IMPROVEMENT OF ORAL DRUG ABSORPTION THROUGH THE INHIBITION OF BREAST CANCER RESISTANT PROTEIN BY PHARMACEUTICAL EXCIPIENTS
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The oral delivery route is the most acceptable route of administration, being more natural and less invasive. It was found that active efflux in the intestinal epithelium is one of mechanism limiting oral absorption of drugs, and thus, inhibition of the active efflux is one of the strategies to improve oral absorption of drugs. Indeed, P-glycoprotein (P-gp) is a well-known ABC transporter limiting oral absorption of drugs, and several excipients are known to inhibit P-gp in the intestine, thereby increasing the oral absorption of P-gp substrates. Recently, breast cancer resistance protein (BCRP/ABCG2) has been demonstrated to limit oral absorption of its substrate compounds in the intestine. The purpose of this study was to examine whether excipients can be used as inhibitor of BCRP. In vitro accumulation studies with BCRP expressing MDCK-II cells elucidated that excipients such as Pluronic P85 and Tween 20 strongly inhibited BCRP function. To further characterize the inhibitory effect of excipients on BCRP function, we performed in vivo oral and intravenous drug administration study in mice. Topotecan was used as test compound which has been shown that BCRP limits oral absorption. Pluronic P85 and Tween 20, given orally 15 min before topotecan administration, increased the area under the plasma concentration-time curve (AUC) of topotecan after oral administration (Fig. 1 (A) and (B)), whereas they were less effective on the AUC of topotecan after intravenous administration in wild-type mice. The ability of excipients to enhance the oral drug absorption can be ascribed to increasing solubility of drugs in the intestinal lumen and/or inhibition of efflux transporters. To obtain a direct evidence, we also examined the effect of excipients in Bcrp (-/-) mice. In Bcrp (-/-) mice, Pluronic P85 and Tween 20 did not affect the AUC of topotecan after oral (Fig. 1 (C) and (D)) and intravenous administration, indicating that increasing drug solubility by the excipients had a minimal effect.

To assess whether Pluronic P85 and Tween 20 might inhibit intestinal BCRP function, we performed in vitro transport study using the everted mouse intestine. Pluronic P85 and Tween 20 significantly increased intestinal absorption rate of topotecan in isolated intestine of wild-type mice, whereas they were no effective in that of Bcrp (-/-) mice, suggesting that Pluronic P85 and Tween 20 could inhibit intestinal BCRP function.

Topotecan is also a weak to moderate substrate for P-gp. Therefore, we investigated intestinal P-gp expression and transport function of wild-type and Bcrp (-/-) mice using a western blot analysis and in vitro transport study in the everted mouse intestine, respectively. These results suggest that there was no significant difference in the intestinal P-gp expression and transport function between wild-type and Bcrp (-/-) mice.

We conclude that Pluronic P85 and Tween 20 can improve the oral bioavailability of BCRP substrates by inhibiting the function of BCRP in the small intestine.

Fig. 1 Plasma topotecan concentration versus time curves in wild-type and Bcrp (-/-) mice orally treated with or without excipients. Wild-type mice (panel (A) and (B)) or Bcrp (-/-) mice (panel (C) and (D)) were given an oral dose of Pluronic P85 (panel (A) and (C)) or Tween 20 (panel (B) and (D)) 15 min before oral dose of topotecan (1 mg/kg). Results are expressed as the mean ± S.D. (n=3). *p < 0.05, **p < 0.01 : Statistically significant differences between with and without treatment of excipients.