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Renal organic anion transporters in drug–drug interactions and diseases

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ABSTRACT

The kidney plays a vital role in maintaining systemic homeostasis. Active tubular secretion and reabsorption, which are mainly mediated by transporters, is an efficient mechanism for retaining glucose, amino acids, and other nutrients and for the clearance of endogenous waste products and xenobiotics. These substances are recognized by uptake transporters located in the basolateral and apical membranes of renal proximal tubule cells and are extracted from plasma and urine. Organic anion transporters (OATs) belong to the solute carrier (SLC) 22 superfamily and facilitate organic anions across the plasma membranes of renal proximal tubule cells. OATs are responsible for the transmembrane transport of anionic and zwitterionic organic molecules, including endogenous substances and many drugs. The alteration in OAT expression and function caused by diseases, drug–drug interactions (DDIs) or other issues can thus change the renal disposition of substrates, induce the accumulation of toxic metabolites, and lead to unexpected clinically outcome. This review summarizes the recent information regarding the expression, regulation, and substrate spectrum of OATs and discusses the roles of OATs in diseases and DDIs. These findings will enables us to have a better understanding of the related disease therapy and the potential risk of DDIs mediated by OATs.

1. Introduction

The kidney is a major excretory organ and participates in the control of systemic sodium and water homeostasis (Wang and Sweet 2013; Yacovino and Aleksunes 2012). The normal renal function is one of the determinants of the elimination of metabolic products, the balance of plasma colloid osmotic pressure and crystal osmotic pressure, and the excretion of exogenous drugs and environmental exposures (Pelis and Wright 2014). When the blood flows through the kidney, substance in plasma is subject to glomerular filtration and active tubular secretion and reabsorption and finally eliminated from the body in the urine (Emami Riedmaier et al. 2012). Through the process, the kidney retains the essential nutritions (e.g., glucose, protein, amino acid, sodium ion, potassium ion and sodium bicarbonate) and removes metabolic waste products and xenobiotics (e.g., creatinine, uric acid, uremic solutes, antiviral drugs and antibiotic) (Chen et al. 2015b; Yin and Wang 2016). The active tubular secretion and reabsorption are mainly mediated by numerous transporters in the basolateral and apical membranes of renal proximal tubule cells, which is totally different from the passive transport during glomerular filtration (Yacovino and Aleksunes 2012; Yin and Wang 2016). Transporters involved in tubular secretion and reabsorption mainly belong to two major superfamilies — ATP-binding cassette (ABC) and solute carrier (SLC) (Koepsell 2013; Konig et al. 2013). Due to the important role in the disposition of endogenous substances as well as drug safety and efficacy, membrane transporters have attracted great attention and been list as a key recommendation for sponsors to consider when evaluating drug-drug interactions by FDA (Giacomini et al. 2010; Morrissey et al. 2013). Generally, SLC transporters extract substrates from the fluid into the epithelium, while ABC transporters extrude substrates out of cells. In the kidney, members of SLC22 family with high expression levels in the plasma membrane of renal tubular epithelial cells are responsible for the substrate uptake from the blood or the glomerular filtrate, after which the substrates are excreted back into urine or blood by ABC transporters including multidrug resistance protein 2 (MRP2; ABCC2) and P-glycoprotein (P-gp; MDR1, ABCB1) (Giacomini et al. 2010; Masereeuw and Russel 2010; Morrissey et al. 2013). One exception is multidrug and toxin extrusion protein (MATE) that is an efflux transporter but belongs to SLC superfamiliy (Giacomini et al. 2010). With the help of these uptake and efflux transporters, renal tubular epithelial cells remove substances from the blood followed by their elimination via the urine and maintain specific compounds from the glomerular filtrate back into the systemic

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circulation. Therefore, the vector transport mediated by renal transporters represents the basis of active tubular secretion and reabsorption. Membrane transporters are involved in the renal elimination of a wide array of metabolites, nutrients, toxins, xenobiotics, and drugs, which contributes to the normal renal function.

The substances underwent active tubular secretion and reabsorption always are charged molecules at physiological pH which are hard to across the plasma membrane through passive diffusion (Pelis and Wright 2014; Yin and Wang 2016). In both tubular secretion and reabsorption, the substance has to be firstly taken up into the tubular epithelial cells. The capability of substance permeating the membrane is the determinant of the rate of active tubular secretion and reabsorption. Therefore, the rate-determining step is considered to be mediated by the active uptake transporter (Fan et al. 2016; Kusuhara and Sugiyama 2009; Parker and Houston 2008). Generally, the anionic and cationic molecules can be recognized by organic anion transport systems and organic cationic transport systems, respectively. The organic anion transport system expresses both in the basolateral membranes and in the apical membranes of the tubular epithelial cells. In human, three multispecific organic anion transporters, OAT1 (SLC22A6), OAT2 (SLC22A7), and OAT3 (SLC22A8), located in the basolateral side, are responsible for substrate uptake from blood (Wang and Sweet 2013). The apical membranes of the proximal tubules express OAT4 (SLC22A11) in the human kidney, although their functional significance is not fully understood (Ekaratanawong et al. 2004; Hagos et al. 2007b; Miyazaki et al. 2005; Yang et al. 2010). Detail information of OATs related to expression, regulation, roles in toxicity, and impact on injury and disease has been reviewed recently (Wang and Sweet 2013). This review focused on the current information (2012–2016) regarding the important role of OATs in diseases and DDIs. New identified OATs substrates, the regulation of OAT expression, the new findings in drug clearance and herb–drug interactions (HDIs)/DDIs mediated by OATs, and potential roles of OATs in various diseases were summarized to further understand OAT function.

2. OATs substrates

In addition to organic anions, OATs recognize some zwitterionic organic molecules as substrates (Koepsell 2013). In fact, the substrates of OATs represent a wide spectrum of chemical structures. First of all, OATs facilitate numerous endogenous substances to permeate the plasma membrane of the tubular epithelial cells, which has been considered to be central to organism homeostasis and the progression of certain disease. Creatinine, uric acid, uremic solutes, and some hormones are proved to be substrates of OATs (Koepsell 2013; Schwenk and Pai 2016; Stieger et al. 2014). In addition, environmental toxins and toxicants (e.g., mycotoxins and pesticides) (Nigam et al. 2015), drugs (e.g., antibiotics, diuretics, non-steroidal anti-inflammatory drugs, antihypertensives, proton pump inhibitors, antivirals, and anticancer agents) (Zhou and You 2007), and natural products in herbs (e.g., flavonoid conjugates, hydroxycinnamic acids, rhein, gallic acid and gentisic acid) can also interact with OATs (Li et al. 2014; Ma et al. 2014; Wang et al. 2013a; Wang et al. 2013b; Wong et al. 2011a; Wong et al. 2011b). The renal elimination and pharmacokinetic behavior of these substrate agents depend on OATs-mediated transport. OATs dysfunction causes the abnormal exposure and changes the efficacy and toxicity of drugs and consequently induces clinically significant DDIs. New identified OATs substrates were list in Table 1 as an update (2012–2016) to the comprehensive table from reference (Wang and Sweet 2013).

3. Regulation of OATs

OATs are membrane protein that can be regulated at both the mRNA and protein level by chemical inducers, hormones, nuclear receptors, transcription factors and diseases (Fig. 1). Generally, genetic regulation is mediated by nuclear receptors which are activated by ligands, translocate to nuclear, and bind to the promoter of OAT. Protein modification through ubiquitination and internalization is another way to directly regulate the activity of OATs.

Nuclear receptors are known to regulate metabolic enzymes and drug transporters via transcriptional and/or post-transcriptional regulation in vitro and in vivo. The regulatory effect of hepatocyte nuclear factor (HNF)-1α homodimer, HNF-1α/HNF-1β heterodimer, and HNF-4α on the promoter activity of OAT1 and OAT3 has been well established (Jin et al. 2012; Wang and Sweet 2013). Activating HNF-1α homodimer, HNF-1α/HNF-1β heterodimer, and HNF-4α induced the promoter activity of OAT1 and OAT3. Recently, transcription factor B-cell CLL/ lymphoma 6 (BCL6), a HNF-1α-interacting protein, was found to induce the expression of rat Oat1 and Oat3 and enhance the promoter activity of human OAT1 (Wegner et al. 2012; Wegner et al. 2014). However, BCL6 does not bind directly or indirectly to OAT1 promoter but increases the protein expression of HNF-1α and thereby indirectly enhances OAT1 gene transcription. The vitamin D receptor (VDR) is a member of the nuclear and steroid receptor superfamily. VDR activation by 1α,25-dihydroxyvitamin D3 down-regulated rOAT1/rOAT3 mRNA expression and rOAT1protein level in rat kidney (Chow et al. 2010; Kim et al. 2014). The concomitant reduction in FXR, SHP, HNF-1alpha and HNF-4alpha mRNA expression was observed after 1α,25-dihydroxyvitamin D3 treatment, suggesting the possibility of cross-talk among the nuclear receptors (Chow et al. 2010). Indeed, liver X receptors (LXRs) was found to modulate the expression of human OAT1 in vitro and mouse Oat1 in vivo (Kittayaruksakul et al. 2012). The protein levels of hOAT1 and mOat1 were decreased following LXR activation. However, the in vitro evidence and direct interaction between these nuclear receptors and OATs promoters is virtually unknown.

Protein kinase C (PKC)-mediated ubiquitination and internalization was considered as import posttranslational regulation of OATs. OAT1 transport activity is inhibited following PKC activation. Further study found two closely related E3 ubiquitin ligases, neural precursor cell expressed, developmentally downregulated 4–1 and 4–2 (Nedd4–1 and Nedd4–2) were important mediators for PKC-regulated hOAT1 ubiquitination, expression, and function (Xu et al. 2016c). There was a physical interaction between OAT1 and Nedd4–1 (Xu et al. 2016a). Among four protein-protein interacting WW domains of Nedd4–1, WW2 and WW3 domains were the interaction site (Xu et al. 2016a). In addition, Nedd4–2 palyed an vital role in the ubiquitination, expression and function of OAT3 through a directly physical interaction (Xu et al. 2016b). In contrast to PKC, hOAT4 transport activity in the kidney COS-7 cells was stimulated by serum- and glucocorticoid-inducible kinase 2 (sgk2). Sgk2 upregulated the protein expression of OAT4 through abrogating Nedd4–2-mediated hOAT4 ubiquitination (Wang et al. 2016a).

Moreover, the local membrane environment had an impact on the expression, function and targeting of human OAT3 and rat Oat3. OAT3 located in Lipid raft domains (LRD; cholesterol-rich domains of the plasma membrane)-rich membranes and co-localized with LRD-rich cytoskeleton proteins exhibited high substrate transportcapacity (Srimaroeng et al. 2013).

4. OATs-mediated HDIs/DDIs

OATs-mediated active tubular secretion represents an important elimination mechanism for substrate drugs. Due to the broad spectrum of substrates, OATs are prone to be the interaction target when two or more OATs substrates are coadministered. Competition or non-competition inhibition of OATs transport function decreases the renal clearance and causes a DDI. In recent years, herbal remedies are widely used to treat illnesses or as food supplements. Herbs always contain complex ingredients, may potentially influence the pharmacokinetics of concomitant drugs, and are frequently reported as risk factors in human by HDIs in metabolism or transporter based mechanisms (Meng and Liu