

Poster Presentations – Field A1. Pharmacology

[PA1-1] [04/20/2001 (Fri) 10:30 – 11:30 / Hall 4]

HPLC Analysis of the Conversion of Hydroxamic Acids into Their Corresponding Carboxylic Acids for Monitoring the Metabolic Hydrolysis of Hydroxamic Acid-based MMPI in Rat

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A HPLC monitoring was used to determine the metabolic hydrolysis of several hydroxamic acid-based matrix metalloprotease inhibitors in the course of the pharmacokinetic study using rat in vivo. As one of the important classes of MMP inhibitors, hydroxamic acids-based compounds are extensively studied for their inhibitory activities against varying MMPs. Many of these compounds are found to be metabolized rapidly in vivo, adversely affecting their utility in treating the disease. Further in vitro and in vivo experiments suggest that the hydrolysis of hydroxamic acids to the corresponding carboxylic acids may be the major route of metabolism of many hydroxamates. Therefore, determination of the susceptibility of these compounds to hydrolysis is critical for the synthesis and selection of metabolically stable drug candidates and for the development of improved orally bioavailable analogs.

[PA1-2] [04/20/2001 (Fri) 10:30 – 11:30 / Hall 4]

The Investigation on the Biodegradation and Release of Norfloxacin Loaded in Poly (DL-lactide-co-glycolide) (PLGA) Nanoparticle

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Various biopolymers to prepare the drug carrier have been used by many investigator due to their biocompatibility and biodegradability. Among these polymers, PLGA, the copolymer of lactide and glycolide, is suitable material as drug carrier in this point. They were approved by the Food and Drug Administration (FDA) for several therapeutic products and can formulate to release macromolecules over a long period. In this study, we prepared the nanoparticle utilizing PLGA by dialysis method without surfactant and physicochemical properties such as particle size and drug contents were investigated against various solvents. And the nanoparticles of PLGA showed good spherical shapes from scanning electron microscopy (SEM) and transmission electron microscopy (TEM) observations. Biodegradation rate of PLGA nanoparticles prepared from DMF was faster than that of acetone, indicating that the biodegradation of PLGA nanoparticles was size-dependent. Resultantly, the higher drug contents and the larger particle size resulted in slower the drug release.

[PA1-3] [04/20/2001 (Fri) 10:30 - 11:30 / Hall 4]

The mechanism of C₂-ceramide-induced contraction of smooth muscle cells in cat esophagus

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We previously have shown that C₂-ceramide (C₂) plays a role in mediating contraction of cat esophagus. We have isolated smooth muscle cells by enzymatic digestion with collagenase F. C₂ induced contraction of smooth muscle cells in cat esophagus, which is blocked by PKC inhibitors, H-7 or chelerythrine. To confirm that PKC-mediated contraction may be isozyme specific, we examined the effect of different PKC antibodies on the contraction. PKC- ϵ antibody inhibited the contraction by C₂, which suggest that PKC- ϵ may mediate the contraction induced by C₂. To characterize the specific PKC isozymes that mediate contraction of the smooth muscle cells, we used N-myristoylated peptides (Myr-PKC) derived from the pseudosubstrate sequences of PKC- $\alpha\beta\gamma$, - α , - δ , and - ϵ . Myr-PKC- ϵ only inhibited the contraction, which was concentration-dependent, suggesting that PKC- ϵ isozyme is involved in the contraction. To examine which MAP kinase is involved in C₂-induced contraction, p44/p42 MAP kinase inhibitor, PD98059, or p38 MAP kinase inhibitor, SB202190 was used. Preincubation of PD98059 only blocked the contraction induced by C₂ in a concentration dependent manner. C₂ increased the intensity of the bands identified by phosphospecific p44/p42 MAP kinase antibody and preincubation of PD98059 decreased the intensity of bands as compared with C₂ stimulated cells.

In conclusion, C₂ produced the contraction of smooth muscle cells. The contraction is mediated by PKC- ϵ -protein, resulting in the activation of p44/p42 MAP kinase

[PA1-4] [04/20/2001 (Fri) 10:30 - 11:30 / Hall 4]

Reversal of multidrug-resistance by benzodiazepin and benzotriazepin analogues in cancer cells

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A major mechanism by which tumor cells can develop resistance to anticancer drugs is by decreasing the intracellular bioavailability of the anticancer drug. Such a multidrug-resistance (MDR) phenotype of tumor cells is usually mediated by the overexpression of a membrane protein, P-glycoprotein (Pgp),