2- DNA and then DNA-drug complexes were formed via docking. After energy minimization for the complexes, we observed whether hydrogen bonding was made up or not.
At the results, the existing DNA-intercalators formed hydrogen bonding with a form (CGCG)2- DNA but didn't with b form (CGCG)2- DNA.

[OD-2] [04/21/2000 (Fri) 11:25 - 11:40 / Rm B113, Bldg 26]

Facile Construction of Oxaphenalene Skeleton by peri Ring Closure. Total Synthesis of Mansonone F

Suh YG, Shin DY°, Min KH, Hyun SS, Jung JK, Seo SY