dismutase(SOD) and glutathione peroxidase(GPX) activities increased in 3 hrs and then decreased or equaled in 6 hrs. The cell viability was declined and the antioxidant enzyme activities changed at 2.5 mM H2O2 and 50 uM cisplatin caused less alteration of the viability. Vitamin E and selenomethionine treated with 2.5 mM H2O2 were increased in the viability and changed in the antioxidant enzyme activities.

[PC1-6] [10/20/2000 (Fri) 15:30 - 16:30 / [Hall B]]

Inhibitory Effects on Several Human Carcinoma Cell Growth of Leuteinizing Hormone-Releasing Hormne Analogues, Leuprolide Acetate.

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Gonadotropin-releasing hormone (GnRH) has been shown to have an inhibitory effect on the growth of several hormone-dependent human tumors. LHRH binding sites and in vitro antiproliferative effects of LHRH analogues have been reported in human endometrial carcinoma cell. The effects of the LHRH agonist, leuprolide was studied on cell cytotoxicity, cell proliferation and cell death of the human endometrial cancer cell lines SNU-685 which was characterized in primary tumors of Korean patient and other cancer cell lines MCF-7, T24 and FB-13P. Antiproliferative effect on cells were determined by colorimetric methods, MTT and MTS/PMS assay. After 48 hr exposure to leuprolide acetate (1-300 μM), the proliferation of SNU-685 cell was reduced with a maximal decrease of about 20 % at 10 μM. Meanwhile, the proliferation of breast cancer cell line, MCF-7, urinary bladder cancer cell line, T24 or primary skin fibroblast, FB-13P cell was not affected significantly by leuprolide acetate.

[PC1-7] [10/20/2000 (Fri) 15:30 - 16:30 / [Hall B]]

Effect of p70 S6 kinase inhibitor on production of nitric oxide in RAW 264.7 cells

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$p70^{S6K}$ plays an important role in the progression of cells from G_0/G_1 to S phase of the cell cycle by translational up-regulation of a family of mRNA transcripts that encode for components of the protein synthetic machinery. Rapamycin, $p70^{S6K}$ inhibitor, has been demonstrated to inhibit the production of nitric oxide (NO) induced by lipopolysaccharide (LPS) but not to reduce the expression of inducible nitric oxide synthase (iNOS), indicating that LPS-mediated NO production occurs via FKBP12-rapamycin-associated protein-dependent pathway by a mechanism probably involving posttranslational modification of iNOS. However, the relationship between LPS-induced NO production and $p70^{S6K}$ pathway is not completely understood. Here, we investigated the regulatory mechanism of iNOS expression by rapamycin. The activity of $p70^{S6K}$ was increased in RAW 264.7 cells treated with 1μg/ml LPS, and this increase was markedly attenuated by pretreatment of rapamycin. In parallel, rapamycin decreased NO production in LPS-stimulated RAW 264.7 cells. Furthermore, treatment with rapamycin led to a decrease in iNOS protein as well as mRNA expression levels. These results indicate that the inhibition of NO production by rapamycin might be mediated by the expression of iNOS regulated at transcriptional level, not the regulation of NOS activity through a posttranslational modification.

[PC1-8] [10/20/2000 (Fri) 15:30 - 16:30 / [Hall B]]

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

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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

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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

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