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Review

Polyspecific organic cation transporters and their impact on drug intracellular levels and pharmacodynamics

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ABSTRACT

Most drugs are intended to act on molecular targets residing within a specific tissue or cell type. Therefore, the drug concentration within the target tissue or cells is most relevant to its pharmacological effect. Increasing evidences suggest that drug transporters not only play a significant role in governing systemic drug levels, but are also an important gate keeper for intra-tissue and intracellular drug concentrations. This review focuses on polyspecific organic cation transporters, which include the organic cation transporters 1–3 (OCT1-3), the multidrug and toxin extrusion proteins 1–2 (MATE1-2) and the plasma membrane monoamine transporter (PMAT). Following an overview of the tissue distribution, transport mechanisms, and functional characteristics of these transporters, we highlight the studies demonstrating the ability of locally expressed OCTs to impact intracellular drug concentrations and directly influence their pharmacological and toxicological activities. Specifically, OCT1-mediated metformin access to its site of action in the liver is impacted by genetic polymorphisms and chemical inhibition of OCT1. The impact of renal OCT2 and MATE1/2-K in cisplatin intrarenal accumulation and nephrotoxicity is reviewed. New data demonstrating the role of OCT3 in salivary drug accumulation and secretion is discussed. Whenever possible, the pharmacodynamic response and toxicological effects is presented and discussed in light of intra-tissue and intracellular drug exposure. Current challenges, knowledge gaps, and future research directions are discussed. Understanding the impact of transporters on intra-tissue and intracellular drug concentrations has important implications for rational-based optimization of drug efficacy and safety.

Contents

Abbreviations: ABC, ATP-binding cassette; ACC, acetyl-CoA carboxylase; AMP, adenosine monophosphate; AMPK, AMP-activated protein kinase; AUC, area under the concentration time curve; C_{max}, maximum plasma concentration; DDI, drug–drug interaction; MATE, multidrug and toxin extrusion; OAT, organic anion transporter; OATP, organic anion-transporting polypeptide; OCT, organic cation transporter; OGGT, oral glucose tolerance test; PBMC, peripheral blood mononuclear cell; PMAT, plasma membrane monoamine transporter; PXR, pregnane X receptor; SLC, solute carrier; TMD, transmembrane domain.

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1. Introduction

The ability of a drug molecule to move through cell membranes is a vital property affecting its pharmacokinetic and pharmacodynamic properties. Lipophilic drugs generally have high membrane permeability and their movement across cell membranes occurs primarily through passive diffusion, a non-mediated process discussed in great details elsewhere in this issue. Hydrophilic drugs, on the other hand, have low membrane permeability, and their efficient uptake into cells and tissues often involve facilitated mechanisms mediated by membrane transporters (also known as carriers). Different from passive diffusion where a drug molecule moves across membranes down its concentration gradient without energy input, carrier-mediated transport can be coupled to a cellular energy source to power uphill transport against the drug concentration gradient. Further, carrier-mediated drug transport is saturable, inhibitable, and highly dependent on the functional characteristics of the membrane transporters expressed in the specific tissues or cell types. In mammalian cells, there are two major types of membrane proteins involved in drug and solute transport: the solute carrier (SLC) and the ATP-binding cassette (ABC) transporters. The past two decades have witnessed an explosion of knowledge in our understandings of the basic biology and pharmacology of various SLC and ABC drug transporters. The *in vivo* roles of these transporters in drug disposition, efficacy, and toxicity are increasingly being appreciated. The clinical significance of transporters as a site of drug–drug interaction and a source for interindividual variability in drug response is also begining to be acknowledged [1–3].

Most drugs are intended to act on targets residing within a specific tissue or cells. While some drugs bind to external cell surface targets (*e.g.* G protein-coupled receptors), others act on intracellular enzymes and receptors residing inside the cell. Thus, it is the unbound drug concentration within the target tissue or cells that is directly responsible for eliciting its pharmacological effect. However, in the clinical setting, direct measurement of drug concentrations in target tissues and cells is difficult to achieve. Measurement of blood or plasma drug concentrations is thus commonly used to establish pharmacokinetic–pharmacodynamic relationships. For drugs that rapidly cross membranes by passive diffusion, plasma concentration is often a good surrogate for tissue concentration because the unbound drug concentration in tissue/cells is at equilibrium with its unbound concentration in plasma at steady state [4,5]. However, if a drug is transported by active uptake and/or efflux drug transporters, such a relationship may no longer exist. For drugs that are substrates of uptake transporters, tissue and/or intracellular drug concentrations can be much higher than drug concentrations in plasma. Conversely, for drugs that are substrates of efflux transporters, concentrations in tissues and cells may be substantially lower than predicted from plasma levels. Increasing evidences suggest that transporters expressed in specific tissues and cells can exert a great impact on local and intracellular drug concentrations, directly influencing their pharmacological and toxicological activities [4,5].

This review focuses on a special group of SLC drug transporters—the polyspecific organic cation transporters, which mediate cellular uptake and efflux of a broad spectrum of drugs, toxins, and endogenous compounds. We first briefly review the molecular and functional characteristics of major organic cation transporters with a special emphasis on their tissue distribution, cellular localization and transport mechanisms. We then highlight the impact of these transporters in controlling tissue and intracellular drug concentrations using literature examples where the roles of locally expressed organic cation transporters have been clearly demonstrated in several tissues (liver, kidney, salivary glands) in *in vivo* or clinical studies. The resulting consequence on pharmacodynamic response and toxicological effects of clinically used organic cation drugs is presented and discussed alongside. Lastly, the current challenges, knowledge gaps and future research directions in this field are briefly summarized and discussed.

2. Molecular and functional characteristics of polyspecific organic cation transporters

Organic cations are structurally diverse endogenous compounds (*e.g.* biogenic amines) and xenobiotics (*e.g.* drugs, environmental toxins) that carry a net positive charge at physiological pH. About 40% of the commonly prescribed drugs exist as organic cations at physiological pH [6]. Many organic cations are hydrophilic and rely on transporters to move across cell membranes. In humans and other mammals, there are a number of SLC transporters that appear to be evolved specifically to handle these structurally diverse organic cations. These polyspecific (or multispecific) organic cation transporters include the classic organic cation transporters 1–3 (OCT1-3) from the SLC22 family, the multidrug and toxin extrusion proteins 1–2 (MATE1-2) from the SLC47 family, and the plasma membrane monoamine transporter (PMAT) from the SLC29 family [7–12]. The molecular and functional characteristics of the major human polyspecific organic cation transporters are summarized below and in Table 1. A variety of clinically used drugs have been identified as the substrates of these transporters, and some selected drug substrates are listed in Table 1.

2.1. Molecular features of OCTs, MATEs, and PMAT

The human OCTs are encoded by the *SLC22* gene family and consist of three closely-related members: OCT1 (*SLC22A1*), OCT2 (*SLC22A2*) and OCT3 (*SLC22A3*). hOCT1 and hOCT2 are 70% identical in protein sequence, whereas hOCT3 shares 50% sequence identity with hOCT1 and hOCT2 [13]. The OCT proteins contain 542–556 amino acids with 12 predicted α-helical transmembrane domains (TMDs) [3]. The COOH- and NH2-terminal ends of the OCTs are intracellular. One large hydrophilic loop is localized to the extracellular side between TMD1 and TMD2 and contains several *N*-glycosylation sites. A large intracellular loop is localized between TMD6 and TMD7 with potential protein kinase C-dependent phosphorylation sites [14].

In excretory organs, OCTs frequently team up with the multidrug and toxin extrusion (MATE) proteins to mediate transepithelial transport of organic cations [15]. Encoded by the *SLC47A* gene family in humans, MATEs include two members: MATE1 (*SLC47A1*) and MATE2 (*SLC47A2*) [15]. Human MATE1 has only one isoform with 570 amino acids in length, while human MATE2 has three isoforms: the full length isoform hMATE2 (602 amino acids), hMATE2-K (566 amino acids) and hMATE2-B (220 amino acids) [9,16]. Both hMATE2 and hMATE2-K are functional, whereas hMATE2-B possesses no transport activity [16]. Human MATEs are predicted to have 13 TMDs with an extracellular carboxyl terminus and an intracellular amino terminus [15,17].

Beside OCTs and MATEs, a newer polyspecific organic cation transporter, the plasma membrane monoamine transporter (PMAT), was recently cloned and characterized by our laboratory [11,12]. By gene ontology, PMAT (SLC29A4) belongs to the equilibrative nucleoside transporter (SLC29) family. However, detailed functional characterization work demonstrated that PMAT functions as a polyspecific organic cation transporter that shares similar substrate specificity and functional characteristics to the OCTs [11,12,18,19]. PMAT is predicted to have 11 TMDs with an intracellular N- and an extracellular C-terminus [11].