

DEVELOPMENT OF DRUG DELIVERY SYSTEM BY UTILIZING ABSORPTION FROM LIVER SURFACE AND ITS APPLICATION

Koyo Nishida, koyo-n@nagasaki-u.ac.jp, Nagasaki University, Graduate School of Biomedical Sciences, 1-14 Bunkyo-machi, Nagasaki 852-8521, JAPAN

Development of drug delivery system (DDS) to achieve site-specific delivery or prolonged retention in the circulation has attracted attention, because new types of drugs are expected to be created with advance in life science and biotechnology such as human genome project. I have tried to develop a new administration route for drug targeting to the liver, since normal drug administration by intravenous and oral route have difficulty in achieving a local site of action in the liver. Although the direct way of application to the liver surface should yield local drug distribution, the drug absorption from the liver surface had not been reported in the literature. Recently, implantable infusion pumps have been developed for treatment of several diseases, and endoscopic and laparoscopic operation techniques have made remarkable progress. Therefore, a combination of these advanced medical technologies and pharmaceutical modifications could make possible the clinical application for a drug to the liver surface in the peritoneal cavity. I have carried out systematic studies to develop a new DDS by utilizing drug absorption from the liver surface.

At first, I established an experimental system employing a cylindrical diffusion cell (i.d. 9 mm) to restrict drug absorption from the liver surface. I have analyzed the absorption mechanism of several organic anions and dextrans with different molecular weights as model drugs, after application to the rat liver surface *in vivo*, by utilizing the diffusion cell. Every compound appeared gradually in the plasma, followed by excretion into the bile and/or urine, indicating possibility of drug absorption from the liver surface. A specific transport system might not be involved in the absorption process from the liver surface, because the effect of dose and transport inhibitors on the absorption was not recognized. In addition, molecular weight and lipophilicity were found to be a determinant factor of absorption from the liver surface. The targeting efficacy to the applied region in the liver was considerably enhanced by application to the liver surface, as compared to intravenous administration. Moreover, I have obtained important physicochemical and pharmaceutical factors determining absorption rate of a drug from the liver surface, for the clinical use. Consequently, drug application to the liver surface could improve availability in the desired site of a new drug such as bioactive compound and genome medicine, by combination with appropriate chemical and pharmaceutical formulation modification.

Furthermore, I have obtained several promising results concerning application of the new DDS to anticancer drugs and gene medicine, since I found preferential distribution of 5-FU and gene transfection. On the other hand, it seems that application of a drug to other organ surfaces would be possible. I have clarified the drug absorption characteristics from the kidney, stomach, cecum and small intestine surface, and applied the physiological findings to other fields.