HYPOCHOLESTEROLEMIC ACTION AND HEPATOBILIARY TRANSPORT OF METHYL-1-(3,4-DIMETHOXYPHENYL)-3-(3-ETHYLVALERYL)-4-HYDROXY-6,7,8-TRIMETHOXY-2-NAPHTHOATE (S-8921) GLUCURONIDE

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Hyperlipidemia, especially hypercholesterolemia, is recognized as a major risk factor for atherosclerosis, leading to coronary heart disease. The hypocholesterolemic agents currently most commonly used worldwide are the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins). Statins have a potent hypocholesterolemic action and few side effects, resulting in good patient compliance. However, statin monotherapy is not necessarily effective in some cases and, thus, combined therapy with other agents having different hypocholesterolemic mechanisms are preferable. Bile acid sequestrants are another type of hypocholesterolemic agent. Although bile acid sequestrants have a beneficial effect, their clinical use is limited. Therefore, it is important and essential to develop a novel hypocholesterolemic agent.

S-8921, synthesized at Shionogi & Co., Ltd., is a novel ileal apical sodium-dependent bile acid transporter (ASBT) inhibitor developed for the treatment of hypercholesterolemia. S-8921 inhibits the intestinal absorption of bile acids, resulting in an increase in the rate of synthesis of bile acids from cholesterol, consequently producing a hypocholesterolemic effect. Oral administration of S-8921 to Sprague-Dawley rats once a day for 3 days inhibits the ileal absorption of taurocholic acid (TCA), and this inhibitory effect reaches a maximum at 4 hr and continues for at least 24 hr after the final dosing. However, the action of S-8921 alone cannot account for the long acting inhibitory effect in rats. Most of the radioactivity recovered in the bile following oral administration of [14C]-S-8921 is associated with its glucuronide conjugate in rats, and the unchanged form is below the limit of detection. S-8921 glucuronide is the major metabolite in rat plasma and, therefore, we investigated the inhibitory effect of S-8921 glucuronide on the absorption of TCA, and its hypocholesterolemic action. S-8921 glucuronide inhibited the rat ileal absorption of TCA as potently as S-8921 in a dose-dependent manner.

In conclusion, S-8921 glucuronide is a more potent inhibitor of ASBT than unchanged S-8921 (approximately 4000 times). The disposition of S-8921 glucuronide plays an important role in its pharmacological action. S-8921 glucuronide was detected both in the portal vein and intestinal lumen after administration of S-8921 into the rat intestinal loop, indicating that S-8921 undergoes glucuronidation in the intestinal epithelial cells. Since, in EHBR (Mrp2-deficient mutant rats), the amount of S-8921 glucuronide excreted into the intestinal lumen was reduced compared with that in Sprague-Dawley rats (76% of the control), Mrp2 is involved in the efflux of S-8921 glucuronide into the intestinal lumen. Then, we investigated the hepatic uptake and biliary excretion of S-8921 glucuronide after oral administration of S-8921. The uptake study using rat hepatocytes demonstrated that [14C]-S-8921 glucuronide was taken up into the liver by carrier-mediated transport, and this uptake was saturable and consisted of both Na+-dependent and Na+-independent mechanisms. In addition, transport studies using cDNA transfected HEK293 cells demonstrated that [14C]-S-8921 glucuronide is a substrate of human OATP1B1, OATP1B3 and NTCP with Km values of 2-4 μM. The biliary clearance of [14C]-S-8921 glucuronide was markedly reduced in EHBR compared with that in Sprague-Dawley rats (1.6 versus 6.1 mL/min/kg). Thus, Mrp2 accounts for the biliary excretion of S-8921 glucuronide as well as its intestinal efflux. Finally, in human OATP1B1/MRP2 double-transfected cells, the basol-to-apical flux of [14C]-S-8921 glucuronide was much higher than the apical-to-basal flux. These results suggest that S-8921 glucuronide may be taken up into hepatocytes by OATP1B1, OATP1B3 and NTCP and excreted into bile via MRP2, and the S-8921 glucuronide excreted into the bile may take part in the pharmacological action in addition to that formed in the intestinal epithelial cells, and excreted into the lumen.

In conclusion, S-8921 glucuronide is a more potent inhibitor of ASBT than its parent compound, and responsible for the hypocholesterolemic action of S-8921. S-8921 glucuronide is formed in the intestine and liver after oral administration of S-8921, and MRP2 is involved in its efflux into the intestinal lumen and bile duct. S-8921 glucuronide is cleared from the blood by multiple transporters, including OATP1B1, OATP1B3 and NTCP in the liver.