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Pharmacology & Therapeutics 109 (2006) 399 – 412

Pharmacology & Therapeutics

www.elsevier.com/locate/pharmthera

Associate editor: L.H. Lash

Human renal organic anion transporters: Characteristics and contributions to drug and drug metabolite excretion

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Abstract

The kidney is a key organ for promoting the excretion of drugs and drug metabolites. One of the mechanisms by which the kidney promotes excretion is via active secretion. Secretion of drugs and their metabolites from blood to luminal fluid in the nephron is a protein-mediated process that normally involves either the direct or indirect expenditure of energy. Renal transporters for organic anions are located in the proximal tubule segment of the nephron. The primary transporters of organic anions on the basolateral membrane (BLM) of proximal tubule cells are members of the organic anion transporter (OAT) family (mainly OAT1 and OAT3). The sulfate–anion antiporter 1 (SAT-1; hsat-1) may also contribute to organic anion transport at the basolateral membrane. On the apical membrane, the multi-drug resistance-associated protein 2 (MRP2) is an important transport protein to complete the secretion process. However, there are several transport proteins on the basolateral and apical membranes of proximal tubule cells in human kidneys that have not been fully characterized and whose role in the secretion of organic anions remains to be determined. This review will primarily focus on the human renal basolateral and apical membrane transporters for organic anions that may play a role in the excretion of drugs and drug metabolites.

Keywords: Kidney; Organic anions; Transport; Human; Excretion

Abbreviations: α-KG, α-ketoglutarate; aa, amino acid; ABCC, Family C of the ATP-binding cassette superfamily; AG, acetaminophen glucuronide; BBM, brush border membrane; BLM, basolateral membrane; DHEAS, dehydroepiandrosterone sulfate; $E_2$17βG, estradiol glucuronide; ES, estrone sulfate; MRP, multi-drug resistance-associated protein; NPT1, type 1 sodium-dependent inorganic phosphate transporter; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OATV1, voltage-driven organic anion transporter 1; PAH, *p*-aminohippurate; SAT-1, sulfate–anion antiporter 1; URAT1, urate transporter 1.

Contents

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doi:10.1016/j.pharmthera.2005.07.005

1. Introduction

The kidney is a key organ for the excretion of drugs and drug metabolites, as more substances are eliminated from the body by renal excretion than any other route (Rozman & Klaassen, 2001). The 2 major mechanisms by which a drug may be renally excreted from the body are glomerular filtration and active secretion of compounds from blood to the fluid within the lumen of the nephron. In a single pass through the kidneys, about 20% of the renal blood flow undergoes filtration at the glomeruli of the nephrons. Substances that are not protein bound in plasma and have molecular weights less than the large plasma proteins may become part of the glomerular filtrate. However, compounds bound to plasma proteins such as albumin are not available for glomerular filtration. If filtered substances are not reabsorbed from the glomerular filtrate as they pass through the nephron, then the compounds will end up in urine and be eliminated from the body.

Tubular secretion can occur as a facilitated transport mechanism down an electrochemical gradient or as an active process (or dependent upon an active process) requiring energy to move chemicals against an electrochemical gradient. Tubular secretion of organic ions is a very efficient process that occurs in the proximal tubule of the nephron and is normally an active process at either the basolateral and/or apical membrane.

Drugs or their metabolites that are substrates for active secretion in the proximal tubule can be organic anions (negatively charged species) or organic cations (positively charged species). Distinct pathways exist for transporting organic anions and cations within proximal tubule cells. Each organic ion transport system has requirements for substrate specificity, transport mechanisms, and proximal tubule localization. In this review, the focus will be on the organic anion transporter (OAT) systems that play a role in the renal secretion of drugs and drug metabolites with an emphasis on what is known about the human systems.

1.1. Tubular secretion of organic anions

Tubular secretion involves protein-mediated uptake of the drug or drug metabolite at the basolateral membrane (BLM) and protein-mediated efflux at the brush border membrane (BBM), also referred to as the apical or luminal membrane. The transport proteins in the membranes affect the apparent permeability of the membrane to organic anions in a substrate-specific manner. During the secretory process, as studied in perfused tubules (mammalian and non-mammalian), the steady-state concentration of organic anion inside the cells is greater than in the tubule lumen (glomerular filtrate), which is greater than in the peritubular fluid/bathing medium (Dantzler, 2002). This process can only occur because the BBM is more permeable to the substrate than is the BLM, a condition that has been demonstrated in numerous species and is requisite of uptake at the BLM being the rate-limiting step in transepithelial transport (Dantzler, 2002). This condition, however, does not hold true for all organic anions. Terlouw et al. (2003) states that in general, the efflux mechanism at the luminal membrane is less efficient than basolateral uptake, resulting in accumulation of organic anions. This condition has been demonstrated for many of the antiviral drugs for which efflux at the BBM is rate limiting, resulting in intracellular accumulation (Russel et al., 2002).

Uptake of substrate at the BLM is often measured as the net accumulation within the cell. Because both cellular energetics (available counter-ions or ATP) and apical efflux will affect net accumulation, uptake is assessed at the initial rate of uptake, during the linear phase for the purpose of kinetic analysis (Sugiyama et al., 2001). Thus, a time course study is normally conducted to determine the linear phase of uptake.

Transepithelial transport can be evaluated in vitro using monolayers of renal cells grown on semipermeable membranes. Transport is evaluated by determining the substrate concentrations in both compartments (basolateral and apical) at the end of an incubation period and calculating