DEVELOPMENT OF NOVEL DRUG DELIVERY SYSTEM BASED ON ORGAN-SELECTIVE INHIBITION OF DRUG ELIMINATION BY ORGAN SURFACE APPLICATION OF PROBENECID AS A MODEL

Koyo Nishida¹, Junya Nishi¹, Shintaro Fumoto¹, Mikiro Nakashima¹, Hitoshi Sasaki² and Junzo Nakamura¹

¹Graduate School of Biomedical Sciences, Nagasaki University; 1-14 Bunkyo-machi, Nagasaki 852-8521 and ²Nagasaki University Hospital of Medicine and Dentistry; 1-7-1 Sakamoto, Nagasaki 852-8501, Japan

Although there have been many studies trying to inhibit efflux transporters such as P-glycoprotein to improve drug availability in the target site, they failed due to even distribution of the inhibitors throughout the body. We attempted to develop novel drug delivery system (DDS) based on organ-selective inhibition of drug elimination process by organ surface application of the inhibitor. We examined the influence of organ (liver or kidney) surface application of probenecid, a typical inhibitor of organic anion transport and glucuronidation, on the disposition characteristics of phenolsulfonphthalein (PSP) as a model. A cylindrical diffusion cell (i.d. 18 or 9 mm) was attached to the liver or right kidney surface of the anesthetized male Wistar rats. PSP (0.5 mg) was administered intravenously at 30 min after probenecid (4 mg) was added to the diffusion cell. For comparison, probenecid was administered intravenously. Both metabolic and renal clearances of PSP were decreased by i.v. probenecid treatment, compared to control. In the case of liver surface application of probenecid, no significant difference was observed in PSP disposition characteristics, probably because of probenecid distribution in the other organs after absorption from the liver surface. While PSP renal clearance was considerably decreased to 20 % of control with no significant effect on biliary and metabolic PSP clearances by kidney surface application of probenecid. It was suggested that kidney surface application of probenecid could inhibit selectively urinary tubular secretion of PSP. Moreover, theoretical pharmacokinetic consideration was performed to optimize DDS based on organ-selective inhibition of drug elimination.

IN VIVO EVALUATION OF NUCLEAR FACTOR KAPPA B OF VARIOUS ORGANS IN RAT CARDIAC ALLOGRAFT REJECTION

Mieko Iwai¹, Yuriko Higuchi¹, Shigeru Kawakami¹, Kiyoshi Mihara², Yusuke Tanigawara¹, Fumiyoshi Yamashita¹ and Mitsuru Hashida¹

¹Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto, Japan, ²Faculty of Pharmacy, Musashino University, Tokyo, Japan, ³School of Medicine, Keio University, Tokyo, Japan

Acute allograft rejection is initiated by antigen presenting cells (APC) maturation including expression of a variety of genes involved in inflammatory cytokines and costimulatory molecules, which are regulated by nuclear factor-kappa B (NFkB). For the treatment of allograft rejection, it is important to inhibit the excess activation of NFkB in APC after transplantation. The purpose of this study was to investigate the activation of NFkB in each organ in the allograft rejection in vivo. The rat heterotopic cardiac transplantation models were prepared with Lewis rats as a recipient and ACI rats for rejection models, Lewis rats for non-rejection models as a donor. The amount of mRNA of NFkB and TNFα in grafted heart, liver, spleen, kidney and lung was measured by reverse transcriptase-polymerase chain reaction. The amount of NFkB mRNA in grafted heart following liver and spleen of rejection models was significantly larger than that of non-rejection models. To investigate the allograft rejection, the amount of TNFα mRNA was also measured. On 4 days after transplantation, the amount of TNFα mRNA significantly increased in grafted heart following liver and spleen of rejection models compared with non-rejection models. Pretreatment of GdCl₃ (20 mg/kg) significantly reduced the mRNA of NFkB and TNFα in grafted heart, liver and spleen of rejection models, suggesting the participation of APC in increase of the mRNA of NFkB and TNFα. In conclusion, APC in grafted heart, liver and spleen are the target cell to inhibit the excess activation of NFkB for the therapy of allograft rejection.