Effect of Leuteinizing Hormone-Releasing Hormone Analogue, Lorelin depot on Testostoerone Suppression and Biochemical Study in Rat

Seong Kon Seo[o1], Mork Soon Park[2], Jin Kyu Park[2] and Pyung-Keun Myung[1]

[1] College of Pharmacy, Chungnam National University, Taejon 305-764, Korea. [2]Dongkook Pharm. Co. Ltd., Jincheon, Korea

Leuprolide acetate is a potent leuteinizing hormone-releasing hormone analogue (leuprorelin, (des-Gly^{10}-D-Leu^{6}-Pro-$NHEt^{9}$)-LHRH acetate). It has been used anticancer drug by suppression the blood level of testosterone in prostate cancer. Lorelin depot, which was composed of leuprolide acetate, was designed for one-month release injectable and biodegradable microsphere of multiple high doses. Here we examined the effect of microsphere lorelin depot, in comparison with Takeda microsphere (Lucrin Depot). Lorelin (leuprolide 3.75 mg/kg of body weight) was administered s.c. to male rat and serum was obtained from rat tail vein. Enzyme immunoassay (EIA) for testosterone was carried out to investigate the effect of lorelin depot. A transient initial high peak (5-7 ng/ml) in serum testosterone level resulting from an initial burst of drug release was observed and the lorelin maintained sustained serum testosteorne levels below 0.5 ng/ml for one month. In addition, the rats were sacrificed after 42 days, morphological changes of brain and testis were observed by LM (light microscopy) and electrophoresis performed to reveal the protein changes of brain and testis.

[PC1-9] [10/20/2000 (Fri) 15:30 - 16:30 / [Hall B]]

Computer-aided molecular docking of ligands into target proteins using FlexiDock

Ahn M[o], Kim C

College of Pharmacy, Ewha Womans University, Seoul, Korea

Prediction of the binding mode of a ligand to its target protein is an important problem in rational drug design. A computer program, FlexiDock with genetic algorithm was used in this study to carry out the molecular docking operation automatically. The program allows for the full flexibility of ligands in the docking calculations, allowing the user to define the flexible bonds during the docking process.
Dihydrofolare reductase which is an attractive target for antiproliferative drug design because of its key role in the synthesis of DNA was used as a target protein. Ligands were docked into the protein active sites and the energy of the protein-ligand complexes were calculated. The results agree well with the X-ray complex structures with very small rms deviations. Docking searches also demonstrated that a new inhibitor with biological activity proven experimentally docks well into the active site of the enzyme. This program may be used to predict the precise binding mode of ligands to target proteins to discover novel lead compounds.

[PC1-10] [10/20/2000 (Fri) 15:30 - 16:30 / [Hall B]]

Powerful flexible docking of inhibitors into target enzymes with QXP

Choi I[o], Kim C

College of Pharmacy, Ewha Womans University, Seoul, Korea

We present an automatic method for docking inhibitors into enzyme binding sites with computer docking program, QXP(Quick eXPlore). Its search algorithms are derived from the method of Monte Carlo perturbation with energy minimization in Cartesian space. This program is reliable, easy to use and sufficiently rapid for full conformational search for flexible cyclic and acyclic molecules. In this study, inhibitors have been docked into dihydrofolate reductase of different species which plays an important role in the process of DNA replication and is therefore a target for anticancer, antibacterial and antifungal drugs. Docking searches of the energy minimized inhibitors have given rms differences between the docked structures and the X-ray crystal structures, of 0.06 to 1.5 Å. It has also demonstrated that a new inhibitor with biological activity proven experimentally docks well into the active site of the enzyme. The results serve to confirm the reproducibility of the program of the X-ray structures and to provide binding modes for new inhibitors to the target enzymes.

[PC1-11] [10/20/2000 (Fri) 15:30 - 16:30 / [Hall B]]

Development of a dry immunotest strip to detect tetrahydrocannabinoid

Choi JE, Lee JR, Choi MJ

Bioanalysis and Biotransformation Research Center, Korea Institute of Science and Technology, Seoul, Korea

A dry immunochromatography strip was developed to detect tetrahydrocannabinol (THC), a major active ingredient of marijuana. △8-THC-BSA was used as a detection probe on the nitrocellulose membrane where BSA was linked at 8 position of THC. Protein A purified anti-THC monoclonal antibody (isotype: IgG1) was labeled with colloidal gold and the antibody-gold conjugate as a tracer was applied on the glassfiber membrane.
Antibody was titrated to find proper coating concentration of THC-BSA on the microtiter plate and the THC binding reactivity of antibody was tested using a competitive inhibition test with samples containing known amounts of THC. The ELISA result showed the THC standard curve in the range of 2~200 ng/ml with 1 ug/ml of coating concentration.
For the dry immunochromatography test strips, a antibody-gold tracer was tested using △8-THC-BSA on the result line to find the resulting line formation by the antigen-antibody reaction. At the optimized condition, the result indicates that the test strip could detect 1 ug/ml of THC in urine.

[PC1-12] [10/20/2000 (Fri) 15:30 - 16:30 / [Hall B]]

thiols / Fe2+ system-mediated Oxidative Inactivation of brain ecto -5'-nucleotidase

Liu XW°, Sok DE

college of pharmacy, chungnam university

Ecto-5'-Nucleotidase, was purified from bovine brain membranes, and
subjected to oxidative inactivation. The 5'-nucleotidase activity decreased slightly after the exposure to either glutathione or Fe^{2+}. The glutathione-mediated inactivation of 5'-nucleotidase was potentiated remarkably by Fe^{2+}, but not Cu^{2+}, in a concentration-dependent manner. Similarly, glutathione exhibited a concentration-dependent enhancement of the Fe^{2+} of an intermediary role of superoxide ions or H_2O_2 in the action of glutathione/Fe^{2+} system, superoxide dismutase and catalase expressed a substantial protection against the inactivation by the glutathione/Fe^{2+} system. Meanwhile, hydroxyl radical scavangers such as mannitol, benzoate or ethanol were incapable of preventing the inactivation, excluding the participation of extraneous