Polyspecific Organic Cation Transport: Insights into the Substrate Binding Site

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ABSTRACT
Positively charged endogenous and exogenous organic compounds of diverse chemical structures are transported by polyspecific organic cation transporters (OCT). In two contributions to the May 2005 issue of Molecular Pharmacology, amino acid residues within the fourth and tenth transmembrane helices of rat OCT1 are described that contribute to cation and corticosterone binding. In a three-dimensional model based on the structure of the lactose permease, these residues are located in a large groove, the binding site for biogenic amines and cationic drugs.

Many widely used pharmaceuticals carry a positive or negative charge and hence are organic cations or anions. The charge renders these compounds hydrophilic, greatly facilitating their solubility in gastrointestinal fluids, plasma, and in the extra- and intracellular aqueous spaces. However, the charge largely decreases the solubility of drugs in lipids and efficiently slows uptake into or release from cells by simple diffusion across cell membranes. Rapid transport of charged drug molecules into hepatocytes for metabolism and biliary excretion, or across small bowel and proximal tubular epithelia for intestinal absorption and renal excretion, requires the presence of transporters (carriers, permeases). Given the large number of drugs and other xenobiotics, these intestinal, hepatic, and renal transporters face the formidable task of efficiently handling chemically unrelated compounds. To do so, these transporters cannot be specific for a single compound or close congeners, as in the majority of Na\(^+/\)H\(^+\)-coupled transporters, but must be polyspecific, showing wider recognition properties.

Meanwhile, several families of polyspecific transporters for organic cations and anions exist: the ATP-driven multidrug resistance transporters [e.g., MDR, P-glycoprotein; ABCB1 (Ambudkar et al., 1999)] and multidrug resistance-associated proteins [MRPs; ABCC family (König et al., 1999; Borst et al., 2000)], as well as the ATP-independent families of organic anion transporting polypeptides [OATPs; solute carrier family SLC21 (Hagenbuch and Meier, 2004)] and organic cation and anion transporters [OCTs, OCTNs, OATs; solute carrier family SLC22 (Koepsell and Endou, 2004)]. The members of the SLC22 family belong to the major facilitator superfamily of uniporters, symporters, and antiporters, which occur in bacteria, lower eukaryotes, plants, and mammals. All members of the SLC22 family are polyspecific and interact with a vast number of endogenous and exogenous compounds including frequently used drugs. In this issue of Molecular Pharmacology, Hermann Koepsell and his associates offer novel insights into the molecular basis of polyspecificity of the rat organic cation transporter 1 (OCT1) (Gorboulev et al., 2005; Popp et al., 2005).

The substrate specificity of the organic cation transporters has been studied in detail previously (Koepsell et al., 2003; Koepsell, 2004). The transporters OCT1 and/or OCT2, for instance, interact not only with endogenous compounds, such as choline, dopamine, histamine, and 5-hydroxytryptamine, but also with receptor antagonists (e.g., phenoxybenzamine, cimetidine), receptor agonists (clonidine, O-methylisoprenaline), ion channel blockers (procainamide, quinidine, meperphenidol, verapamil), psychoactive drugs (desipramine), antivirals (acyclovir, ganciclovir), antidiabetic agents (metformin, phenformin), antimalarial agents (quinine), and other drugs (Koepsell, 2004). A detailed comparison between rat OCT1 and rat OCT2 performed earlier (Arndt et al., 2001)
laid the basis for the present contribution by Gorboulev et al. (2005) in this article. Using electrophysiological and tracer techniques, Arndt et al. (2001) found a series of substances for which OCT1 and OCT2 had considerably different affinities. These substances included cyanine 863, quinine, procainamide, mepiperphenidol, and O-methylisoprenaline, which showed 5 to 70 times higher IC_{50} values (i.e., had lower affinities) for OCT2 than for OCT1, and corticosterone, aspartate 475 [identified previously as contributing to organic cation binding (Gorboulev et al., 1999)] are all located in the large cleft and are therefore easily accessible for organic cations. The clusters of functionally important residues turned out to be spatially separated, offering various niches for binding of organic cations. Nonidentical but overlapping binding sites for organic cations have been postulated earlier on the basis of the first mutational studies on OCT1 (Gorboulev et al., 1999) and are strongly supported by the present findings.

Why are the articles by Gorboulev et al. (2005) and Popp et al. (2005) an important development in the field? First, they provide an example of a thorough and analytical characterization of transporters and mutants thereof, using several control experiments, investigation that took the authors 3 years to complete. Second, the strategy to use differential affinities of two transporters for the detection of amino acids involved in the binding of corticosterone can be adopted to other transporters of the SLC22 family, and possibly to members of other transporter families. Third, we are learning from these two contributions how nature makes transporters polyspecific (e.g., by offering large sites with various anchor points for binding). Subsequent experiments exploiting further substrates will refine the present picture.

References

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