MECHANISM OF HEPATOBILIARY TRANSPORT OF S-8921 GLUCURONIDE

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S-8921, synthesized at Shionogi & Co., Ltd., is a novel ileal sodium-dependent bile acid transporter inhibitor developed for the treatment of hyperlipidemia. S-8921 is metabolized to its glucuronide both in the intestine and liver. It has been elucidated that S-8921 glucuronide is more potent inhibitor for ASBT than S-8921. Most of radioactivities in the bile following oral administration of [14C]-S-8921 were associated with its glucuronide in rat, and thus S-8921 glucuronide excreted into bile may be the principal pharmacological active form. We investigated the mechanism of hepatic uptake and biliary excretion of S-8921 glucuronide in vivo and in vitro. Radioactivities associated with plasma and bile specimens following intravenous administration of [14C]-S-8921 glucuronide at 1 mg/kg in normal and Mrp2-deficient mutant rats (Sprague-Dawley rats and EHBR, respectively) were determined. The biliary clearance of [14C]-S-8921 glucuronide was decreased in EHBR compared with that in SD rats (1.5 versus 6.5 mL/min/kg), suggesting an involvement of Mrp2 in the biliary excretion. This was confirmed by in vitro study using double-transfected cells, which express both hepatic uptake and efflux transporters (OATP2/MRP2, and Oatp4/Mrp2). The basal-to-apical transport of [14C]-S-8921 glucuronide in rat Oatp4/Mrp2 double-transfected cells was observed. Such vectorial transport of this compound was also observed in human OATP2/MRP2 double-transfected cells. These results suggested that S-8921 glucuronide might be taken up into hepatocyte by OATPs and excreted into bile via MRP2 in rat and human.