

UDCA and HS-1030 increased sub-G1 population. HS-1199 and HS-1200 also increased G1 phase population. In DNA fragmentation assay, the cells were harvested at 24 and 48 hr after the synthetic of bile acids. As results, UDCA, CDCA, HS-1030, HS-1183 and HS-1199 shows DNA ladders but not HS-1200. Western blotting performed using poly(ADP-ribose) polymerase, Bax, p53, p27, caspase-3, and cyclin E, cyclin B and -actin. In Western blots, UDCA, CDCA, HS-1030, HS-1183 lead to apoptosis. And HS-1200 shows G1 cell cycle arrest manners, interestingly only HS-1200 increased Bax level.

[PA1-12] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

Effect of Synthetic Bile Acid Derivatives on the Cell Cycle Modulation of HT-29 Human Colon Cancer Cells

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We studied the effects of ursodeoxycholic acid (UDCA) and its synthetic derivatives, HS-1030 and HS-1183, and chenodeoxycholic acid (CDCA) and its synthetic derivatives, HS-1199 and HS-1200, on the human colon adenocarcinoma cell line, HT-29 (p53 mutant type). The effects on cell viability and growth were assessed by MTT assay and cell growth study. While UDCA and CDCA exhibited no significant effect, their novel derivatives inhibited the proliferation of HT-29 cell line in a concentration- and time-dependent manners. Especially, HS-1199 and HS-1200 showed the most significant anti-proliferative effects on HT-29 cell line. According to propidium iodide staining and flow cytometry analysis, this effect may be a result from S cell cycle arrest. Furthermore, we observed the level of cyclin-dependent kinase inhibitor p21 was increased after the treatment of HS-1183, HS-1199, and HS-1200. The findings suggest that these cytotoxic effects of novel bile acid derivatives on human colon adenocarcinoma cells were mediated via apoptosis through a p53-independent pathway.

[PA1-13] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

Effects of cationic polyamines under 10 kD range of molecular weight on basic and induced mucin release from airway goblet cells

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In this study, we tried to investigate whether polymerized basic amino acid e.g. poly-L-lysine(PLL) which has the molecular weight under 10 kD significantly affects the physiological and stimulated mucin release from cultured hamster tracheal surface epithelial cells. Confluent primary hamster tracheal surface epithelial(HTSE) cells were metabolically radiolabeled with 3H-glucosamine for 24 hr and chased for 30 min in the presence of either PLLs or adenosine triphosphate(ATP) and PLL to assess the effects on basic or ATP-stimulated 3H-mucin release. Possible cytotoxicities of PLLs were assessed by measuring lactate dehydrogenase(LDH) release from HTSE cells during treatment. The results were as follows : (1) PLLs significantly inhibited basic mucin release from cultured HTSE cells in a dose-dependent manner from the range of 46mer(M.W. 9,600) to 14mer ; (2) PLL 46mer significantly inhibited the stimulated mucin release by ATP from cultured HTSE cells ; (3) there was no significant release of LDH from cultured HTSE cells during treatment. We conclude that PLLs inhibit

both physiological and stimulated mucin release from airway epithelial cells without significant cytotoxicity and PLL lost its activity under the range of 14mer. This finding suggests that polymer of basic amino acid like PLL might function as a regulator for hypersecretion of mucus manifested in various respiratory diseases.

[PA1-14] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

A newly antiarrhythmic drug CW-2202 is ideal in treating atrial fibrillation

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A number of patients suffering from atrial fibrillation are increasing and many cardiologists are trying to develop the ideal antiarrhythmic drugs for atrial fibrillation. Previously, we found out that CW-2202, a furanocoumarin derivative inhibited the hKv1.5 current expressing predominantly in human atrium without affecting the HERG current expressing mainly in ventricle. From those results, we proposed that CW-2202 would be one of the leading compound in developing the ideal antiarrhythmic drugs for atrial fibrillation. In this study, we examined the effects of CW-2202 on cardiac action potentials as well as K⁺ currents expressed in Ltk-cells using conventional microelectrode technique and patch clamp method. CW-2202 reduced the tail current amplitude recorded at -50 mV after 250 ms depolarizing pulses to +60 mV, and slowed the deactivation time course resulting in a 'crossover' phenomenon when the tail currents recorded under control conditions and in the presence of CW-2202 were superimposed. These results indicate that CW-2202 primarily block activated hKv1.5 channels in a time-, voltage-, frequency- and concentration-dependent manner. Additionally, CW-2202 prolonged the action potential durations of atrial myocytes and Purkinje fibers in a dose-dependent manner. These results strongly suggest that CW-2202 could be an ideal antiarrhythmic drug specific for atrial fibrillation.

[PA1-15] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

Induction of apoptosis by benz[f]indole-4,9-dione analog in human lung cancer cells through p53-dependent mechanism

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A synthetic naphthoquinone alkaloid, 2-amino-3-ethoxycarbonyl-1-methyl pyrolo (3,2-b) naphtho-4,9-dione (compound 1), showed a potent cytotoxicity in a panel of cancer cell lines with an IC₅₀ ranged from 0.1 to 0.3 microgram/mL. Prompted by a potent cytotoxic activity, the mechanism action study was performed with cultured A549 of human lung cancer cells. Flow cytometric analysis showed G2/M cell cycle arrest and microscopic investigation was also characterized with apoptotic morphological features. The apoptotic cell death was induced in a concentration- and time-dependent manners. In addition, Compound 1 increased p53 expression level in A549 cells. But the bcl-2 protein level was not much affected. Our results demonstrate that compound 1 may be a good candidate for additional evaluation as a potential therapeutic agent for human lung cancer and possibly other types of cancer. (This work was supported in part by Korea research Foundation Grant, KRF-2001-005-F00023).

[PA1-16] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]