ADMINISTRATION OF ANTIBACTERIAL DRUG ALTERS BILE ACID HOMEOSTASIS THROUGH ELEVATED EXPRESSION OF BILE ACID TRANSPORTER AND SYNTHESIZING ENZYME
Masaaki Miyata, Hiroki Yamakawa, Hideaki Kuribayashi, Mayumi Hamatsu, Yuki Takamatsu and Yasushi Yamazoe
Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3, Aramaki, Aoba-ku, Sendai, 980-8578 Japan

[Purpose] Administration of antibacterial drug decreases intestinal levels of enterobacteria, that biotransform conjugated primary bile acids (BAs) into unconjugated BAs and secondary BAs, resulting in alteration of BA pool composition. Expression levels of BA transporters and synthesizing enzymes are regulated by BA signaling. In the present study, we investigate the influence of antibacterial drug administration in BA homeostasis and expression levels of BA transporters and synthesizing enzymes.

[Methods] C57BL/6N male mice were administered with 100 mg/kg of ampicillin (ABPC) for 3 days. BA compositions was determined by HPLC. mRNA levels were measured by qRT-PCR. Bsep protein amounts in hepatic crude membranes and Asbt protein amounts in ileal brush-border membranes were measured by Western blotting.

[Results] Administration of ABPC significantly increased hepatic and portal blood BA concentrations, BA amounts in intestinal lumen and biliary BA output rate whereas it decreased fecal BA excretion rate. The levels of enterobacteria-biotransformed BAs such as unconjugated BAs and secondary BAs (cholic acid, taurodeoxycholic acid, etc.) in intestinal lumen were decreased to below detection limits (< 0.01 μmol). Hepatic Cyp7a1 mRNA levels and microsomal cholesterol 7α-hydroxylase activity were significantly increased. Hepatic Bsep and ileum Asbt expression (mRNA and protein) levels were significantly increased whereas ileal Ostα/β, Ilbap, Fgf15 and Shp mRNA levels were significantly decreased.

[Conclusions] Administration of antibacterial drug increases BA pool size through elevation of both hepatic BA synthesis and ileal BA absorption due to increased expression of hepatic Cyp7a1 and Bsep, and of ileal Asbt.

PATHOPHYSIOLOGICAL ROLE OF CHENODEOXYCHOLIC ACID ON HEPATIC DISPOSITION OF METFORMIN VIA ORGANIC CATION TRANSPORTER 1 IN ACUTE CHOLESTASIS
Tomohiko Kurata, Yuichi Muraki1, Takuya Iwamoto2 and Masahiro Okuda1,2
1Department of Clinical Pharmacy and Biopharmaceutics, Mie University Graduate School of Medicine and 2Department of Pharmacy, Mie University Hospital, Mie 514-8507, Japan

[Purpose] Organic cation transporter 1 (OCT1), which regulates hepatic disposition of various cationic drugs, was reported to be decreased in patients with cholestasis as well as rats with bile duct ligation (BDL). However, little is known about the regulation mechanism of OCT1 in acute cholestasis. Hepatocyte nuclear factor 4α (HNF-4α) was recently reported to be a key regulator for the hepatic handling of drugs, and its transactivation potential may be modulated by chenodeoxycholic acid (CDCA). The present study aimed to clarify the role of CDCA on the function and expression levels of rOCT1 in acute cholestasis.

[Methods] Acute extrahepatic cholestasis was made by common bile duct ligation (BDL) of male Wistar rats (9-weeks old) for 24 hours. Hepatic uptake clearance of metformin was evaluated following i.v. bolus administration of 5 mg/kg metformin. The expression level of rOCT1 protein was analyzed by western blotting. The mRNA levels of rOCT1 and HNF-4α in rat liver and primary cultured rat hepatocytes were measured by reverse-transcription coupled real-time PCR. [Results and Discussion] Initial hepatic uptake clearance of metformin was significantly decreased in BDL rats compared with sham rats. The expression levels of rOCT1 protein and mRNA in the liver were markedly lower in BDL rats than in sham rats. In addition, HNF-4α mRNA level in the liver was significantly decreased by BDL. Furthermore, expression levels of rOCT1 and HNF-4α mRNAs in primary cultured rat hepatocytes were decreased by direct exposure to CDCA in a dose-dependent manner. [Conclusion] CDCA should mediate the decreased expression and function of hepatic rOCT1 during acute cholestasis, where decreased levels of HNF-4α may be involved.