POLYETHYLENEIMINE AS A NOVEL POTENTIAL ABSORPTION ENHANCER FOR IMPROVING THE SMALL INTESTINAL ABSORPTION OF POORLY ABSORBABLE DRUGS
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[Purpose] Recently, various kinds of absorption enhancers have been adopted to improve the intestinal absorption of poorly absorbable drugs including calcitonin and alendronate. However, the effects of many conventional absorption enhancers were generally much greater in the large intestine than those in the small intestine. In this study, to develop a highly effective absorption enhancer in the small intestine, we selected polyethylenimine (PEI), a cationic polymer, as an absorption enhancer and examined the effects of PEI on the small intestinal absorption of poorly absorbable drugs.

[Methods] 5(6)-carboxyfluorescein (CF), calcitonin and alendronate were used as models of poorly absorbable drugs, and various types of PEI were used. Intestinal absorption of drugs was examined by an in situ closed loop method using male Wistar rats. Blood samples were collected, and then plasma concentrations of drugs were analyzed. To evaluate intestinal membrane damage, the release of lactate dehydrogenase (LDH) was measured after the absorption study.

[Results and Discussion] The absorption of CF from the small intestine was significantly improved by the co-administration of PEI and its absorption enhancing effect was concentration-dependent. PEI also significantly increased the small intestinal absorption of calcitonin and alendronate. Next, we evaluated intestinal membrane damage in the presence of PEI. The LDH activity was increased by the co-administration of PEI, suggesting that PEI caused intestinal mucosal damage to some extent, but it was much lower compared to the conventional enhancers.

[Conclusions] In conclusion, PEI is effective for improving the small intestinal absorption of poorly absorbable drugs including calcitonin and alendronate.

ROLE OF OXIDATIVE STRESS ON DECREASED INTESTINAL ABSORPTION OF CYCLOSPORINE A BY LIVER ISCHEMIA-REPERFUSION INJURY IN RATS
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[Purpose] Our previous study suggested that the oral bioavailability of cyclosporine A (CsA) was decreased by increased first-pass metabolism due to elevated CYP3A and P-glycoprotein specifically in the upper small intestine after liver ischemia-reperfusion (I/R) injury (Ikemura et al., J Pharmacol Exp Ther, 328: 249-55, 2009). The aim of the present study is to clarify factor(s) mediating the decreased intestinal absorption of CsA by liver I/R injury. [Methods] Rats were subjected to 60 min partial hepatic ischemia and treated intravenously with an antioxidant TroloxTM (an analogue of α-tocopherol) (2.5 mg/kg) or vehicle 5 min before reperfusion. At 12 h after reperfusion, the rats received CsA at doses of 10 mg/kg for both oral administration in vivo and intraloop administration to the upper small intestine by in situ loop method. Oxidative stress was assessed by the determination of malondialdehyde (MDA) in plasma.

[Results and Discussion] Plasma MDA level was significantly increased by liver I/R, and this increase was prevented by Trolox administration prior to reperfusion, suggesting antioxidative effect of Trolox. Trolox restored the decreased area under the blood concentration-time curve of orally administered CsA by the liver I/R injury to the levels of those in sham rats. Furthermore, initial absorption rate of CsA in the upper small intestine was comparable to those in sham rats when Trolox was used. [Conclusions] These results suggest that oxidative stress should play a key role in the decreased oral bioavailability of CsA by the liver I/R injury. In addition, administration of Trolox prior to reperfusion could be beneficial for preventing decreased bioavailability of CsA by the liver I/R injury.