Journal of Pharmaceutical Sciences 105 (2016) 484–496

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Review

Why Does the Intestine Lack Basolateral Efflux Transporters for Cationic Compounds? A Provocative Hypothesis

William R. Proctor [1], Xin Ming [1], David Bourdet [1], Tianxiang (Kevin) Han [1], Ruth S. Everett [2], Dhiren R. Thakker [2,*]

[1] Division of Molecular Pharmaceutics, UNC Eshelman School of Pharmacy, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599
[2] Division of Pharmacotherapy and Experimental Therapeutics, UNC Eshelman School of Pharmacy, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599

ARTICLE INFO

Article history:
Received 8 October 2015
Revised 18 November 2015
Accepted 20 November 2015

Keywords:
intestinal absorption
intestinal epithelia
transporters
organic cation transporter
drug transport
metformin

ABSTRACT

Transport proteins in intestinal epithelial cells facilitate absorption of nutrients/compounds that are organic anions, cations, and zwitterions. For two decades, we have studied intestinal absorption and transport of hydrophilic ionic compounds, with specific focus on transport properties of organic cations and their interactions with intestinal transporters and tight junction proteins. Our data reveal how complex interactions between a compound and transporters in intestinal apical/basolateral (BL) membranes and tight junction proteins define oral absorption, and that the BL membrane lacks an efflux transporter that can transport positively charged compounds. Based on our investigations of transport mechanisms of zwitterionic, anionic, and cationic compounds, we postulate that physicochemical properties of these ionic species, in relation to the intestinal micro pH environment, have exerted evolutionary pressure for development of transporters that can handle apical uptake/efflux of all 3 ionic species and BL efflux of anions and zwitterions, but such evolutionary pressure is lacking for development of a BL efflux transporter for cationic compounds. This review provides an overview of intestinal uptake/efflux transporters and describes our studies on intestinal transport of cationic, anionic, and zwitterionic drugs that led to hypothesize that there are no cation-selective BL efflux transporters in the intestine.

Introduction

The intestinal epithelium is a formidable barrier to the absorption of orally administered small molecule drugs, which constitute a majority of the marketed pharmaceutical products. The rationale for this is clear; it is the single layer of cells that separates the intestinal lumen and the blood supply to the intestine, and thus, as a first line of defense, must prevent the entry of the intestinal contents into the systemic circulation. The physical and biochemical architecture of the intestinal epithelium is designed to optimize the absorption of nutrients, but at the same time it creates an effective barrier to protect the body against foreign compounds.[1]

The intestinal epithelium comprises tightly packed columnar cells, called enterocytes, interspersed with a small number of other types of cells with specialized function (e.g., secretion of mucin or hormones). The tightly packed enterocytes provide both the absorptive surface, as well as a barrier to the drugs being absorbed across the intestinal epithelium. The highly constrained intercellular space between neighboring enterocytes is further restricted by the presence of the “tight junctions.” These tight junctions are multiprotein complexes that form pore-like structures spanning the intercellular space by the interactions of extracellular folds of transmembrane proteins such as the occludins and claudins.[2,3] The tight junctions not only restrict the movement of drug molecules across the epithelium but also restrict the movement of proteins

Present address for William R. Proctor: Department of Safety Assessment, Genentech, Inc. South San Francisco, CA.
Present address for David Bourdet: Department of Clinical Pharmacology and DMPK, Theravance Biopharma U.S., Inc., South San Francisco, CA.
Present address for Tianxiang (Kevin) Han: Department of Metabolism and Pharmacokinetics, Bristol-Myers Squibb, Princeton, NJ.
Conflict of interest: The authors disclose that they have no personal, financial, or nonfinancial conflicts of interest.
* *Correspondence to:* Dhiren R. Thakker (Telephone: +1-919-962-0092; Fax: +1-919-966-3717).
E-mail address: dhiren_thakker@unc.edu (D.R. Thakker).

http://dx.doi.org/10.1016/j.xphs.2015.11.040
0022-3549/

that are embedded in the cell membrane and the lipids that make up the membrane, such that the lipids and proteins on one side of the tight junction cannot traverse to the other side of the tight junction. As a result, the enterocyte membrane on one side of the tight junction that faces the intestinal lumen, called the apical (AP) membrane, contains distinctly different lipids and proteins than does the membrane on the serosal side of the tight junctions, that is, the basolateral (BL) membrane.

Absorption of drugs from the intestinal lumen into the bloodstream requires that the drugs traverse the single layer of enterocytes that line the intestinal lumen (Fig. 1a). Although lipophilic nonionic drugs can traverse the epithelium by transcellular passive diffusion (that involves concentration gradient-driven diffusion across the AP membrane, through the cytosolic space, and across the BL membrane), hydrophilic and charged small molecule drugs require transport proteins to facilitate their transcellular movement. Hydrophilic compounds, either charged or uncharged, can traverse the epithelium *via* paracellular transport, which involves concentration gradient-driven diffusion through the intercellular space across the tight junctions; but this process is much less efficient than transcellular passive diffusion because of a lower surface area that is available to drug molecules for paracellular versus transcellular transport and because of the additional restriction to movement across the tight junctions.

There are numerous transport proteins in the AP membrane (Fig. 1b) that have evolved to facilitate the absorption of nutrients such as amino acids, peptides, sugars, lipids, and vitamins, as well as other organic anions, cations, and zwitterions. These transporters are generally known as uptake transporters. In addition to uptake transporters that facilitate the transport of compounds across the cell membrane into the cell, the enterocyte membrane also contains the so-called efflux transporters that can actively pump compounds across the membrane from the inside of the cell to the outside. Efflux transporters in the AP membrane of the enterocytes attenuate the absorption of compounds by either preventing their entry from the intestinal lumen into the cell or actively pumping the compounds out of the cell across the membrane. Examples of these transporters include P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance–associated protein 2 (MRP2) (Fig. 1b). These transporters are also known as ABC transporters, a reference to the presence of the amino acid sequence that is ATP binding cassette. Although there are exceptions, P-gp typically transports lipophilic cations and a few lipophilic neutral compounds, the MRP family of transporters typically transports anionic or zwitterionic compounds and BCRP typically transports anionic compounds but can also transport cations. It is intuitive that compounds that require transporters to enter the cell across the AP membrane would also require transporters to exit the cell across the BL membrane for

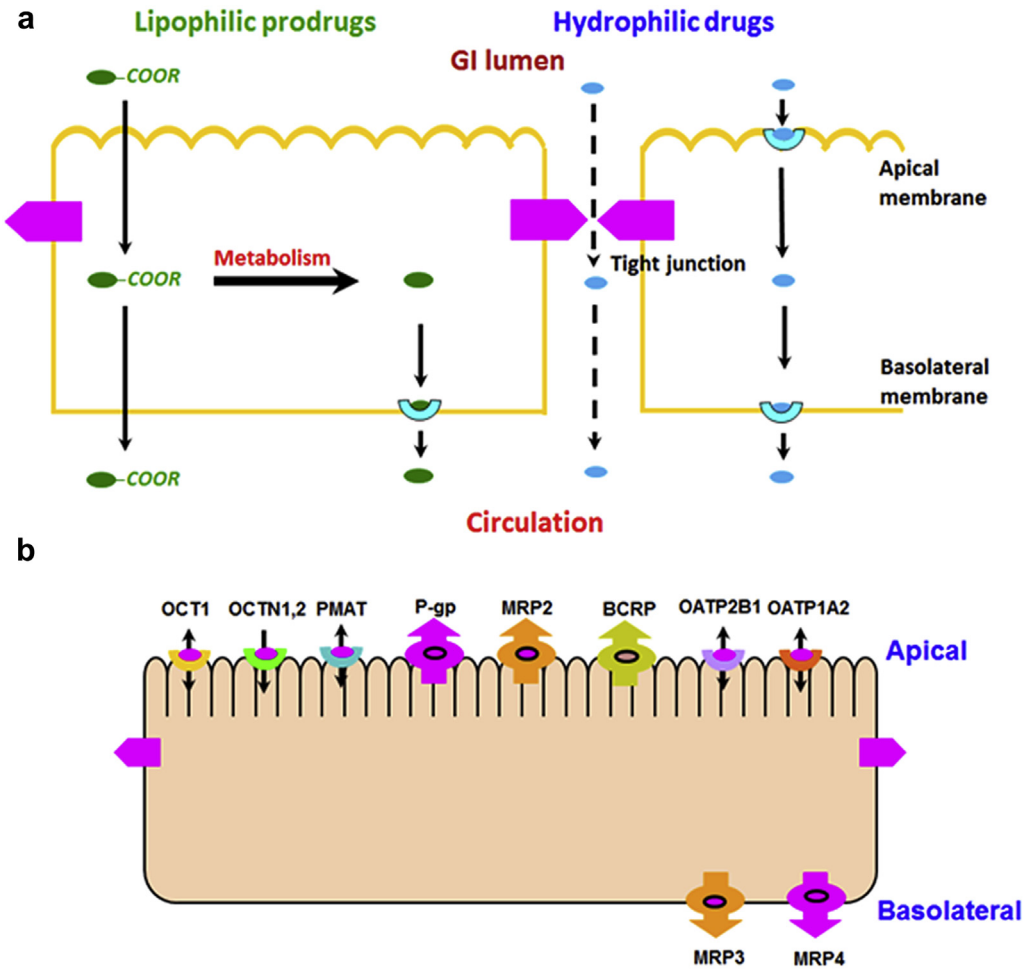

Figure 1. (a) An overview of the intestinal absorption of drugs and prodrugs. For hydrophilic drugs, BL transporters are as important as AP transporters in the efficient transcellular transport of drugs across the intestine. Carrier-mediated BL efflux may control the transcellular transport of some prodrugs. (b) Major human intestinal drug transporters. Arrows denote transport direction.