Drug Transport and Targeting

Intestinal Transport

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1. INTRODUCTION

The intestine is the major absorption site for nutrients such as amino acids and sugars. Water and electrolytes, such as $\text{Na}^+$, $\text{K}^+$, $\text{HCO}_3^-$, $\text{Cl}^-$, $\text{Ca}^{2+}$, and $\text{Fe}^{2+}$, are also transported via the intestine to body fluids. One or more mechanisms transport these solutes and ions across the intestinal epithelia, including passive diffusion, facilitated diffusion, and active transport. In addition, pinocytosis occurs at the base of microvilli and may also contribute to the uptake of protein (Johnson, 1997).

Different regions of the intestine exhibit distinct transporters and significant variability in permeability. For example, the bile acid transporters are only found in the lower part of the small intestine, the ileum. Membrane transporters in the intestine also show axial heterogeneity. If a pathological process destroys primarily brush border membrane cells, the absorptive capacity of the epithelium will be impacted to a much greater extent than the secretory capacity. There are several clinical disorders that involve membrane transporters. Hartnup disease, for example, is a hereditary disorder in which the active transport of dipolar amino acids is de-
ficient in both renal tubules and the small intestine. The disease is usually benign, because protein digestive products are also absorbed in the form of small peptides.

While a variety of drugs are absorbed from the intestine by passive diffusion, the absorption of hydrophilic drugs is enhanced by specific transporters in the intestine. Many peptide-like drugs, such as cephalosporins and angiotensin-converting enzyme (ACE) inhibitors, depend on the intestinal dipeptide transporter for efficient absorption. Nucleosides and their analogues for antiviral and anticancer drugs also depend on the nucleoside transporters to be taken up. Therefore, utilization of the intestinal epithelial transporters to facilitate the absorption of drugs or prodrugs appears to be an attractive strategy for improving the bioavailability of poorly absorbed drugs (Tsuji and Tamai, 1996).

The purpose of this chapter is to generally describe the pharmaceutical and pharmacological relevance of intestinal transporters. Detailed information on individual intestinal transporters are described elsewhere in this book. In this chapter, selected transporters will be discussed as drug delivery and targeting sites for better bioavailability.

2. INTESTINAL TRANSPORTERS

2.1. General Description of Intestinal Transporters

There are a variety of membrane transporters in the intestinal membrane as shown in Table I. Various solutes, such as amino acids, sugars, peptides, nucleosides, bile acids, inorganic phosphate, organic anions and cations, as well as several vitamins, are absorbed by their own specific transporters. Many transporters, including the following, are located in the brush border (or apical) membrane: Na⁺/B amino acid transporter, β-aminic acid transporter, Na⁺/glucose cotransporter, fructose transporter, and Na⁺/nucleoside transporter. Some transporters are only located in the basolateral membrane: Na⁺/A amino acid transporter, Na⁺/ASC amino acid transporters, GLUT2 hexose transporters, and Na⁺-independent folic acid transporter. Among others, the following exist in both membranes: y⁺ amino acid transporters, Na⁺/H⁺ antiporters, and inorganic phosphate transporter.

Many transporters have isoforms. For example, the facilitated glucose transporters (GLUT) have five different isoforms (Wright et al., 1994). Among them, GLUT5 is found in the brush border membrane, and GLUT2 is located in the basolateral membrane of the human intestine. In the brush border membrane one can find the Na⁺/glucose cotransporter (SGLT1), which is responsible for sugar absorption. Glucose and galactose are transported into the enterocyte across the brush border membrane by SGLT1, and then they are transported out across the basolateral membrane by a facilitated sugar transporter (GLUT2). Fructose is tak-