FUNCTIONAL EXPRESSION OF CARNITINE/ORGANIC CATION TRANSPORTER OCTN1 (SLC22A4) IN MOUSE SMALL INTESTINE
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[Purpose] Carnitine/organic cation transporter OCTN1 (SLC22A4) is expressed in various organs and transports various organic cations in vitro, although its physiological role in vivo has not yet been clarified. Recently, we have clarified that ergothioneine (ERGO), a naturally occurring antioxidant, is a good in vivo substrate for OCTN1. Therefore, the aim of the present study is to clarify the functional expression of OCTN1 in small intestine using ERGO as a typical substrate. [Methods] We used octn1 gene knockout (octn1-/−) mice for in vivo studies. Plasma concentration and tissue distribution of [3H]ERGO after i.v. and p.o. administration were compared between wild-type and octn1+/− mice. Small intestinal transport of [3H]ERGO was examined in the everted sac and isolated enterocytes. [Results and Discussion] Tissue-to-plasma concentration ratio of [3H]ERGO in almost all organs of octn1-/− mice was much lower that in wild-type mice, indicating that ERGO is an in vivo substrate for OCTN1. Gastrointestinal absorption after p.o. administration of [3H]ERGO in octn1+/− mice was lower than that in wild-type mice. This result was compatible with much lower uptake of [3H]ERGO in everted sac prepared from octn1+/− mice, compared with wild-type mice. The uptake of [3H]ERGO in everted sac of wild-type mice was much reduced when Na+ was replaced with other cation, suggesting Na+-dependent transport of [3H]ERGO by OCTN1. The uptake of [3H]ERGO was also observed in isolated small intestinal cells. [Conclusions] OCTN1 is functionally expressed in mouse small intestine and would be involved in gastrointestinal absorption of its substrate.

CONTRIBUTION OF P-GLYCOPROTEIN AND CYTOCHROME P450 3A TO INTESTINAL FIRST-PASS DISPOSITION IN RATS
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[Purpose] Drug efflux by intestinal P-gp may decrease the bioavailability of many CYP 3A substrates. In this study, we tried to evaluate the effect of P-gp and CYP3A on the intestinal absorption and availability of drugs in rats. [Method] Intestinal absorption of digoxin was investigated by the simultaneous perfusion technique of intestinal lumen and blood vessels utilizing dexamethasone (DEX)-treated rats with different expression levels of P-gp and CYP3A, and the intestinal absorption clearance and intestinal extraction ratio were estimated for digoxin. Midazolam was chosen as an inhibitor of both P-gp and CYP3A to investigate their effects on the absorption kinetics of digoxin by using the in-vitro Ussing chamber method and simultaneous perfusion technique. Using the parameters obtained in the above studies, the transport clearance via P-gp and metabolic clearance via CYP3A were calculated. [Result and Discussion] There was not any notable change in the intestinal absorption clearance, but the intestinal extraction ratio significantly increased in DEX-treated rats compared with control rats. The addition of midazolam concentration-dependently decreased the intestinal extraction ratio, but did not significantly change the intestinal absorption clearance. The multiple linear regression analysis did not indicate quantitative contribution of each protein to the intestinal extraction of digoxin. However, the metabolic process via CYP3A was suggested to be more important by the metabolic clearance and transport clearance via P-gp calculated based on the in-vitro transport study. [Conclusion] The absorption clearance of digoxin is not affected by the change in P-gp or metabolic activity, but the intestinal extraction of digoxin was regulated by both proteins and CYP3A would be more important.