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Peptide delivery—pitfalls and possibilities

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Non-invasive delivery of peptide and protein drugs will soon become a reality. This is due partly to the repertoire of new technologies that promise to improve the bioavailability of peptide and protein drugs from the oral, buccal, nasal, pulmonary, and transdermal routes of drug administration. Polymers that are either degradable, mucoadhesive, or site-specific are a key element of these technologies. A potential pitfall is the lack of attention to polymers that may manipulate the biology of the underlying epithelial cells, thereby altering drug absorption.

During the past three years, chitosans of varying degrees of acetylation and molecular weight have been investigated as potential penetration enhancers. The efficacy and toxicity of these polycationic polymers are a function of their degree of acetylation and molecular weight. In an attempt to improve the aqueous solubility of chitosans at neutral pH, Kotzé et al. partially quarternized (12%) chitosan of 25% acetylation and found that the resulting derivative elicited prompt, pronounced, and reversible opening of the tight junctions in Caco-2 cells. The net result was a 32- to 60-fold increase in mannitol (m.w. 182) transport, a 167- to 373-fold increase in FITC-dextran 4,000 (m.w. 4,400) transport, and a 28- to 73-fold increase in buserelin (m.w. 1,300) transport.

In 1994, we reported that 4-phenyl-azobenzoxy-carbonyl-Pro-Leu-Gly-Pro-D-Arg (Pz-peptide, m.w. 777), a hydrophilic pentapeptide that is a substrate for collagenase-like enzymes, was transported essentially intact across the descending colon and other intestinal segments. The extent of intestinal penetration of Pz-peptide was better than that of more lipophilic atenolol, timolol and propranolol. Presumably, Pz-peptide was transported across the intestinal mucosa mainly as a result of its action on the tight junctions.

Another development contributing to the realization of noninvasive delivery of peptide and protein drugs via transmucosal routes is a better understanding of the endogenous transport mechanisms, including paracellular transport, carrier-mediated transport, and transcytosis. A pitfall is that insufficient effort has been committed to cataloging the assortment of transport mechanisms in each absorptive mucosa.

To date, the alveoli of the lungs and the conjunctiva of the eye are the only two absorptive mucosae besides the intestinal mucosa that are demonstrated to be equipped with the full complement of drug transport mechanisms, namely, simple diffusion, carrier-mediated transport, and endocytosis. Using rat alveolar cell primary cultures, we demonstrated that Gly-L-Phe was transported by a carrier-mediated mechanism whereas Gly-D-Phe permeated the alveolar epithelial monolayers by a paracellular simple diffusion mechanism. The latter was also the case for thyrotropin releasing hormone and arginine vasopressin. Equivalent pore analysis based on the transport of FITC-dextrans of m.w. spanning 4 to 40 kD revealed a population of large equivalent pores with 5.6 nm radius, through which polar solutes may pass. By contrast, insulin and horseradish peroxidase appeared to undergo non-specific fluid phase endocytosis. Both proteins were metabolized to the extent of approximately 50%.

In addition to endocytosis as a mechanism for transporting macromolecules, the conjunctiva appears to be capable of transporting dipeptides by the H^+-coupled dipeptide transporter PepT1 or its isoform. An iteractive series of studies based on molecular modeling, site-directed mutagenesis, and peptide uptake studies has revealed Tyr 167 and several other amino acid residues in the twelve membrane-spanning domains of the PepT1 transporter as being critical to its function.