signaling molecules. Thirty subtypes of PTPs have been identified in human genomes. Among PTPs, PTP1B has been suggested as a negative regulator of insulin signaling. Overexpression of this enzyme has been known as a cause of obesity and type II diabetes, so it is a target for drug discovery. However, PTPs are involved in several signaling pathways, it is possible that PTPs inhibition may give rise to unwanted side effects. Therefore, specific PTP1B inhibitors that may be free of side effects and highlight the potential of selective therapeutic efficacy in targeting PTP1B are required.
The 73,000 compounds were screened using high-throughput experimental techniques for searching compounds that inhibited PTP1B. 4-nitrophenyl phosphate assay has been used for the first assay in the format 96-well plate. Using this assay system, we have discovered 61 hit compounds. For the sencond screening, hit compounds are assayed with phosphotyrosine peptide as substrate. Finally, we test isozymes selectivity of each compounds. In this schedule, we are screening for discovering the novel drug of anti-obesity and anti-diabetes.

[PA1-8] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

Growth inhibition and cell cycle phase-specific apoptosis induced by celecoxib in human NSCLC cells in vitro.

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Cyclooxygenase-2 (COX-2) is an inducible enzyme which produces prostanoids by various stimuli. Overexpression of COX-2 in many tumor types indicates its association with tumor progression, which has been a promising target for chemoprevention and chemomodulation. We studied conc- and time-dependency of COX-2 inhibition, growth inhibition, and cell cycle arrest induced by celecoxib, a selective COX-2 inhibitor, in human non-small cell lung cancer (NSCLC) A549 cells. COX-2 activity $IC_{50}$and IC_{80} for 24hr exposure were approx. 0.1 and 1μM, respectively. The inhibition increased with prolonged exposure, i.e., 20% at 6hr to 60% at 24hr when exposed to 0.1μM. Cytotoxic IC_{50} after 6hr exposure was 110μM and decreased to 20μM after 72hr exposure. These conc were about 600 fold higher than those of COX-2 inhibition. Fifty μM (cytotoxic $IC_{80,72hr}$) of celecoxib induced G1 phase arrest and apoptosis in cells in G1 phase. In summary, (1) the drug conc inducing COX-2 inhibition and cytotoxicity were different by more than 600 folds in human NSCLC cells, suggesting that these two effects may not have direct causal relationship, and (2) growth inhibition and apoptosis induced by celecoxib are associated with G1 phase arrest, which may be important in designing of combination regimen of celecoxib. Changes in expression level of COX-2 and other factors at higher conc are under investigation to elucidate the mechanism of growth inhibition by celecoxib in human NSCLC cells.

[PA1-9] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

4-Hydroxy nonenal (HNE) Induces Apoptosis and Cell Cycle Arrest in Bovine Aortic Endothelial Cells

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4-Hydroxy nonenal (HNE) is a lipid peroxidation product derived from oxidized ω-6 polyunsaturated fatty acids, such as arachidonic acid. HNE is widely used as a marker of lipid peroxidation. To study the hypothesis that HNE may induce apoptosis and cell cycle arrest, we estimated cytotoxicity of HNE

in BAE (bovine aortic endothelial) cells. Anti-proliferative effects were examined by morphological changes and MTT assay after exposure to different time (0-3 hr) and concentration (3-7 μM) of HNE. As results, we observed apoptotic bodies with propidium iodide staining and detected induction of apoptosis by HNE with flow cytometry assay and DNA fragmentation on both conditions. We also studied apoptosis related events with Western blotting. BAE cells exposed to HNE for 0 and 3 hr resulted in increased poly(ADP-rebose) polymerase cleavage, up-regulation of Bax, and p53 proteins. Even though there was no decrease of Bcl-2 level, we observed the change of Bax/Bcl-2 ratio at a certain experimental condition. In addition, HNE caused G2 phase cell cycle arrest as flow cytometry assay. These data suggest that HNE contribute apoptosis and cell cycle arrest in BAE cells. We are under the study of cell cycle modulation effects by HNE on the levels of cyclins D and E and cdks, PCNA, pRb expression change and ATP depletion.

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

Inhibitory effects of resveratrol analogs on lipopolysaccharide-induced cyclooxygenase-2 activity in RAW264.7 cells

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It has been known that resveratrol, a phytoalexin present in grapes mainly, has antioxidant, anti-inflammatory, and cancer chemopreventive activity. One mechanism of its anti-inflammation and cancer prevention is considered to modulate cyclooxygense-2 (COX-2) activity. Since COX-2 plays an important role in inflammation and carcinogenesis, the potential COX-2 inhibitors have been considered as anti-inflammatory or cancer chemopreventive agents. In order to discover novel chemopreventive agents, we synthesized about thirty analogs of resveratrol and evaluated their COX-2 inhibitory activity with the production of prostaglandin E_2 (PGE_2) in RAW264.7 cells. As a result, several compounds showed more potent inhibitory activity than resveratrol. Especially, [3-(4-methoxyphenyl)-vinyl]thiophene (Compound 1) and [3-(4-methoxyphenyl)-vinyl]furan (Compound 2) were potential inhibitors. Further studies are under way to investigate their mechanism of action whether affecting COX-2 expression and transcriptional regulation or not. This study suggests that these compounds might be potential candidates for developing anti-inflammatory or cancer chemopreventive agents.

[PA1-11] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

The Antiproliferative Effects of Bile Acids and Their Derivatives on HepG2 Human Hepatocellular Carcinoma Cells

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We studied on the antiproliferative effects of bile acids and their derivatives on HepG2 human hepatocellular carcinoma cells. Ursodeoxycholic acid (UDCA) and its synthetic derivative HS-1030, and chenodeoxycholic acid (CDCA) and its synthetic derivatives, HS-1199 and HS?200, were used. We focused on the regulation of cell cycle and induction of apoptosis by these bile acid derivatives. Although UDCA and CDCA exhibited no significant effect on the viability of the cells utilized at the concentration ranges tested, their synthetic derivatives decreased their viability in a concentration dependent manner as determined by MTT assay. Flow cytometric analysis demonstrated that the