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Commentary

Physiological and pharmacokinetic roles of H^+/organic cation antiporters (MATE/SLC47A)☆

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ABSTRACT

Vectorial secretion of cationic compounds across tubular epithelial cells is an important function of the kidney. This uni-directed transport is mediated by two cooperative functions, which are membrane potential-dependent organic cation transporters at the basolateral membranes and H^+/organic cation antiporters at the brush-border membranes. More than 10 years ago, the basolateral organic cation transporters (OCT1-3/SLC22A1-3) were isolated, and molecular understandings for the basolateral entry of cationic drugs have been greatly advanced. However, the molecular nature of H^+/organic cation antiport systems remains unclear. Recently, mammalian orthologues of the multidrug and toxin extrusion (MATE) family of bacteria have been isolated and clarified to function as H^+/organic cation antiporters. In this commentary, the molecular characteristics and pharmacokinetic roles of mammalian MATEs are critically overviewed focusing on the renal secretion of cationic drugs.

1. Introduction

The secretion of drugs and xenobiotics is an important physiological function of the renal proximal tubules. Transport studies using isolated membrane vesicles and cultured renal epithelial cells have suggested that the renal tubular secretion of cationic substances involves the concerted actions of two distinct classes of organic cation transporters: one facilitated by the transmembrane potential difference at the basolateral membranes and the other driven by the transmembrane H^+ gradient (H^+/organic cation antiporter) at the brush-border membranes [1–3]. A prototype substrate, tetraethylammonium (TEA), has been used for the functional characterization of these organic cation transport systems in the kidney.

The first membrane potential-dependent organic cation transporter (OCT1) was isolated from the rat kidney in 1994 [4]. Subsequently, we isolated rat (r) OCT2 cDNA [5]. Currently, there are three isoforms (OCT1-3/SLC22A1-3), and the physiological and pharmacokinetic roles of these transporters have been characterized from various standpoints. There are several excellent reviews documenting the historical developments and recent progress in the understanding of OCT families [6–10].

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Abbreviations: MATE, multidrug and toxin extrusion; MPP, 1-methyl-4-phenylpyridinium; NMN, N^1-methylnicotinamide; OCT, organic cation transporter; OCTN, novel organic cation transporter; SLC, solute carrier; SNP, single nucleotide polymorphism; TEA, tetraethylammonium.

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On the other hand, the molecular identification of H^+/organic cation antiport systems has not been progressed. Although several candidates for H^+/organic cation antiporters such as OCT2p [11], OCTN1 (SLC22A4) [12,13], and OCTN2 (SLC22A5) [14] have been proposed, all reports lacked direct and enough evidences to support the biochemical and physiological characteristics of H^+/organic cation antiport systems. For example, Tamai et al. [12] reported that OCTN1 may serve as a H^+/organic cation antiporter, because it can mediate the pH-dependent transport of TEA, and is localized at the brush-border membranes of renal proximal tubules. However, the following findings may not support that OCTN1 functions as classical H^+/organic cation antiport systems: (i) TEA transport by OCTN1 is electrogenic [13], whereas TEA transport by classical H^+/organic cation antiport systems is electroneutral [15], (ii) the renal expression level of OCTN1 is relatively weak [16], and (iii) OCTN1 has been demonstrated to mediate the Na^+-dependent transport of the fungal antioxidant, ergothioneine with much greater catalytic efficiency than for TEA [17,18]. Thus, no candidate fully satisfies the characteristics of H^+/organic cation antiport systems, and the true molecular nature of this transporter has been veiled for a long time.

2. Cloning of MATE/SLC47

In 1998, Tsuchiya and his colleagues [19] identified a novel multidrug transporter in *Vibrio parahaemolyticus* and its homolog in *Escherichia coli*, named NorM and YdhE, respectively. These two transporters were assigned to a new family of transporters designated as the multidrug and toxin extrusion (MATE) family [20]. Although the overall properties of the MATE family in bacteria have not been elucidated, some transporters mediated the H^+- or Na^+-coupled export of cationic drugs [20–22].

Based on these findings, Moriyama and his colleagues [23] searched for mammalian orthologues of MATE-type transporters using genomic databases, and succeeded in the isolation of cDNAs encoding orthologues of the bacterial MATE family, i.e., human (h) MATE1 (GenBank accession no. NP-060712), hMATE2 (NP-690872), mouse (m) MATE1 (AAH31436), and mMATE2 (XP-354611). Subsequently, we also reported the cDNA cloning of hMATE2-K (AB250364) [24], hMATE2-B (AB250701) [24], and rat (r) MATE1 (AB248823) [25]. Furthermore, other groups have reported the cloning of cDNAs for rMATE1 (AAH88413) [26], rabbit (rb) MATE1 (EF120627) [27], and rbMATE2-K (EF121852) [27]. The MATE family was assigned as the SLC47 family (SLC47A1: MATE1, SLC47A2: MATE2 and MATE2-K) by HUGO Gene Nomenclature Committee in 2007.

3. Concerns for nomenclature and classification

3.1. *hMATE2, hMATE2-K, and hMATE2-B*

During the course of our cloning process, the original hMATE2 cDNA could not be isolated, alternatively cDNAs for hMATE2-K and hMATE2-B were isolated [24]. As compared to the original hMATE2 cDNA, the hMATE2-K cDNA lacked 108 base pair (bp) in exon 7, and the hMATE2-B cDNA contained an insertion of 46 bp in exon 7. The open reading frame of the hMATE2-K cDNA was 1698 bp long, coding for a 566-amino acid protein. That of hMATE2-B was 660 bp long and encoded a 220-amino acid protein. hMATE2-K, but not hMATE2-B, exhibited the transport activity of TEA. Based on these findings, we originally described hMATE2-K as a splicing variant of hMATE2. However, subsequently, Zhang et al. [27] also isolated rbMATE2-K cDNA instead of rbMATE2 cDNA. So far, transport characteristics of the original hMATE2 remain unclear, whereas those of hMATE2-K and rbMATE2-K were clearly demonstrated [24,27,28]. Although the identification and characterization of the original hMATE2 should be carried out, MATE2-K is currently the only functional isoform in the MATE2 subfamily.

3.2. *mMATE2*

Moriyama's group classified rodent MATE2 (mMATE2 and rMATE2) as MATE3 family based on an amino acid alignment [29,30]. Dog, opossum and chimpanzee MATE3 are also members of MATE3 family [29,30]. This classification may be supported by tissue expression, i.e., human and rabbit MATE2-K are specifically expressed in the kidney, but rodent MATE2 is predominantly expressed in the testis [30]. In addition, based on the genomic database, it was found that there are no rodent isoforms corresponding to hMATE2-K. In order to avoid the misunderstanding of nomenclature, it would be reasonable to rename mMATE2 and rMATE2 as mMATE3 and rMATE3, respectively.

4. Structure

Human, mouse, rat, and rabbit MATE1 consists of 570, 532, 566, and 568 amino acid residues, respectively [23,25–27]. Phylogenetic trees of MATE1 and MATE2-K from various species are shown in Fig. 1A. A comparison of the multiple alignments of these MATE1 sequences revealed a similar overall homology except for the C-terminus of mMATE1 (Fig. 1B). Instead of the original mMATE1 (AAH31436, mMATE1a), another protein with 567 amino acid residues was registered in the NCBI database [CAI25734], which was recently reported as mMATE1b [31]. mMATE1b had almost the same C-terminal amino acid sequence as the other MATE1 proteins (Fig. 1B). In the cDNA of mMATE1b, a nucleotide 1528 ''A'' of the mMATE1a cDNA is deleted. mMATE1b has similar transport properties with mMATE1a and is localized at the renal brush-border membranes [31,32].

Hydropathy analysis in the original paper suggested that the hMATE1 protein contains 12 transmembrane domains, with both the C- and N-terminal located inside the cell. The secondary structure of various MATEs was examined by using transmembrane domain (TMD)-predicting programs such as SOSUI (http://sosui.proteome.bio.tuat.ac.jp/~sosui/proteome/sosuiframe0.html), TopPred (http://www.sbc.su.se/~erikw/toppred2/), TMHMM (http://www.cbs.dtu.dk/services/TMHMM-2.0/), and HMMTOP (http://www.enzim.hu/