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Traditionally, cancer chemotherapy have focused on cytotoxic intervention at the level of DNA replication. While cytotoxic agents have shown limited efficacy against rapidly growing tumor cells, they cause serious toxic and side effects due to attack against both normal and neoplastic cells without distinction. Since the role of oncogenic ras protein in human tumors have been dicovered, medicinal chemists have paid their attention to the ras activation catalyzed by farnesyltransferase in the hope of developing cancer cell-specific agent without toxicity on normal cells. YH3939 inhibited farnesylation of H-ras and K-ras4B by purified human farnesyltransferase with IC50 values of less than 1.0 nM. Enzyme kinetic studies of YH3939 have demonstrated that it is competitive with respect to ras protein. YH3939 showed potent inhibition on anchorage dependent and independent soft agar growth of human tumor cells which express mutant K-ras. Furthermore, the processing of oncogenic ras in K-ras4B transformed fibroblast and A549 human lung tumor cell lines was disrupted by YH3939. This accounts for the ability of YH3939 to inhibit tumor cell growth and to abolish the malignancy of cancer cells by blocking oncogenic Ras activity. Therefore, our findings indicate that YH3939 is a potent inhibitor of Ras processing with robust anti-tumor properties.
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[PA1-6] [04/18/2002 (Thr) 14:00 - 17:00 / Hall E]

Antioxidative Effect of In Rat Hippocampal Slice, Compound SY-013, A New Stilbene Derivative.

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Resveratol (trans-3,4',5-trihydroxystilbene) is naturally occuring phytoalexin found in grapes. This ingredient was found to act as a antioxidant agent, anticancer agent and cardiovascular disease drug. Recently, It is feasible to study possible neuroprotective effect of resveratrol against neural injury through chronic administration of the compound to experimental animals. But, Virgili et al reported that resveratrol have not significant degree of neuroprotection because of resveratrol structure being high polar. Our study was designed to search for alternative materials like resveratrol derivatives, which having non polar, high bioactivities. SY-013 (Compound I), which is resverarol derivatives, with a lower polarity than resveratrol for Compound I was synthesized by single step process. To evaluated which Compound I could exert the protective effects on ischemic-induced neuronal damage, Compound I were treated to the reaction medium from the hipocampal slice in ischemic condition. Also It was studied for whether it is directly associated radical scavenge activity.
Our results suggest the compound I has exerted to prevent loss of ATP under ischemic condition in the hippocampal slice. And It suppressed the increase on the radical producing in PC12 cell line.

[PA1-7] [04/18/2002 (Thr) 14:00 - 17:00 / Hall E]

OST-3964, A Human Cathepsin K Inhibitor, Inhibits Bone Resorption In Vitro

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Cathepsin K is a cystein protease that plays an essential role in osteoclast-mediated degradation of organic matrix of bone. This enzyme promises the future therapy for the excessive bone resorption such as

osteoporosis. We have produced a small molecule inhibitor of human cathepsin K, OST-3964, that potently and selectively inhibits the enzyme with the subnanomolar range of IC50. We evaluated the bone resorption inhibitory potency of this agent in three in vitro systems including rabbit, rat and human osteoclast-mediated bone resorption assay .
OST-3964 demonstrated about 10 times more potent inhibition of neonatal rabbit osteoclast-mediated bone resorption than reference compound SB-357114. It also inhibited rat osteoclast-mediated bone resorption but in much higher concentration than in rabbit, reflecting the reported structural difference of cathepsin K between rat and human species. Neonatal rat osteoclasts are much smaller in size and the resorption activity is weaker than the neonatal rabbit one, and this is the first report to quantify the level of the biochemical marker of bone resorption in vitro in rat system, which is regarded as the more exact endpoint to assess the osteoclast resorption activity than commonly used resorption pit number or area. Finally, OST-3964 inhibited the human osteoclast-mediated bone resorption with similar potency to rabbit. Actually, human osteoclasts is difficult to obtain and we, through coculture of human peripheral blood monocytes and UMR-106 rat osteosarcoma cell line, made it possible.
These data show cathepsin K inhibition by OST-3964 results in a significant reduction of bone resorption in vitro and the further preclinical research is ongoing.

[PA1-8] [04/18/2002 (Thr) 14:00 - 17:00 / Hall E]

A newly developed antiarrhythmic drug CW-2201 is ideal in treating atrial fibrillation

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An ideal antiarrhythmic agent would selectively prolong the action potential duration more in extraordinarily depolarized cardiac myocytes than in normal cells, and show tissue selectively. Previously, we found out that CW-2201, a benzopyran derivative selectively inhibited the hKv1.5 current expressing predominantly in human atrium without affecting the HERG current expressing mainly in ventricle. Additionally, CW-2201 inhibited the K+ current in isolated human atrial myocytes. From those results, we proposed that CW-2201 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-2201 on the action potentials in rabbit heart using conventional microelectrode technique. CW-2201 prolonged the action potential durations of atrial, ventricular myocytes and Purkinje fibers in a dose-dependent manner. However, the effect of CW-2201 on atrial APD was frequency-dependent whereas the effect of CW-2201 on the APDs of ventricular myocytes and Purkinje fibers was not frequency-dependent. Additionally, CW-2201 induced hKv1.5 block was frequency-dependent and inhibits the human atrial K+ current. These results strongly suggest that CW-2201 could be an ideal compound for atrial fibrillation

[PA1-9] [04/18/2002 (Thr) 14:00 - 17:00 / Hall E]

Influence of CCCP on Catecholamine Secretion from the Perfused Rat Adrenal Medulla

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It has been shown that elevation of the intracellular free [Ca2+] ([Ca2+]i) triggers a wide variety of cellular functions and is a common mechanism by which external signals elicit cytosolic events (Clapharm, 1995, Berridge, 1997). An increase in [Ca2+]i can arise by release of Ca2+ from endogenous stores (mitochondria and endo/sarcoplamic reticulum) and/or influx of external Ca2+ across the plasma membrane. The membrane-permeable weak acids carbonylcyanide m-chlorophenylhydrazone (CCCP) and carbonylcyanide p-(trifluoromethoxy)phenylhydrazone (FCCP) are found to collapse the negative mitochondrial membrane potential that is the driving force for Ca2+ uptake (Gunter and Pfeiffer 1990). The contribution of mitochondria in shaping the histamine-induced Ca2+ increase was studied using ruthenium red and the two proton ionophores CCCP and FCCP in bovine adrenal chromaffin cells. Both mitochondrial uncouplers reversibly increased [Ca2+]i and induced an inward current leading to cell membrane depolarization (B?ing, 2001). Therefore, the present study was attempted to investigate the effect of CCCP