Investigation of Drug Transport Mechanism: Experience with H_2-Antagonists and New Chemical Entities

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Drug metabolism and pharmacokinetics disciplines have been widely applied throughout drug discovery process in an effort to optimize pharmacokinetic properties in parallel with potency and selectivity, thereby decreasing the attrition rate in drug development phases. Since current drug discovery efforts are focused mainly on oral therapeutics, understanding the oral absorption characteristics of new chemical entities has become an important task during the discovery process. Among various factors known to affect oral drug absorption intestinal transport often plays an important role. Intestinal transport occurs via diverse mechanisms including passive diffusion, carrier-mediated transport and transcytosis; the transport characteristics of a drug molecule are defined by its transport mechanism. Delineating the transport mechanism, therefore, will provide important insights toward understanding the oral absorption characteristics of a drug molecule.

My presentation aims to discuss the findings of our investigation on the intestinal transport mechanism of the H_2-antagonists, ranitidine and famotidine, and some new chemical entities. In our studies using Caco-2 cells as an *in vitro* model for the human intestinal epithelium we found that the secretory transport of both the H_2-antagonists and the new chemical entities were facilitated by active transport systems. Our studies further demonstrated that the putative secretory transporters are distinct from known drug transporters such as P-gp, MRP, and OCT; the molecular identity of the putative transporters remains to be determined. In summary we have identified unknown transport systems that facilitate the secretory transport of H_2-antagonists and new chemical entities in Caco-2 cells.