INTESTINAL ABSORPTION OF METHYLPREDONISOLONE BY P-GLYCOPROTEIN AND ITS REGULATION BY ESSENTIAL FATTY ACIDS IN INFLAMMATORY BOWEL DISEASES
Satoshi Wakabayashi, Mikio Tomita, Masahiro Hayashi
School of Pharmacy, Tokyo Univ. of Pharm. and Life Sci., 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

<Purpose> In inflammatory bowel diseases (IBD), the nutritional therapy is mostly performed in addition to drug therapy. Recently, essential fatty acids (EFA), such as linoleic acid (LA) and alpha-linolenic acid (α-LnA), are used in the nutritional therapy of IBD. On the other hand, methylprednisolone (MP), which is used in the drug therapy of IBD, is known as a substrate of P-glycoprotein (P-gp). We investigated the intestinal absorption and pharmacokinetics of MP and their regulation by EFA using model rats of IBD.

<Method> IBD model rats were produced by dextran sodium sulfate (DSS) treatment. Rats were fed 7% DSS in drinking water for 5 days. One % LA or 1% α-LnA was orally administered for 5 days. The protein level of P-gp and mdr1a mRNA were detected by Western Blotting and RT-PCR, respectively. Quantitative analysis of MP was carried out by UV-HPLC.

<Results> The mdr1a mRNA levels of jejunum, ileum and colon were significantly decreased in DSS-treated rats (DSS rats). The recovery effects of LA and α-LnA on the decrease in mdr1a mRNA were observed in jejunum and ileum, but not in colon. The protein level of P-gp was also decreased in jejunum in DSS rats. The administration of LA or α-LnA ameliorated the down regulation of protein level in jejunum. The P-gp function in jejunum evaluated from in vitro permeation study of MP was decreased in DSS rats, but was recovered in the EFA administration group. These results suggest that the administration of EFA decreases jejunal absorption of MP and thus, increases the selective uptake of MP into colonic epithelial cells, resulting in enhancement of the MP therapeutic effects.

FUNCTIONAL CHARACTERISTICS OF THE CARRIER-MEDIATED FOLATE TRANSPORT SYSTEM IN THE RAT SMALL INTESTINE
Sayaka Ueda¹, Katsuhisa Inoue¹, Yayoi Hayashi² and Hiroaki Yuasa¹
¹Graduate School of Pharmaceutical Science, Nagoya City University, 3-1 Tanabe-dori, Mizuho-ku, Nagoya 467-8603 and ²College of Pharmacy, Kinjo Gakuin University, 2-1723 Omori, Moriyamaku, Nagoya 463-8521, Japan

The mechanism of carrier-mediated intestinal folate transport has been of great interest because mammals require the ingestion of preformed folate (vitamin B₉) to meet their needs for one-carbon moieties to sustain key biosynthetic reactions. Reduced folate carrier 1 (RFC1) is so far the only cloned carrier that has been suggested to be involved in such folate transport. However, RFC1-mediated transport has been characterized to be optimal at near neutral pH when cloned, while carrier-mediated intestinal folate transport is known to be optimal at acidic pH. We therefore examined the functional characteristics of the carrier-mediated folate transport system in detail in the everted sacs of the rat small intestine, using tritiated folate and methotrexate, a folate analogue. The uptakes of folate and methotrexate were both highly saturable, indicating the involvement of carrier-mediated transport system at an acidic pH of 5.5, while they were negligibly small at around neutral pH. The uptakes of folate and methotrexate were mutually inhibited by methotrexate and folate, respectively, suggesting that the folate carrier is shared by methotrexate, although it has higher affinity for folate as the Michaelis constant was smaller for folate (1.2 μM) than for methotrexate (5.8 μM). These characteristics of the folate carrier are in agreement with those of a cloned pH-sensitive folate transporter (PSFT) that has recently been cloned by us, rather than RFC1. Another striking feature of PSFT activity found in the rat small intestine is that it is absent in the lower one-third of the organ. It is currently under investigation if the distribution of the mRNA of PSFT along the rat small intestine is in agreement with that of PSFT activity.