aim was to investigate that curcumin can influence the early phase of fibrogenesis in animal model of fibrosis induced by carbon tetrachloride, to investigate whether curcumin could act mainly by direct action on cultured rat hepatic stellate cells in vitro, and thus to estimate the posibilities as a candidate for therapeutics agent of hepatic fibrosis.
Methods : Effects of curcumin were investigated by histological and immunohistochemical examination in a carbon tetrachloride model of hepatic fibrosis in rats . Futhermore we also examined the effects of curcumin on cultured rat hepatic stellate cells, which play an important role in the pathogenesis of hepatic fibrosis, activation to investigate whether it could act mainly by direct action on hepatic fibroblastic cells.
Results : Histological and Immunohistological examination showed that curcumin reduced the accumulation of collagen and the number of smooth muscle alpha actin positive-stellate cells in the liver. In *in vitro* study, Moreover, curcumin reduced platelet derived growth factor-induced proliferation, smooth muscle-alpha actin expression, collagen synthesis in a dose-related manner in cultured rat hepatic stellate cells.
Conclusins : These results indicated that curcumin can inhibit hepatic fibrosis as a potent inhibitor of hepatic stellate cells and thus may become a valuable anti-fibrogenic agents

[PE1-27] [10/19/2000 (Thr) 15:00 - 16:00 / [Hall B]]

Transferrin as a targeting ligand for DNA/cationic liposome complex

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Among the promising cancer therapy is targeting of the drug to tumor cells via receptor specific ligands. The use of cationic liposomes as nonviral vehicles for gene delivery is becoming increasingly prevalent in the field of gene therapy. Transferrin(Tf) has been used as a ligand for delivering liposomes mostly due to the increased number of transferrin receptors(TfR) found on tumor cells as compared to normal cells. Liposomes were prepared by reverse-phase evaporation method using dimethyldioctadecyl amoniumbromide(DDAB), cholesterol(Chol), and maleimide delivatized phospholipid(MPB-PE). Tf was conjugated to liposomes via the reaction of a MPB-PE with a thiol introduced into the protein by a heterobifunctional cross-linking agent, N-succimidyl-3-(2-pyridyldithio)propionate(SPDP). Physico-chemical characterization of Tf-liposomes was done using scanning electron microscope(SEM), transmission election microscope(TEM) and zeta-sizer. Mean diameter of liposome or Tf-liposome was about 150nm. The transfection efficiency of Tf-liposome mesured by β-galactosidase expression from pCMVβ-gal in HeLa cells was compared to Lipofectin by using 5-bromo-4-chloroindol-3-yl beta-D-galactopyranoside ('X-Gal') staining and chlorophenol red beta-D-galactopyranoside.

[PE1-28] [10/19/2000 (Thr) 15:00 - 16:00 / [Hall B]]

Preparation and Characterization of Poly(D,L -lactide-co-glycolide) Microspheres containing PEGylated Peptide

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Biodegradable poly(D,L-lactide-co-glycolide) (PLGA) microspheres containing polyethylene glyco (PEG)-modified peptides were prepared by solvent evaporation/extraction method. Insulin and salmon calcitonin were used as model peptides, which were bioconjugated with succinimidyl succinate monomethoxy-PEG (SS-mPEG) to improve biological stability. The release test was

performed in 10 mM phosphate buffer saline, pH 7.4 (containing 0.02% Tween 80), and the release properties were compared with microspheres containing native peptides. The PLGA microspheres containing native peptides demonstrated an initial rapid release in the early stage of incubation, whereas the microspheres containing PEGylated peptides rarely showed initial burst release and, instead, the release began at day 15. The release profile of PEGylated peptides from the microsphere exhibited a near zero order kinetic behavior during 20 days. Consequently, the PEG conjugation of peptide was demonstrated to be the potential way to add desirable function, (1) to minimize initial burst release and (2) to control the release rate of drug from microspheres, to the microsphere for controlled drug delivery.

[PE1-29] [10/19/2000 (Thr) 15:00 - 16:00 / [Hall B]]

Polyethylene glycol (PEG)-modified Glucagon-like Peptide-1 (GLP-1) which have increased metabolic stability and improved biological activity

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Glucagon-like Peptide-1 (GLP-1) has great potential in diabetes therapy due to its glucose-dependent stimulation of insulin secretion, but this has been limited due to its rapid degradation, primarily by dipeptidyl peptidase IV (DPP IV). To overcome this problem, GLP-1 was modified with polyethylene glycol (PEG) and the metabolic stability and biological activity was tested in vitro and in vivo. Mono-PEGylated GLP-1 was separated by size-exclusion chromatography (SEC) and characterized by matrix-assisted laser desorption/ionization time of flight (MADI-TOF) mass spectrometry. Incubation of GLP-1 with DPP IV resulted in degradation of native GLP-1 (7-36) amide to GLP-1 (9-36) amide, while mono-PEG-GLP-1 was resistant to DPP IV degradation. The in vitro and in vivo biological activities were investigated by measuring cyclic AMP production in RINm5F cells and blood glucose levels lowered after intravenous administration to rats, respectively. The results of the experiments demonstrate that modification of GLP-1 with PEG increased the plasma stability against DPP IV without impairing significantly its insulinotropic activity. This may indicate that this modification can improve the potential of GLP-1 in the treatment of type-II diabetes.

[PE1-30] [10/19/2000 (Thr) 15:00 - 16:00 / [Hall B]]

Characterization of Carbohydrate-Directed PEGylation of Ricin A Chain

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Ricin A chain, toxic subunit of plant toxin ricin from Ricinus Communis, has been modified by carbohydrate-directed PEGylation to prolong circulating half-life. The site-directed PEGylation of the carbohydrate was compared to non-specific PEGylation of amino residues of RTA. The carbohydrate of RTA was oxidized with sodium m-periodate and modified with monomethoxy polyethylene glycol-hydrazide (MPEG-HZ, MW 5,000). PEGylation of amino group of RTA was performed with mPEG-succinimydyl propionate (MPEG-SPA, MW 5,000). The PEG-modified RTAs were purified by size-exclusion HPLC and characterized by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS). RTA, RTA-MPEG-HZ and RTA-MPEG-SPA were radioiodinated by chloramine T-method and injected i.v. to rats. Blood clearance and tissue distribution were investigated. The systemic clearance of the RTA-MPEG-HZ and RTA-MPEG-SPA were reduced 64.8% and 34.1%, respectively, compared to native RTA. It was observed that RTA-MPEG-HZ was accumulated in the liver less than the RTA-MPEG-SPA and native RTA. The liver uptake of the RTA-MPEG-HZ and RTA-MPEG-SPA were reduced 62.4% and 32.6%, respectively, compared to native RTA. The kidney uptake of both RTA-MPEG-HZ and RTA-MPEG-SPA was also lower than that of native RTA. The site-directed PEGylation of the