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Therapeutic implications of renal anionic drug transporters

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ABSTRACT

One of most important functions of the kidney concerns the clearance of endogenous waste products, exogenously administered drugs as well as environmental exposures. In addition to glomerular filtration, active tubular secretion is an efficient mechanism for extracting compounds from the circulation and excreting them into the urinary compartment, and it presents one of the determinants of a drug's pharmacokinetic behavior. The renal proximal tubules are equipped with a range of transporters, which can be roughly divided into a system for organic anions and one for organic cations, each consisting of multiple carriers with overlapping substrate specificities that cooperate in basolateral drug uptake and luminal excretion. Drug transporters are often involved in clinically significant drug–drug interactions, leading to unexpected changes in drug plasma levels. Similar effects may be observed for the interaction of drugs with endogenous substrates and food components. Furthermore, disease states could affect the expression and/or function of transport systems as well, mainly through regulation of gene transcription. Finally, inter-individual variability and gender differences exist in the expression of drug transporters, which affect overall renal drug handling. This review highlights recent knowledge of the renal organic anion system with special reference to the therapeutic implications associated with variations in transporter activity and drug interactions.

Contents

1. Introduction — general role of anionic drug transporters

The efficacy and toxicity of a drug result from its pharmacologically active target site concentrations, which are influenced by the pharmacokinetic characteristics of the drug. Drug transporters have increasingly been recognized in modulating these characteristics, because they are expressed in various tissues and play a significant role in transporting drugs into and out of the target sites. Numerous ingested drugs are absorbed in the intestinal tract, collected in the liver where they are either excreted into bile or transported back into

Abbreviations: ABC, ATP-binding cassette; BCRP, breast cancer resistance protein; CMPF, 3-carboxy-4-methyl-5-propyl-2-furanpropionate; CsA, cyclosporine A; DHEAS, dehydroepiandrosterone sulfate; EHBR, Esai hyperbilirubinaemic Sprague–Dawley rat; ET, endothelin; GSH, glutathione; GY/TR$^-$, Groningen yellow/transport deficient; HA, hippurate; IA, indole acetate; IS, indoxyl sulfate; LPS, lipopolysaccharide; MPA, mycophenolic acid; MPAG, MPA glucuronide; MRP, multidrug resistance (associated) protein; NLT, novel liver-specific transporter; NO, nitric oxide; NPT, sodium/phosphate cotransporter; NRTI, nucleoside analog reverse transcriptase inhibitor; NSAIDs, non-steroidal anti-inflammatory drugs; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; PAH, p-aminohippurate; PEPT, proton oligopeptide cotransporter; SLC, solute carrier; SLCO, organic anion transporting polypeptide gene; SNP, single nucleotide polymorphism; ^{99m}Tc-MAG3, technetium-99m mercaptoacetyltriglycine; URAT, urate transporter.

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the sinusoids to be eliminated by the kidney, unaltered or as metabolites. In addition to glomerular filtration, renal xenobiotic clearance is determined by the interplay of secretory and reabsorptive processes in the tubular system, involving several 'polyspecific' transporters, i.e. transport proteins that accept compounds of different sizes and molecular structures. Many drugs or their phase II metabolites are organic anions; therefore, the renal organic anion transport system can have an important impact on the drug's pharmacokinetic behavior. Two major transporter families are involved: 1) the solute carrier family (SLC), and 2) the ATP-binding cassette (ABC) superfamily. Transporters belonging to the ABC family are primary active efflux transporters; they use energy derived from ATP hydrolysis to mediate the active cellular efflux of drugs, often against a steep diffusion gradient (see for reviews e.g. Schinkel & Jonker, 2003; van de Water et al., 2005; Szakacs et al., 2008). Many of the SLC family members facilitate the cellular influx of substrates, either by facilitated diffusion acting as a channel, or by secondary active transport coupled to the exchange or cotransport of endogenous (organic) ions to provide the driving force (Zhang et al., 2002; Hagenbuch & Gui, 2008; Duan & You, 2010). Certain SLC transporters exhibit efflux properties or are bidirectional, depending on the concentration gradients of substrate and coupled ion across the membrane (Hediger et al., 2004). SLC transporters can be highly efficient carriers, in particular the organic anion transporting polypeptides (OATP; *SLCO*) that mediate the uptake of lipophilic compounds, even if they are highly bound to plasma proteins (Mikkaichi et al., 2004b). An overview of the different transporters identified in human kidney is given in Fig. 1 and their characteristics are presented in Table 1. Note that gene symbols and functional protein names often differ. Fig. 2 shows the intra-nephron distribution of the organic anion transporters. Over the past years, knowledge of the molecular identity of these transporters and their substrate specificity has increased considerably and has been summarized in various detailed review articles (Wright & Dantzler, 2004; Nies et al., 2008; El-Sheikh et al., 2008a; Ahn & Nigam, 2009; Kusuhara & Sugiyama, 2009). However, the clinical implications of many of these new discoveries have not yet been established.

Transport proteins are often involved in adverse drug reactions that are caused by drug–drug or drug–food interactions. Furthermore, the expression levels of drug transporters may be altered under disease conditions. It is known that renal failure can influence the expression levels of uptake and efflux transporters, not only in the kidney but also in the liver and gastrointestinal tract. This implies that a disturbed renal function may also affect the pharmacokinetics of drugs that are eliminated by nonrenal excretion. Obviously, this could lead to important adverse reactions if the drugs are administered without dose adjustment for reduced renal function, in particular for compounds with a narrow therapeutic window. In addition, variabilities in gender, age or expression levels due to polymorphisms may affect renal drug handling. Transporter protein science is a rapidly evolving field of pharmacology and this review highlights recent knowledge of the renal organic anion system, with emphasis on the therapeutic implications associated with variations in transporter activity and drug interactions.

2. Renal transporters — structure and mechanism

2.1. Solute carrier transporters

The solute carrier family consists of 48 gene subfamilies, with over 380 family members (Fredriksson et al., 2008). Most critical with respect to renal organic anion transport, are the transporters belonging to the *SLC22A* subfamily. Furthermore, members of the SLC15A, SLC17A and SLC21/SLCO have been implicated in renal anionic drug handling.

2.1.1. SLC15, SLC17

The proton oligopeptide cotransporter family is rather small and comprises four members. Two members, *SLC15A1* (PEPT1) and *SLC15A2* (PEPT2), are expressed in the apical membrane of the proximal tubules (Shen et al., 1999). Hilgendorf et al. (2007) showed that the gene expression levels of PEPT1 and PEPT2 are both low as compared to other drug transporters, but PEPT2 expression is somewhat higher than PEPT1. Various investigations (reviewed in

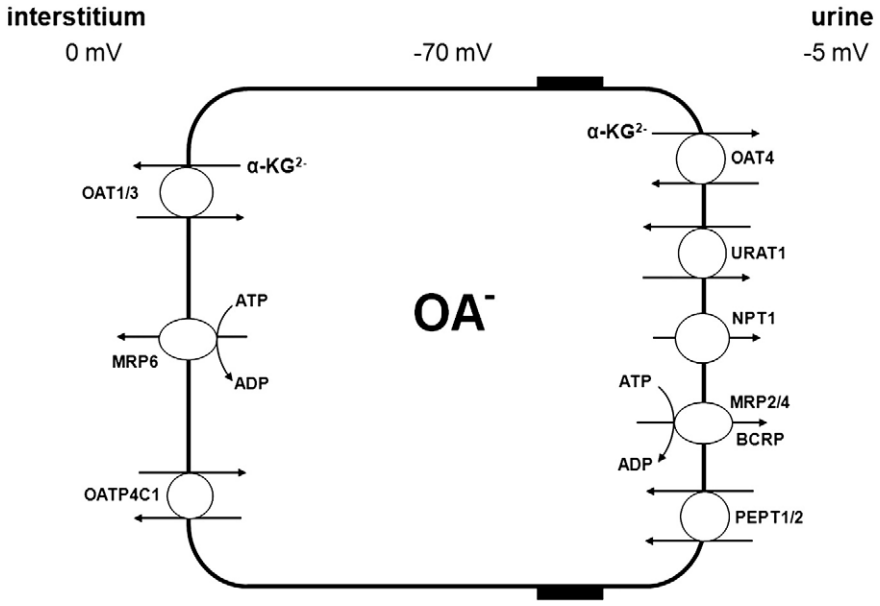

Fig. 1. Proximal tubule cell model postulating mechanism mediating organic anion (OA^-) uptake and secretion. Active uptake of anionic drugs into cells via the organic anion transporters 1 and 3 (OAT1/3) occurs in exchange of dicarboxylates, preferably α-ketoglutarate, for which a gradient exist through indirect coupling to Na^+-α-ketoglutarate cotransport. In addition, the organic anion transporting polypeptide, OATP4C1, mediates the uptake of anionic drugs, probably via exchange with bicarbonate. Urinary secretion of OA^- is mediated by the multidrug resistance proteins 2 and 4 (MRP2/4) and breast cancer resistance protein 1 (BCRP). The role of MRP6 in the basolateral membrane is still unclear with regards to renal drug clearance. The phosphate transporter, NPT1 could be involved in anionic drugs secretion as well. OAT4 and the urate transporter, URAT1, could be involved in OA^- efflux, but may also be involved in reabsorption via exchange mechanisms. The peptide transporters, PEPT1/2, mediate luminal uptake of peptide drugs.