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INVOlVEmENt OF OATp TRANSPORTER IN INTESTINAL ABSORPTION OF FLUOROQUINOLONE CIPROFLOXAXIN
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Many reports suggested that transporters are involved in the tissue distribution and excretion of fluoroquinolones, including efflux transporters BCRP and P-gp. However, no influx transporters had been identified. Recently, we demonstrated that several fluoroquinolones are substrates of OATp1A23, which is presumed to be expressed at the apical membrane of human small intestinal epithelial cells. However, it is not clear whether intestinal absorption of fluoroquinolones is explained by such transporters or not. The present study was aimed to clarify the contribution of transporters in the intestinal absorption of fluoroquinolones in rats by focusing mainly on oatp1a5, which is expressed at apical membranes of enterocytes. Ciprofloxacin showed increased uptake by oatp1a5-expressing Xenopus oocytes. Appearance of ciprofloxacin in the intestinal vascular perfusate was increased in the presence of ivermectin and 7,8-benzoﬂavone, inhibitors of P-gp and bcrp, respectively, after administration into the jejunal- and ileal-loops in rats, which was consistent with changes in the disappearance from each intestinal loop. Furthermore, the increased permeability of ciprofloxacin by ivermectin and 7,8-benzoﬂavone was signiﬁcantly decreased by the coadministration of several oatp1a5 inhibitors (fexofenadine, naﬁnigine, and taurocholate), showing that the both of oatp and efflux transporters could be involved in the intestinal membrane transport of ciprofloxacin. These results suggested that oatp1a5 is responsible for the intestinal absorption of ciprofloxacin at least partially.


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INVOlVEmENt OF CONCENTRATIVE NUCLEOSIDE TRANSPORTERS (CNTs) IN INTESTINAL ABSORPTION OF FTD, A NOVEL ANTITUMOR NUCLEOSIDE, IN RATS
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A novel functional antitumor nucleoside, a combined form of α,α,α-trifluorothymidine (FTD) and its metabolic inhibitor, is being developed. In Caco-2 cells monolayer membrane permeability study, FTD hardly penetrated to cell membrane, while was rapidly appeared in plasma after oral administration to human and rats. Thus in vitro permeability was not consistent with in vivo absorption. In this study, we investigated the intestinal uptake of FTD in rats to clarify the apical absorption mechanisms, and identified the reason for the difference in permeability of FTD between Caco-2 cells and small intestinal tissues. To investigate the uptake mechanism of FTD to small intestinal tissue, the inverted sacs method was conducted by using rat small intestine. Transport experiments in Xenopus oocytes expressing rat CNTs were performed to confirm involvement of these transporters in the intestinal absorption of FTD. Furthermore, expression of CNTs mRNA in rat small intestine and in Caco-2 cells were also determined by RT-PCR technique. In inverted sacs experiments, uptake of FTD occurred in biphasic manner, indicating some uptake mechanisms existed in small intestine. The uptake of FTD was remarkably reduced under the Na+-free condition, and was inhibited by pyrimidine nucleosides, NaNO3 and 2,4-DNP. The uptake of FTD by Xenopus oocytes expressing rat CNT1, not CNT2, was significantly greater than that by water-injected oocytes, and the Km value of FTD for CNT1 was about 55 μmol/L. Furthermore, CNT1 mRNA was detected in rat small intestine, but not detected in Caco-2 cells. In conclusion, It is considered that no expressions of CNTs in Caco-2 cells are one of the reasons why FTD shows low permeability in Caco-2 cells monolayer. These results suggest that CNT1 play an important role of the small intestinal absorption of FTD.