Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Pharmacology

Go with the flow — membrane transport in the gut

Editorial overview

David T Thwaites

Current Opinion in Pharmacology 2013, **13**:843–846

For a complete overview see the Issue

Available online 19th October 2013

http://dx.doi.org/10.1016/j.coph.2013.09.019

David T Thwaites
Institute for Cell & Molecular Biosciences, Faculty of Medical Sciences, Framlington Place, Newcastle University, Newcastle upon Tyne NE2 4HH, UK
e-mail: d.t.thwaites@ncl.ac.uk

David Thwaites is Professor of Epithelial Physiology at Newcastle University. His research interests are in understanding how mammalian membrane transporters operate by identifying the physiological function, molecular identity and substrate selectivity of nutrient and drug transporters in the gastrointestinal tract, kidney and in cancer tissues.

The primary function of the gastrointestinal tract is the assimilation of nutrients from diet. The final stages of digestion and almost all absorption take place in the small intestine and, to a lesser extent, the large intestine. Thus, the intestinal epithelium, the single layer of polarised, differentiated cells that lines the wall of the intestine, sits at the interface between the outside world and the internal environment of the human body. It is across this epithelial barrier that all essential nutrients, vitamins, electrolytes and fluid are absorbed. Many toxins and waste products can be secreted directly across the intestinal epithelium or excreted through the biliary route. The gastrointestinal tract is of great interest to the pharmacologist, and the pharmaceutical industry beyond, because most patients, if given the opportunity, would choose to take medication orally rather than have it delivered by any other route. In addition, many drugs and metabolites are lost from the body by active secretion from the intestine and liver. Thus, the intestinal epithelium is a major target for clinical intervention to improve bioavailability and modulate gut function.

To allow net transport in either the absorptive or secretory direction, the polarised cells in the small intestine (enterocytes), large intestine (colonocytes) and liver (hepatocytes) express a distinct set of membrane transport proteins in their apical and basolateral membrane domains. Each epithelial cell type mediates net solute and ion movement through the coordinated activity of an array of membrane transport proteins (primary active transporters or pumps, secondary active cotransporters or antiporters, and channels).

The series of 10 reviews in this edition of Current Opinion in Pharmacology have been written by leading experts in each respective field and focus on the function of membrane transporters in the gastrointestinal tract. These membrane transport proteins can be viewed as targets for pharmacologists for three reasons. Firstly, membrane transporters in the gut can directly transport drugs and metabolites, either in the absorptive or secretory direction. Thus, membrane transporters can be targeted to improve bioavailability of orally delivered drugs. Secondly, membrane transporters and channels can be targets *per se* for pharmacological intervention by selective inhibitors or enhancers, where such intervention may be required under certain pathophysiological conditions. Thirdly, membrane transport protein expression can be modulated either by upregulation or downregulation in pathophysiological situations where there is a requirement to either augment or reduce transport, respectively.

The first article in this series, by Misaka, Müller and Fromm [1], highlights recent observations from clinical studies in humans regarding the function of the drug efflux pumps P-glycoprotein (ABCB1), breast cancer resistance

protein (BCRP, ABCG2) and multidrug resistance protein 2 (MRP2, ABCC2), in the gut. These drug efflux proteins function as important defence mechanisms by protecting the body from toxins but also secrete drugs and metabolites into the intestinal lumen. The article reviews recent observations that emphasise that these efflux pumps are important in drug transport as they limit bioavailability of drugs, are sites of drug–drug interaction, and are subject to both inhibition and induction, both of which will modify rates of drug transport [1]. The second article by Tang, Hendrikx, Beijnen and Schinkel [2], nicely complements that by Misaka *et al.* [1] but focuses on evidence from studies using genetically modified mice. Tang *et al.* [2] include information on both secretory and absorptive transporters highlighting the potential key roles in intestinal drug transport of the multidrug resistance proteins Mrp2, Mrp3 (Abcc3), and Mrp4 (Abcc4), the organic cation transporters Octn1 (slc22a4) and Octn2 (slc22a5), and the equilibrative nucleoside transporter Ent1 (slc29a1). A recent review by van Waterschoot and Schinkel [3] summarises information from genetically modified mice for the important roles of the ATP-binding cassette (ABC) transporter P-glycoprotein and the drug metabolising enzyme cytochrome P450 3A (CYP3A) in intestinal drug handling, and very nicely supplements those by Misaka *et al.* [1] and Tang *et al.* [2].

A key observation from the reviews described above is that expression and activity of the drug efflux pumps may be subject to modulation by factors from the gastrointestinal lumen. This theme is continued in the next three reviews. Tamai and Nakanishi [4] review recent findings with the organic anion transporting polypeptide OATP2B1 (SLCO2B1) which is expressed at the brush-border membrane of the human small intestine and is involved in absorption of drugs such as the anti-allergy drug fexofenadine. Evidence supports the presence, within OATP2B1, of either multiple binding pockets for distinct substrates or multiple binding sites within a single pocket. OATP2B1 function and expression are modulated by common components of fruit juices (e.g. flavonoids) demonstrating that OATP2B1 in the intestine is a site not only for drug–drug but also drug-food/beverage interactions. Wenzel [5] continues this theme and describes recent investigations into the roles of dietary flavonoids in the control of both absorptive and secretory transporters in the small intestine. Evidence is available to support roles for dietary flavonoids in control of both glucose absorption and homeostasis, and drug efflux across the intestinal wall. These natural compounds will likely prove useful lead structures in the development of treatments for diabetes and cancer. The review by Ganapathy, Thangaraju, Prasad, Martin and Singh [6] focuses on the fascinating mutual relationship between man and the prokaryotic content of his colonic lumen. The signalling factors are the short chain fatty acids (SCFA) butyrate and propionate produced in the colon by bacterial fermentation of non-digested dietary fibre. The SCFAs 'signal' by either undergoing transport by the sodium-coupled monocarboxylate transporter SMCT1 (SLC5A8) or by binding to the SCFA receptors GPR109A and GPR43. The anti-inflammatory and tumour-suppressive functions associated with these transporters and receptors highlights them as potential targets for pharmacologists in the development of tools for the treatment of inflammatory bowel disorders and colonic cancer.

Another absorptive transporter with potential for development as a target in cancer treatment is the proton-coupled folate transporter PCFT (SLC46A1). Zhao and Goldman [7] review the latest observations with this folate carrier which is expressed at the luminal surface in the small intestine and is defective in hereditary folate malabsorption. Antifolates used in cancer treatment are delivered intravenously but PCFT could play an important role in reabsorption from the gut lumen of those undergoing enterohepatic circulation. Antifolates with selectivity for PCFT (over the ubiquitous reduced folate carrier RFC (SLC19A1)) are being developed and the increased activity of PCFT at the acidic pH values found in solid tumours could favour this carrier as a route for targeted delivery of anticancer agents. Like PCFT, the proton-coupled di/tripeptide transporter PepT1 (SLC15A1) is also expressed at the brush-border surface of the human small intestine and is responsible for both nutrient and drug transport. PepT1 is perhaps the best characterised of all the absorptive SLC/solute transporters with potential as targets for oral drug delivery. Brandsch [8] summarises recent studies with PepT1 which is a major mechanism for the absorption of several β-lactam antibiotics and the anti-viral prodrug valacyclovir. Brandsch [8] also highlights the potential of a prodrug approach to improve oral bioavailability of poorly absorbed compounds and discusses recent developments with new PepT1 prodrug substrates of zanamivir, oseltamivir and didanosine. Targeting drugs to intestinal absorptive transporters to improve oral bioavailability requires detailed knowledge of the substrate specificity of each individual transport protein. There are many carrier proteins that could prove to be useful portals for drug transport across the brush-border membrane of the intestinal epithelium, which is perhaps the first major barrier to drug absorption. PCFT [7] and PepT1 [8] were chosen here as pardigms but many other transporters with similar potential as routes for drug transport across the wall of the human small intestine exist and they have been reviewed elsewhere [9,10].

The remaining three articles in this special edition focus on fluid and electrolyte transport in the gastrointestinal tract. Thiagarajah and Verkman [11] provide an excellent review of recent advances in the development of