Roles of organic anion transporters (OATs) and a urate transporter (URAT1) in the pathophysiology of human disease

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Abstract
Renal proximal and distal tubules are highly polarized epithelial cells that carry out the specialized directional transport of various solutes. This renal function, which is essential for homeostasis in the body, is achieved through the close pairing of apical and basolateral carriers expressed in the renal epithelial cells. The family of organic anion transporters (OATs), which belong to the major facilitator superfamily (SLC22A), are expressed in the renal epithelial cells to regulate the excretion and reabsorption of endogenous and exogenous organic anions. We now understand that these OATs are crucial components in the renal handling of drugs and their metabolites, and they are implicated in various clinically important drug interactions, and their adverse reactions. In recent years, the molecular entities of these transporters have been identified, and their function and regulatory mechanisms have been partially clarified. Workers in this field have identified URAT1 (urate transporter 1), a novel member of the OAT family that displays unique and selective substrate specificity compared with other multispecific OATs. In the OAT family, URAT1 is the main transporter responsible for human genetic diseases. In this review, we introduce and discuss some novel aspects of OATs, with special emphasis on URAT1, in the context of their biological significance, functional regulation, and roles in human disease.

Key words Organic anion transporter · Urate (uric acid) · Urate transporter · Organic cation transporter

Introduction
In the kidney, the renal proximal and distal tubules have two important roles: they remove waste products from the blood to the urine, and at the same time they regulate the blood levels of many important molecules. These important function of the tubules is achieved by a cohort of transporters and channels expressed in the apical and basolateral membranes of the cells. Expressing specifically in the appropriate domains of cell membranes, the transporters and channels carry out bidirectional transport of their essential substrates across the tubular epithelial cells, which regulates the concentration and the equilibrium of these substrates.

Research into the molecular basis of transporters has progressed over the past 10 years. Among diverse transport systems in the kidney, the organic anion transport system has been the focus of intense scientific and medical interest because of its roles in the excretion of many clinically important pharmaceuticals.1-3 In recent years, molecular cloning approaches have identified several members of “multispecific” organic anion transporters (OATs) which belong to the amphiphilic solute transporter family (SLC22A) with organic cation transporters (OCTs) (Fig. 1).4,5 To date, five members of the OAT family (OAT1 – OAT5) have been identified and functionally characterized.6-14 One of the hallmarks of the OAT family is their ability to accept a wide variety of organic compounds (multispecific), which requires only a hydrophobic backbone and a negative charge in the structures of their substrates.15 Studies of the substrate selectivity and specificity of OATs revealed that a wide variety of drugs are good substrates for OATs. They include antibiotics, nonsteroidal antiinflammatory drugs (NSAIDs), loop and thiazide diuretics, angiotensin converting enzyme (ACE) inhibitors, anticancer drugs, and antivirals, suggesting that these transporters are regulators of the blood concentrations of the drugs by manipulating their excretion and reabsorption in the kidney1,2 (Fig. 1).
Although the roles of the OAT family in the renal handling of various drugs have been understood, the biological importance of each member in a whole tissue or organ and its responsibility for human disease have been largely unknown because of a lack of generation of the corresponding knockout mice, and no discovery of a human genetic disease in which genes encoding OATs are impaired. The substrate specificity for OAT family members overlaps considerably, which makes it difficult to assess the individual contribution of each transporter to the tissue transport capacity as a whole. Recently, the generation and characterization of OAT3 knockout mice has been reported, which described for the first time the biological roles of OATs in vivo.16 This emerging evidence confirms the important roles of the transporters in human genetic or common (non-genetic) diseases. Here, we first describe the function and regulation of URAT1 that is essential for urate homeostasis, and then focus on the roles of URAT1 and OATs in the pathophysiology of human diseases such as renal hypouricemia and chronic renal failure.

**Function of URAT1**

Urate transport in the human kidney

In vertebrates, urate (uric acid) is an intermediate product of purine metabolism, which is oxidized to water-soluble...