A Novel Strategy for Drug Delivery System Using a Claudin Modulator

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Recent progress in pharmaceutical genomics and proteomics has made it possible to perform high-throughput screening of drug candidates. However, current drug delivery systems are useful for only a few drugs, and a more widely applicable system is needed. The first step in the absorption of any drug is crossing of the epithelia. Therefore, modulation of paracellular uptake is an attractive target for the delivery of a wide variety of drugs to target tissues. Claudin is integral membrane protein that acts as the sealing component of tight junctions. Here, we examined whether a claudin modulator, the C-terminal fragment of *Clostridium perfringens* enterotoxin (C-CPE), can be used for the development of a drug delivery system. Treatment of rat jejunum with C-CPE enhanced the absorption of dextran (MW 4000) without injuring the intestinal mucosa. C-CPE was 400-fold more potent at enhancing the jejunal absorption of dextran than capric acids, which are clinically used to enhance absorption. C-CPE lacking part of the C-terminus did not bind to claudin-4 and did not enhance jejunal absorption. To determine functional residue in the C-terminus, we performed site-directed mutagenesis. We found that several amino acids play a pivotal role in binding to claudin and enhancing absorption. These findings are the first to suggest that a claudin modulator is a promising candidate for modifying drug absorption and, therefore, as drug delivery system.