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Cover story

Rational design of agents to transiently increase paracellular permeability

Oral delivery of peptide and protein drugs has been a long-sought goal of the pharmaceutical industry. Beyond the obvious benefits of improved patient convenience and compliance, oral administration could also better align the biological properties for those biopharmaceuticals whose primary site of action involves targets within the intestine, its submucosa, and/or the liver. Extensive efforts have been made to overcome the poor absorption of biopharmaceuticals from the small intestine and/or colon. It is relatively easy to protect labile biopharmaceuticals from acidic condition in the stomach and from the maelstrom of enzymatic activities within the small intestine [1]. Once deposited on the apical surface of the intestinal mucosa, however, physical and biological barriers imposed by the intestinal epithelia to non-selective uptake of macromolecules ultimately block the efficient oral delivery of biopharmaceuticals.

Small molecular drugs are typically absorbed across the intestinal mucosa by a mechanism that involves partitioning events between membrane lipid and aqueous environments, a process known as transcellular transport. The physicochemical properties of biopharmaceuticals (e.g., hydrodynamic radius and hydrophilicity) are incompatible with transcellular transport. Thus, other approaches have been explored, such as receptor-mediated endocytosis, which might lead to transcytosis. The majority of efforts to overcome the epithelial barrier, however, have focused on enhancing the movement of solutes between adjacent enterocytes, known as paracellular transport. Here, the goal is to transiently open the paracellular route by altering/disorganizing the properties of tight junction structures to improve the flux of peptide and small protein therapeutics, such as calcitonin and insulin [2]. In this approach, formulation additives for enhancing paracellular flux have been identified through empirical efforts with subsequent studies attempting to understand and define their mechanism of action.

In this issue, Professor Randall Mrsny and his group at the University of Bath describes the opposite approach, identifying formulation components to incite a defined mechanism of action [3]. In this case, an endogenous mechanism that dynamically controls tight junction function through the phosphorylation state of myosin light chain (MLC) was targeted by rationally designed agents. Their approach is innovative in several ways. They rationally designed new permeation enhancing agents to affect specific cellular targets, in this case protein–protein contact sites, which modulate regulatory proteins that control the function of MLC phosphatase (MLCP). These enhancing agents were designed to be stable in the intestinal environment and membrane permeable to allow them to reach the interior of enterocytes where MLCP functions at tight junction structures to control epithelial barrier properties.

Since the duration of action for these permeant inhibitors of phosphatase (PIP) peptides will correlate with their residence time in enterocytes to block regulatory-MLCP events, their actions in vivo will be transient, with the duration dependent upon intracellular residence time and potency. The Mrsny team showed that the MLC phosphorylation state correlated with uptake of a biologically active solute (insulin), that topically applied PIP peptides localized to intracellular sites adjacent to tight junction structures, and that delivery of insulin into the portal circulation could be achieved; providing crucial support for the anticipated mechanism of action. Thus, one of the most valuable benefits from these studies is that a defined mechanism of action can now be monitored during safety and efficacy studies that involve higher species and possibly during human trials. Lack of a defined mechanism of action has been a limitation in the development of previous approaches involving increased paracellular permeability, since the empirical nature of these formulations can require continued empirical 'tuning' when moving between species.

Finally, work from the Mrsny group represents how current efforts in peptide and protein pharmaceuticals are moving toward using cellular and systemic biological principles to address challenges that previously were examined by physicochemical strategies. Our improved understanding of how biological barriers of the body function in health and disease has provided new clues and possible approaches to identify improved drug delivery strategies. The true potential application of this approach can only be assessed by more studies involving multiple exposures using clinically viable oral dosage forms. These caveats notwithstanding, the work by the Mrsny team represents an important leap forward in rational formulation design for enhancing the paracellular uptake of biologically active peptide and small protein therapeutics.

References

[1] Sam Maher, Ben Ryan, Aoife Duffy, David J. Brayden, Formulation strategies to improve oral peptide delivery, Pharm. Pat. Anal. 3 (3) (2014) 313–336.
[2] Vivek Gupta, Byeong Hee Hwang, Nishit Doshi, Samir Mitragotri, A permeation enhancer for increasing transport of therapeutic macromolecules across the intestine, J. Control. Release 172 (2013) 541–549.
[3] Alistair Taverner, Ruggero Dondi, Khaled Almansour, Floriane Laurent, Siân-Eleri Owens, Ian M. Eggleston, Nikoletta Fotaki, Randall J. Mrsny, Enhanced paracellular transport of insulin can be achieved via transient induction of myosin light chain phosphorylation, J. Control. Release 210 (2015) 189–197.

Kinam Park
Purdue University
Departments of Biomedical Engineering and Pharmaceutics
West Lafayette, IN 47907, USA
E-mail address: kpark@purdue.edu

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