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QUANTITATIVE ANALYSIS OF CONTRIBUTION OF OATP TRANSPORTERS FOR HEPATIC DRUG UPTAKE IN RATS
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Organic anion transporting polypeptides (OATPs) are important as a molecular mechanism for the hepatic uptake of drugs. In rat liver, Oatp1a1, Oatp1a4, and Oatp1b2 are expressed at basolateral membrane. We have previously demonstrated that hepatic uptake of beta-lactam antibiotics is likely mediated by common organic anion transporter, while molecular mechanism remains to be clarified. Recently, we reported that nafcillin, a high biliary excretion type beta-lactam antibiotic, was mainly taken up by liver via Oatp1a4 in rats and OATP1B3 in humans by in vitro, while in vivo contribution has not been examined yet. The aim of the present study was to evaluate the in vivo contribution of Oatp1a4 to hepatic handling of nafcillin in rats. Nafcillin (10 mg/kg) with or without rifampicin (20 mg/kg) as an Oatp1a4 inhibitor was i.v. administered and PK parameters were compared. Plasma concentration of nafcillin after administration in combination with rifampicin was higher than those nafcillin alone. Biliary excretion clearance and Kp liver were significantly decreased by coadministration of rifampicin. Selective inhibitor study also suggested the involvement of Oatp1a4 in hepatic uptake of nafcillin by liver. Accordingly, it was confirmed that nafcillin was predominantly taken up by the liver via Oatp1a4. So, it seems that Oatp molecules selectively transport their substrates and an identification of the contributing Oatp molecules is important to realize species difference of hepatic disposition. 1) Nakakariya M et al., Pharm. Res 25:575-585 (2008). 2) Nakakariya M et al., DMPK in press (2008).

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ASSOCIATION BETWEEN OCT3/SLC22A3 EXPRESSION AND CYTOTOXIC EFFECT OF OXALIPLATIN IN COLORECTAL CANCER CELLS
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Oxaliplatin is the third-generation platinum agent, and is used against colorectal cancers as a key drug of FOLFOX regimens. Its objective response rate for colorectal cancer is superior to cisplatin. However, the molecular mechanism(s) is unclear underlying the difference in clinical response between oxaliplatin and cisplatin against colorectal cancer. We previously reported that the substrate specificity of organic cation transporter 2 (OCT2/SLC22A2) and multidrug and toxin extrusion (MATE/SLC47A) was one of the key factors of cisplatin-induced nephrotoxicity. We also found that oxaliplatin, but not cisplatin, was transported by OCT3/SLC22A3. In the present study, we hypothesized that the substrate specificity and expression level of OCT3 affect the difference in the anticancer effect between oxaliplatin and cisplatin against colorectal cancer. In human colorectal cancer-derived cell lines, the expression level of OCT3 mRNA was higher than that of other organic cation transporters. The cells with the high level of OCT3 mRNA showed high release of LDH and accumulation of platinum after the treatment with oxaliplatin. However, the amount of platinum accumulated following cisplatin-treatment did not differ among these cells. The expression of OCT3 mRNA in cancerous and normal colon derived from Japanese patients was also measured by real-time PCR. The level of OCT3 mRNA in cancerous colon was higher than that of normal colon (P=0.0247). In conclusion, the uptake of oxaliplatin into the colorectal cancer cells via OCT3 was suggested to be one of the important molecular mechanisms for its anti-colorectal cancer effect.