Function and Regulation of Peptide Transporters

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Peptide transporters expressed in the small intestine and kidney mediate the absorption of di- and tripeptides, and also function as drug transporters to transport various peptide-like drugs such as oral β-lactam antibiotics. We have clarified physiological and pharmacokinetic significances of H^+/peptide cotransporters (PEPT1 and PEPT2) and the basolateral peptide transporters based on the molecular and cellular biological characterization and *in vivo* analyses.

1. cDNA Cloning, Structure and Functional Analyses of PEPT1 and PEPT2

cDNAs for rat PEPT1 and PEPT2 were isolated, and their structure, expression and transport characteristics were determined. The usefulness of the intestinal PEPT1 for drug delivery of poorly absorbed drugs was demonstrated. Using mutagenesis and amino acid modification techniques, essential histidine residues for transport function were identified.

2. Computational Simulation of PEPT1 and the Basolateral Peptide Transporters

Modeling and computer simulation techniques were applied to transporter studies for PEPT1 and the basolateral peptide transporter. Using this novel methodology, efflux properties of the basolateral peptide transporter were clarified, and the transport models of PEPT1 for various charged substrates (14-state model) were proposed and verified.

3. Regulation and Transcriptional Mechanisms of PEPT1

Expression profiles of 20 kinds of drug transporters including PEPT1 along the human digestive tract were determined. We demonstrated that the intestinal PEPT1 was regulated by fasting and diurnal rhythm, and that these regulations affected the pharmacokinetic properties of substrate drugs. Transcription factors to regulate the PEPT1 gene expression such as Sp1, Cdx2 and PPARα were identified for the first time.